Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Annex to Background document

to the Opinion on the Annex XV dossier proposing restrictions on
The following substances in single-use baby diapers

- The following polycyclic aromatic hydrocarbons (PAHs): benzo[c]fluorene, benz[a]anthracene, cyclopenta[c,d]pyrene, chrysene, 5-methylchrysene, benzo[e]acephenanthrylene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[e]pyrene, benzo[def]chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene, dibenzo[def,p]chrysene, naphtho[1,2,3,4-def]chrysene , benzo(r,s,t)pentaphene, dibenzo[b,def]chrysene
- The following polychlorinated dibenzo-p-dioxins (PCDDs): 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD
- The following Polychlorinated dibenzofurans (PCDFs): 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, OCDF
- The polychlorobiphenyls (PCBs) (DL-PCBs and NDL PCBs : PCB 81, PCB 77, PCB 123, PCB 118, PCB 114, PCB 105, PCB 126, PCB 167, PCB 156, PCB 157, PCB 169, PCB 189)
- Formaldehyde

ECHA/RAC/RES-O-0000007017-78-01/F
ECHA/SEAC/RES-O-0000007046-77-01/F

EC Numbers	CAS Numbers
n/a	n/a

Revision n. 5

21/12/2021

Change history

Revision n.	Reason for change	Date	Prepared by
5	Background document	21/12/2021	Dossier submitter

CONTENT

Annex A: Manufacture and uses 1

A.1. Composition of single-use baby diapers 1

A.2. The market of single-use baby diapers 8

A.2.1. Manufacture, import and export of single-use baby diapers 8

A.2.1.1. Global market 8

A.2.1.2. European market of single-use baby diapers for infants and young children 10

A.2.2. Sales and consumption of single-use baby diapers 11

A.2.2.1. In Europe 12

A.2.2.2. In France 13

A.3. Supply chain and life cycle of single-use baby diapers 16

A.4 The use of single-use baby diapers 23

A.5.Uses advised against by the registrants 25

Annex B: Information on hazard and risk 26

B.1. Identity of the substance(s) and physical and chemical properties 26

B.1.1. Name and other identifiers of the substance(s) 26

B.1.2. Composition of the substance(s) 27

B.1.3. Physicochemical properties 27

B.1.4. Justification for grouping 33

B.2. Manufacture and uses (summary) 33

B.3. Classification and labelling 33

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) 33

B.3.2. Classification and labelling in classification and labelling inventory/ Industry's self classification(s) and labelling[1] 33

B.4. Environmental fate properties 33

B.5. Human health hazard assessment 33

B.5.1 PAHS 33

B.5.1.1. Toxicokinetics (absorption, metabolism, distribution and elimination) 34

B.5.1.2. Acute toxicity 39
B.5.1.3. Irritation 39
B.5.1.4. Corrosivity 39
B.5.1.5. Sensitisation 39
B.5.1.6. Repeated dosed toxicity 39
B.5.1.7. Mutagenicity 39
B.5.1.8. Carcinogenicity 44
B.5.1.9. Toxicity for reproduction 63
B.5.1.10. Other effects 64
B.5.1.11. Derivation of DMELs 65
B 5.2 PCDD/Fs and PCBs 81
B.5.2.1. Toxicokinetics (absorption, metabolism, distribution and elimination) 81
B.5.2.2. Acute toxicity 91
B.5.2.3. Irritation 91
B.5.2.4. Corrosivity 91
B.5.2.5. Sensitisation 91
B.5.2.6. Repeated dosed toxicity 91
B.5.2.7. Mutagenicity 96
B.5.2.8. Carcinogenicity 98
B.5.2.9. Toxicity for reproduction 101
B.5.2.10. Other effects 102
B.5.12.11. Mode of action 106
B.5.12.12. Derivation of DNEL(s)/DMEL(s) 106
B.5.3. Formaldehyde 116
B.5.3.1. Toxicokinetics (absorption, metabolism, distribution and elimination) 117
B.5.3.2. Acute toxicity 118
B.5.3.3. Irritation 119
B.5.3.4. Corrosivity 119

B.5.3.5. Sensitisation 119

B.5.3.6. Repeated dosed toxicity 120

B.5.3.7 Mutagenicity 121

B.5.3.8. Carcinogenicity 123

B.5.3.9. Toxicity for reproduction 125

B.5.3.10. Other effects 125

B.5.3.11. Derivation of DNEL(s)/DMEL(s) 126

B.6. Human health hazard assessment of physicochemical properties 128

B.6.1. Explosivity 128

B.6.2. Flammability 128

B.6.3. Oxidising potential 128

B.7. Environmental hazard assessment 128

B.8. PBT and vPvB assessment 128

B.9. Exposure assessment 128

B.9.1. General information on releases and exposure 128

B.9.1.1. Summary of the existing legal requirements 128

B.9.1.2. Summary of the effectiveness of the implemented operational conditions and risk management measures 128

B.9.2. Use: Traditional single-use baby diapers 128

B.9.2.1. General information 128

B.9.2.2. Exposure estimation 129

B.9.2.3. Exposure assessment 136

B.9.2.4. Selection of exposure parameters 147

B.9.4. Other sources (for example natural sources, unintentional releases) 158

B.9.3. Overall environmental exposure assessment 158

B.9.4. Combined human exposure assessment 158

B.10. Risk characterisation 158

B.10.1. Manufacturing 158

B.10.1.1. Human health 158

B.10.1.2. Environment ... 158
B.10.2. Use: Traditionnal single-use baby diaper ... 158
B.10.2.1. Human health ... 158
B.10.2.2. Workers ... 172
B.10.2.3. Consumers ... 172
B.10.2.4. Indirect exposure of humans *via* the environment ... 172
B.10.2.5. Combined exposure ... 172
B.10.2.6. Environment ... 172
Annex C: Justification for action on a Union-wide basis ... 173
Annex D: Baseline ... 174
Annex E: Impact Assessment ... 177
E.1. Risk Management Options ... 177
E.1.1. French and European regulations ... 177
E.1.2. Certification labels and standards ... 178
E.1.3. Proposed options for restriction ... 181
E.1.4. Discarded restriction options ... 181
E.1.5. Other Union-wide risk management options than restriction ... 181
E.2. Alternatives ... 182
E.2.1. Description of the use and function of the restricted substances ... 182
E.2.1.1. Good practices to keep single-use baby diapers safe ... 182
E.2.1.2. Identification of contamination sources and critical steps ... 184
E.2.1.2.1. Possible contamination sources for PAHs ... 184
E.2.1.2.2. Possible contamination sources for PCDD/Fs ... 188
E.2.1.2.3. Possible contamination sources for DL-PCBs ... 192
E.2.1.2.4. Possible contamination sources for formaldehyde ... 194
E.2.1.2.5. Conclusion about possible sources of contamination and recommendations 196
E.2.2. Identification of potential preventive actions and alternative materials and techniques to remove contaminants ... 198
E.2.2.1. Substitution and technical solutions related to raw materials ... 198

E.2.2.1.1. Moving to totally chlorine-free (TCF) pulp 199

E.2.2.1.2. Substitution of types of glues used 200

E.2.2.1.3. Removal or substitution of wetness indicator 201

E.2.2.1.4. Removal or substitution of pigments 201

E.2.2.2. Alternative techniques to manufacturing process 202

E.2.2.2.1. Further controlling process temperatures 202

E.2.2.2.2. Moving to glueless diapers 202

E.2.2.2.3. Moving to Fluffless diapers 204

E.2.3. Risk reduction, technical and economic feasibility, and availability of alternatives 206

E.3. Restriction scenario(s) 211

E.4. Economic impacts 211

E.5. Human health impacts 212

E.6. Risk reduction capacity 212

E.7. Other impacts, practicability and monitorability 212

E.7.1. Social impacts 212

E.7.2. Wider economic impacts 213

E.7.3. Distributional impacts 213

E.8. Practicality and monitorability 213

E.9. Proportionality (comparison of options) 221

E.10. Comparison of Restriction Options 221

Annex F: Assumptions, uncertainties and sensitivities 222

Annex G: Stakeholder information 227

Annex H: Key elements underpinning the RAC conclusions on information on hazards 229

Annex I: Break-even analysis 239

References 242

Appendix : SCL methodology study 250

TABLES

Table 1 : Summary of the composition of single-use baby diapers 1

Table 2 : Bills of materials (BOMs) for average units of single-use baby diapers sold in Europe in 1987, 2005 and 2011 and related LCI datasets (Cordella et al., 2015)......................... 8

Table 3: Average price for branded and store brands single-use baby diapers for Europe and 5 countries in 2012 (source : NirYoav, 2012) 13

Table 4: Single-use baby diapers unit price on the French market (2019)....................... 14

Table 5: Single-use baby diapers unit price on the French market in 2020 (store brands) . 15

Table 6: Single-use baby diapers unit price on the French market in 2020 (branded diapers) 15

Table 7 : Chemical and physical properties of the substances included in the restriction proposal 28

Table 8 : Overview of oral bioavailability studies (taken from: RIVM, 2016) 34

Table 9: Detailed information on the dermal absorption data (this refers to BaP unless otherwise stated) as used for setting a dermal absorption fraction (adapted from: RIVM, 2016). 36

Table 10: Mutagenicity/carcinogenicity of polycyclic aromatic hydrocarbons: overall overview of regulatory evaluations (adapted from ECHA 2019) 40

Table 11 : Overview of key studies for PAH-mixtures for the endpoint carcinogenicity (taken from ECHA 2019 45

Table 12 : Incidences of tumours in liver and forestomach in male and female Wistar rats following treatment with pure BaP (5 days per week, for 104 weeks) (Kroese et al. 2001; Wester et al. 2012) (taken from: ECHA, 2019) 46

Table 13 : Polycyclic aromatic hydrocarbon composition of coal tar mixtures [a] (taken from: ECHA, 2019) 47

Table 14 : Incidences of neoplasms in female B6C3F1 mice fed BaP for 2 years (Culp et al., 1998) (taken from: ECHA, 2019).. 49

Table 15 : Incidences of neoplasms in female B6C3F1 mice fed coal tar mixtures I and II for 2 years (Culp et al., 1998) (taken from: ECHA, 2019) 51

Table 16: Number of tumour-bearing animals in coal tar mixture treated groups (A: coal tar mixture 1, B: coal tar mixture 2). Analysis by Schneider et al. (2002), based on the study of Culp et al. (1998) (taken from: ECHA, 2019) 52

Table 17 : $BMDL_{10}$ for BaP, PAH2, PAH4 and PAH8 (calculated by EFSA, 2008) based on total tumour-bearing animals in the 2-year carcinogenicity study on coal tar mixtures by Culp et al. (1998) 52

Table 18 : Incidences of forestomach and lung tumours in female A/J mice fed pure BaP for 260 days (Weyand et al., 1995) (taken from: ECHA, 2019) 53

Table 19 : Incidences of lung tumours in female A/J mice fed MGP for 260 days (Weyand et al., 1995) (taken from: ECHA, 2019) 54

Table 20 : Doses (in µg) applied in skin dropping experiments, in relation to benzo[a]pyrene (Schmähl et al., 1977) (taken from: ECHA, 2019) 55

Table 21 : Incidences of skin tumours (percentages in brackets) in female NMRI mice topically administered PAHs 2 d/wk for their entire lifespan (Schmähl et al., 1977) (taken from: ECHA, 2019) 56

Table 22 : Dose levels of the individual PAHs tested topically on mice (Habs et al., 1980) (taken from: ECHA, 2019) 57

Table 23 : Incidence of skin tumours in female NMRI mice topically administered with various PAHs (Habs et al., 1980). See Table B 15 for details on the applied dose levels (taken from: ECHA, 2019) 57

Table 24 : Concentration of PAHs in a condensate of Citrullus colocynthis seed used (Habs et al., 1984) (taken from: ECHA, 2019) 58

Table 25 : Incidences of skin tumours in female NMRI mice topically administered with BaP for 2d/wk (Habs et al., 1984) (taken from: ECHA, 2019) 58

Table 26 : Incidences of skin tumours in male C3H/HeJ mice (Warshawsky and Barkley, 1987) (taken from: ECHA, 2019) 59

Table 27 : Tumours observed following administration of BaP to SENCAR mice in the complete carcinogenesis protocol (Nesnow et al., 1983) (taken from: ECHA, 2019) 60

Table 28 : Tumours observed following administration of coke oven main extract, roofing tar extract, and gasoline vehicle exhaust extract to SENCAR mice in the complete carcinogenesis protocol (Nesnow et al., 1983) (taken from: ECHA, 2019) 60

Table 29 : Case-control studies of skin cancers and exposure to PAHs (taken from IARC, 2010) 62

Table 30: Endocrine disrupting effect of polycyclic aromatic hydrocarbons: overview of evaluations (website consulted 28/08/2020) 65

Table 31: No threshold dermal HRV and DMEL for BaP or PAHs 67

Table 32 : Dermal studies of BaP considered for calculation of dermal cancer slope factor, Benchmark dose calculations and slope factors (adapted Knafla et al., 2006) 69

Table 33 : Summary of Cancer Bioassay Studies used to determine dermal slope factor of B[a]P (adapted from Knafla et al., 2011) 70

Table 34: Dermal DMELs obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All dose levels in mg BaP/kg bw/d, DMEL in ng BaP/kg bw/d (adapted from BAuA, 2010) 72

Table 35 : Overview of dermal DMEL ranges obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All values in ng/kg bw/d (adaptaed from BAuA, 2010) 74

Table 36 : Overview of dermal DMEL ranges obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All values in ng/kg bw/d (adaptaed from BAuA, 2010) 76

Table 37 : Dermal DMEL derived for BaP from Knafla et al. (2006) 76

Table 38 : Comparaison between EFSA PAH8 approach, PAHs searched and detected in single-use baby diapers 79

Table 39: TEFs proposed by various organisations for PAHs 80

Table 40 : Dermal absorption of PCDDs/furans 85

Table 41: Endocrine disrupting effect of dioxins/furans: overview of evaluations 103

Table 42: Endocrine disrupting effect of PCBs: overview of evaluations 104

Table 43: Summary of the recent papers dealing with new insights in TCDD-induced epigenetic Methylation/Demethylation of target genes (from Patrizi et al., 2018) 104

Table 44: Summary of the recent papers dealing with new insights in TCDD-induced epigenetic histone(from Patrizi et al., 2018) 105

Table 45 : Summary of the recent papers dealing with new insights in the role of ncRNAs in mediating TCDD toxicity (from Patrizi et al., 2018) 105

Table 46 : No threshold HRVs for PCDD/Fs and DL-PCBs 107

Table 47 : Chronic oral threshold chronic HRVs for PCDD/Fs and DL-PCBs 109

Table 48 : HRVs for PCBs 114

Table 49 : endocrine disrupting effect of formaldehyde: overview of evaluations (website consulted : 28/08/2020) 125

Table 50 : Chronic oral-route threshold HRVs for formaldehyde 126

Table 51 : Aggregated results from the 2018 and 2019 SCL studies (extraction through an urine simulant) 132

Table 52 : Measured levels of targeted substances in single use baby diapers 137

Table 53 : Detected, semi-quantified or quantified chemicals in tested baby by Danish EPA (2009) 140

Table 54 : Levels of PCDDs and PCDFs in baby diapers (Wiberg et al., 1989) 146

Table 55 : Concentrations of dioxins and furans in baby diapers (Schecter et al., 1998) 146

Table 56 : Percentage of children wearing single-use baby diapers (all types) (UK Environment Agency, 2005b) 148

Table 57 : Distribution of body weight (kg) according to sex and age for children aged zero to 17 years (n = 2697) (ANSES, 2017b) 149

Table 58 : Information gathered through the call for evidence on exposure frequency 153

Table 59 : Summary of the data on the frequency of use of single-use diapers............. 154

Table 60 : Values of the frequency of use retained in the restriction proposal............... 154

Table 61 : Information about baby diapers weight according to the call for evidence...... 155

Table 62 : Average weight of a single-use diaper 156

Table 63 : Reported diapers weight (Group'Hygiène 2019) 156

Table 64 : values of the parameters used in the exposure assessment........................ 157

Table 65: Permissible intake of certain elements, derived from Annex 0 of the June 1985 advice by the Scientifid Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds, as published in report EU 12964 EN (from RIVM, 2008).............. 160

Table 66 : Transfer from the material to the skin and reflux ratio 162

Table 67 : RCR for each PCDD quantified in the SCL studies 165

Table 68 : RCR for each PCDF quantified in the SCL studies...................................... 165

Table 69 : RCR for each DL-PCB quantified in the SCL studies.................................... 166

Table 70 : DNEL used to define a migration limit for PCBs 167

Table 71 : Migration limit not to be exceeded in the entire diapers 168

Table 72 : RCR (for an excess risk of 10^{-06})for each PAH detected in the SCL studies 168

Table 73 : RCR for all the substances in the scope 169

Table 74 : Migration limits not to be exceeded in the entire single-use baby diaper........ 172

Table 75 : Temperatures in diaper production 187

Table 76 : Summary of the possible PAH contamination sources 188

Table 77 : Summary of the possible PCDD/Fs contamination sources 192

Table 78 : Summary of the possible DL-PCBs contamination sources 194

Table 78 : Summary of the possible formaldehyde contamination sources 195

Table 79 : Limit of detection according to the solvent extraction in a shredded entire diaper analysis 213

Table 80 : Composition of the urine simulant used (Colón et al., 2015) 214

Table 81 : Methods used to dose the chemicals 215

Table 82 : Values of the blanks for the 2019 SCL study 216

Table 83 : Comparative values regarding chemicals in the scope in other media............ 218

Table 84: Assumptions, uncertainties and sensitivities... 222

Table 85 : List of Stakeholders consulted by the Dossier Submitter in the preparation of the restriction proposal 227

FIGURES

Figure 1 : Diaper Absorbent Core Wood Pulp Fluff (source : technicaltextile.net) 4

Figure 2 : Diaper super absorbant polymer (SAP) 5

Figure 3 : Typical composition of a single-use baby diaper in 2004, 2011 and 2013 (Sources: EDANA, 2005, 2011 and 2015).. 7

Figure 4 : Global turnover of single-use baby diapers sector 2016-2022 (Businesscoot, 2020) 9

Figure 5 : Global single-use baby diapers market forecast 2017-2024............................. 9

Figure 6 : Global baby diapers market revenue, by product, 2016 (source : grandviewresearch.com) 10

Figure 7 : Revenue in the Baby Diapers segment - European market (in million €)(source : www.Statista.com) 11

Figure 8 : European baby diapers retail market - Sales volumes in million units sold (EDANA hearing, 2015 figures-Euromonitor) 12

Figure 9: Sales volumes for diapers and diaper pants in metropolitan France (Group'Hygiène hearing, 2017 reported in ANSES, 2019) 14

Figure 10 : The value chain of non wovens (EDANA, 2011).. 17

Figure 11 : Typical life cycle of a generic single-use baby diaper 17

Figure 12 : Typical manufacturing diagram of a single-use baby diaper 19

Figure 13 : Single-use baby diapers during manufaturing process (Drylock website) 20

Figure 14: Use of the various types of diapers according to country in children between the ages of zero and 24 months (%) (source : Thaman and Eichenfield, 2014) 24

Figure 15: Dermal absorption data based on literature in vitro and in vivo data in soil or solvent (acetone/ethanol). Circles indicate mean, -/+ indicate reported minimum and maximum values or are an approximation of the range obtained by taking mean -/+ 2SD (taken from: RIVM, 2016). 36

Figure 16: Toxic equivalency factors proposed by the WHO (1998 and 2005) for PCDD/Fs and DL-PCBs 116

Figure 17: Change in the average weight of a single-use diaper between 1980 and 2010 (Group'Hygiène, 2015).. 155

Figure 18 : Innovations in the manufacture of glueless baby diapers (based on Fameccanica 2018) 203

Figure 19 :Example of vent holes on single-use baby diapers packaging....................... 205

RAC and SEAC box

RAC and SEAC found that there is not a sufficient justification for a restriction.

Their evaluation of the restriction proposal is outlined in detail in the RAC and SEAC opinion.

Annex A: Manufacture and uses

A.1. Composition of single-use baby diapers

The main report presents an overview of the composition of a single-use baby diaper (section 1.1.3). Herein more details are provided of each component.

Table 1 : Summary of the composition of single-use baby diapers

External protective parts	Composition
Topsheet	Nonwoven produced from synthetic fibres (usually polypropylene, otherwise polyethylene or polyester) or bioplastics derived from corn starch and sugar cane, masterbatch pigment and surfactant +/- lotion
Acquisition layer (optional)	PET (polyethylene terephthalate) or cellulose and polyester fibres or polypropylene
Ear tabs (front and back ears)	Polyamide and polyethylene (front ears) or polypropylene fibres and elastomer (back ears)
Core	Superabsorbent polymer (SAP) encapsulated in wood cellulose fibres (fluff pulp) Polypropylene and polyethylene fibres, masterbatch pigment and surfactant (upper and lower tissues)
Backsheet	Low-density polyethylene (LDPE) or a mixture of nonwoven with a film (LDPE) or nonwoven produced from synthetic fibres (polyethylene and polypropylene) or bioplastic fibre film produced from lactic acid (PLA) or a mixture of polyethylene and starch (Master-Bi) or corn starch or nonwoven made of natural viscose or polyurethane or Low density polyethylene and calcium carbonate (polymer film)
Leak guard	Hydrophobic polypropylene nonwoven
Elastics	Thermoplastic polymers Lycra (polyurethane), Spandex, natural and synthetic rubber or polyester foam, elasthanne

Fasteners	Polyamide and polyethylene
Glue (for gluing the various sheets of the diaper)	Hot-melt adhesive Or copolymer rubber and starch
Lotion (optional)	Pharmaceutical-grade purified petrolatum (= Vaseline), stearyl alcohol, paraffinum liquidum, aloe barbadensis extract (aloe vera)
Pigments (optional)	No disperse dye Soy-based dyes (eco-friendly diapers)
Fragrances (optional)	No information provided
Wetness indicator **(optional)**	pH indicator (e.g. bromophenol blue)
Packaging	Polyethylene

Nonwovens: The production of nonwovens (including single-use baby diapers but also other Absorbent Hygiene Products(AHP)) takes place in three stages, although modern technology allows an overlapping of some stages, and in some cases all four stages can take place at the same time. These stages are: web formation, web bonding, finishing treatment and converting[1]:

- **Web formation:** Nonwovens manufacturing starts by the arrangement of fibres in a sheet or web. The fibres can be staple fibres or filaments extruded from molten polymer granules. Main nonwoven technologies used are in short fibre airlaid and Carded. In short fibre airlaid the fibres, which are always relatively short, are fed into a forming head by an airstream. The forming head assures a homogeneous mix of all fibres. By air again, a controlled part of the fibre mix leaves the forming head and is deposited on a moving belt, where a randomly oriented web is formed. Compared with carded webs, airlaid webs have a lower density, a greater softness and an absence of laminar structure. Airlaid webs offer great versatility in terms of the fibres and fibre blends that can be used. Carding is a mechanical process which starts from bales of fibres. These fibres are 'opened' and blended after which they are conveyed to the card by air transport. They are then combed into a web by a carding machine, which is a rotating drum or series of drums covered by card wire (thin strips with teeth). The precise configuration of cards will depend on the type of fibre and the basis weight to be produced. The web can be parallel-laid, where most of the fibres are laid in the machine direction, or they can be randomised. Typical parallel-laid carded webs result in good tensile strength, low elongation and low tear strength in the machine direction

[1] https://www.edana.org/nw-related-industry/how-are-nonwovens-made

and the reverse in the cross direction. Machine parameters and fibre mix can be varied to produce a wide range of fabrics with different properties.

- **Web bonding**: webs have a limited initial strength right after the web formation (depending on various bonding mechanisms). The web needs therefore to be consolidated in one or the other way. The choice of the web consolidation method strongly depends on functional properties that are needed as well as on the type of fibres used. There are three basic types of bonding: thermal bonding (cohesive bonding), mechanical bonding and chemical bonding.
  - Chemical bonding refers to the application of a liquid-based bonding agent to the web. Three groups of materials are commonly used as binders-acrylate polymers and copolymers, stryrene-butadiene copolymers and vinyl acetate ethylene copolymers. Water based bonder systems are the most widely used but powered adhesives, foam and in some cases organic solvent solutions can be found. The binder can be applied in many ways. It can be applied uniformly by impregnating, coating or spraying or intermittently, as in print bonding.
  - In mechanical bonding, the strengthening of the web is achieved by inter-fiber friction as a result of the physical entanglement of the fibers.
  - The thermal bonding uses the thermoplastic properties of certain synthetic fibers to form under controlled heating. In some cases, the web fiber itself can be used, but more often a low melt fiber of bicomponent fiber is introduced at the web formation stage to perform the binding function later in the process.

- **Finishing treatments** can be either mechanical (stretching, perforating, crimping etc.) or chemical. With the latter one can modify the surface of the fibres and the nonwoven to change the haptics or the repellency of the nonwoven. Nonwovens can be made conductive, flame retardant, water repellent, porous, antistatic, breathable, absorbent and much more according to the applications it will be used for. They can also be coated, printed, flocked, dyed or laminated to other materials.

- **Converting**: Nonwoven manufacturing ends usually with large rolls of product. Converters convert this roll good into a consumer product. Sometimes converting is done in 2 steps. Before manufacturing the finished product one might want to bring the rolled good one step closer to the final product by slitting, cutting, folding, sewing or heat sealing.

Fluff pulp comes from wood (shown in Figure 1) and is cellulose used as a part of the core of the diaper to absorb liquids. It gives good absorbing capacity to the diaper. The pulp has qualities such as high ratio of fibres to weight, lower coarseness and shorter fiber length. It is also homogenous and uniform short fiber. The capacity of normal wood pulp fluff is around 10 cc of water per gram of pulp when the diaper is not under pressure. But when subjected to 5 KPa of pressure its capacity becomes less than 2cc (technicaltextile.net). Hence super absorbent polymer (SAP) is also needed to hold the liquids under pressure (see below). Wood pulp sheets come from pine trees, which are generally obtained from the forests. Immediate absorption of wood pulp fluff is the reason for its usage in the single-use baby diapers. Liquids are absorbed in the void spaces between the fibres known as capillaries and it is also due to the surface tension angle between the water and the fibres.

Figure 1 : Diaper Absorbent Core Wood Pulp Fluff (source : technicaltextile.net)

The fluffy pulp can also consist of grafted cellulose and starch, interlinked carboximethyl cellulose derivatives and modified hydrophilic polyacrylics (Mendoza *et al*., 2019a).

It has to be noted that some diapers manufacturers now produce low-fluff or fluffless baby diapers. For more details, please see Annex E.2.2.2.3.

The fluff pulp is bleached through different bleaching processes before being supplied to the diapers manufacturers (for more details of bleaching processes, please see Annex E.2.2). Bleaching of cellulose is a necessary step because it allows getting cellulose that is directly usable by diapers and hygiene products manufacturers: lignine, which is one of the main wood component must be removed from fibers and must be made hydrophilic. It is also bleached to remove other coloured impurities and to make it more absorbent. Before the 1990s, elemental chlorine was used. In the late 1980s, bleaching processes began to change due to high concentrations of PCDDs in wood pulp bleached using chlorine dioxide (JRC, 2015). Bleaching with elemental chlorine was gradually eliminated from the pulp industry and is no longer used for 10 years now. As reported in ANSES (2019), today, various bleaching methods are used:

- the ECF (elemental chlorine free) method, which uses chlorine dioxide; this is the most commonly process used worldwide today to bleach cellulose (95% of cellulose producers) (Counts *et al.,* 2017);
- the EECF (enhanced elemental chlorine free) method, which uses oxygen and/or slow heating;
- the TCF (totally chlorine free) method, which uses hydrogen peroxide, oxygen or ozone is used by 5% of cellulose producers (Counts *et al.,* 2017).

ECF is the most widely used method. It should be specified that ECF processes with chlorine dioxide reduce the quantity of chlorinated products but do not eliminate them. More information on bleaching processes is available in annex E.2.2.1.1 and in section 2.4.1.1.1 in the main report.

The Dossier Submitter would like to underline that the EECF bleaching method was not mentioned by the companies consulted as a process used to bleach fluff pulp.

SAP is a sodium polyacrylate with varying degrees of cross-linking. To the naked eye, superabsorbent polymers appear as a white powder (100 to 800 µm in diameter) (low cross-linking) or very small beads (high cross-linking) (Figure 2). In the presence of water, they absorb fluids and turn into a soft and deformable gel. They are prepared by inverse suspension polymerisation which requires the presence of hydrocarbon solvents and surfactants. SAP's absorption capacity is influenced by several parameters:

- the charge density along the polymer chains,
- the cross-linking density: the more cross-linked SAP is, the less it swells up and the less deformable the gel,
- the ionic strength of the liquid: a SAP absorbs up to 500 times its weight in pure water but only 60 times its weight in saline solution (Gourmand and Corpart, 1999). According to EDANA, SAP absorbs up to 300 times its weight in water without releasing it (EDANA, 2015).

SAP was produced in the early 1970s in Japan and in the United States and was introduced into baby diapers in the early 1980s. By the early 1990s, SAP was widely used in single-use baby diapers and incontinence products[2] and its use in these products has continued to grow.

Figure 2 : Diaper super absorbant polymer (SAP)

Glues used to assemble the different parts of a single-use baby diaper are generally hot melt adhesives, i.e. thermoplastic adhesives in solid form, designed to be melted by a heating element to provide it with adhesion properties). The main resins used in hot-melt adhesives are ethylene-vinyl acetate copolymer, polyamides, polyolefins (mainly polyethylene) and polyesters. As presented in Table 1 above, glues can also be copolymer rubber (e.g. SBR, EPDM) and starch. Unfortunately the composition of any of these glues could not be obtained from suppliers due to confidentiality and business secret.

For more details about how the different parts of a diaper are glued and bonded together, please see Annex A.3.

It has to be noted that some diapers manufacturers now produce so-called 'glueless' baby diapers based on alternative bonding technologies. For more details, please see Annex E.2.2.2.2.

Some parts of a diaper may be dyed with **pigments**. Most major manufacturers of single-use baby diapers use pigments they consider "safe" for use in baby diapers, with no disperse dyes (Dey *et al*., 2016b). Local skin effects such as irritation and sensitization are also assessed

[2] http://www.edana.org/discover-nonwovens/how-they're-made/superabsorbents

for the pigments used in baby diapers, by undertaking patch tests on adult skin self-evaluated as sensitive. No cases of skin irritation or sensitization have been found. Although manufacturers consider the use of these pigments to be safe, they try to limit exposure and transfer to babies' skin. Interior pigments are incorporated into the polymer resin, thus minimising their release. Exterior colours adhere to the backsheet and are covered by a layer of polypropylene fibres to minimise skin contact (Dey *et al*., 2016b; Counts *et al.,* 2017). Masterbatch pigments such as the ones used in the topsheet or the core is a concentrated mixture of pigments and/or additives encapsulated during a heat process into a carrier resin which is then cooled and cut into a granular shape. Masterbatch allows the processor to colour raw polymer economically during the plastics manufacturing process. It should be noted that these pigments serve no technical purpose in diapers and are added only for aesthetic reasons. Some pigments may be however responsible for the presence of PCDDs (for more details see Annex E.2.1)

Fragrances were sometimes added (Kosemund *et al.*, 2009; Counts *et al.*, 2017). When this is the case, very small amounts are added beneath the core. These fragrances must comply with the Code of Practice of the International Fragrance Association (IFRA) and have been assessed to ensure they are not sensitising or allergenic (Counts *et al.*, 2017). Since ANSES published its report, all companies claimed to have removed fragrances from their diapers.

In certain diapers, **lotions** are intentionally added to help protect babies' skin. According to Counts *et al.* (2017), the lotion in their diapers contains the following ingredients: a very small quantity (less than 0.10 g in a diaper for newborns) of pharmaceutical-grade purified petrolatum (a protective barrier, commonly called Vaseline®), stearyl alcohol (an emollient commonly used for its moisturising properties), paraffinum liquidum (a protective barrier), and aloe barbadensis extract (aloe vera, for softness).

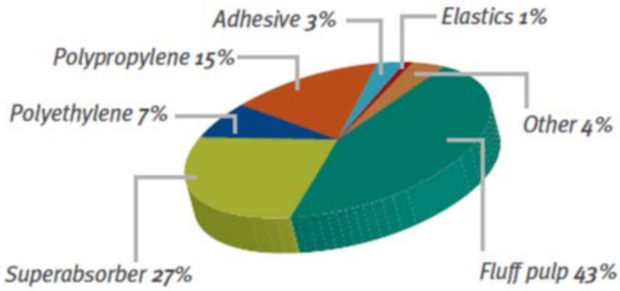
Some diapers and toilet training pants include a **wetness indicator**. It is a feature that reacts to exposure of liquid as a way to discourage the wearer to urinate in the training pants, or as an indicator for parents that a diaper needs changing. Many diapers that contain a wetness indicator seem to use a chemical called bromophenol blue. Bromophenol blue (CAS 115-39-9) is a pH indicator meaning that it changes colour depending on the surrounding acidity or alkalinity. This chemical is self classified as acute Tox.4 (Harmful in contact with the skin and harmful is inhaled) and Eye Irrit.2. In diapers, bromophenol blue appears yellow when the diaper is dry, but the slightly alkaline pH of urine causes its colour to change to blue when the diaper is wet. Other patents suggest that some other diapers use chemicals that are sensitive to moisture as indicators, though it is unclear how these compounds cause a colour change to appear. For more information, please see main report, section 2.4.1.1

According to EDANA, no contaminants such as **PCDD/Fs, DL-PCBs, pesticides, herbicides** or **halogens** are intentionally used in or added to baby diapers during the manufacturing process of a diaper or the manufacturing of their raw materials.

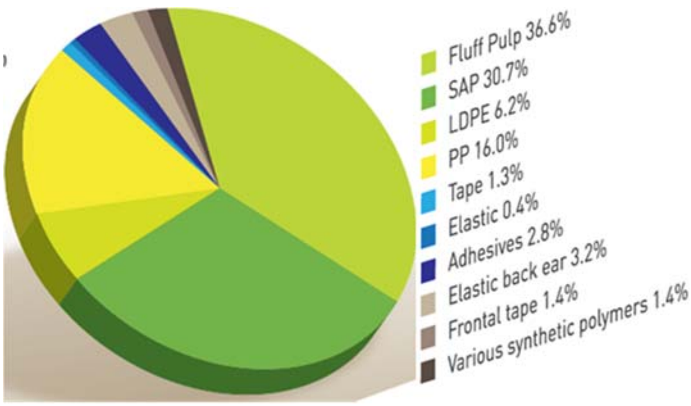
<u>Changes in composition</u>

The composition of single-use baby diapers has evolved over time: they are now thinner and more absorbent than their "ancestors", more comfortable to wear for babies, and more convenient for parents (Figure 3). The average weight of a single-use bay diaper decreased from 64.6 g in the late 1980s to 33.3 g in 2013, i.e. an almost 50% reduction over a 25-year period (EDANA, 2005, 2011 and 2015; Group'Hygiène, 2015). This has been achieved through the reduction in the thickness of nonwoven films and by decreasing the fluff pulp content. This in turn has been enabled by the introduction of SAP used to build the absorbent core of the diapers (Mendoza *et al.*, 2019b). In the late 1980s, single-use baby diapers were made primarily of fluff pulp (52.8 g/diaper). The quantity of fluff pulp decreased, reaching 9.1 g/diaper in 2013, while the quantity of SAP sharply increased between the late 1980s and 2013, rising from 0.7 g/diaper to 12.6 g/diaper, thus explaining the decrease in weight.

In 2004



In 2011



In 2013

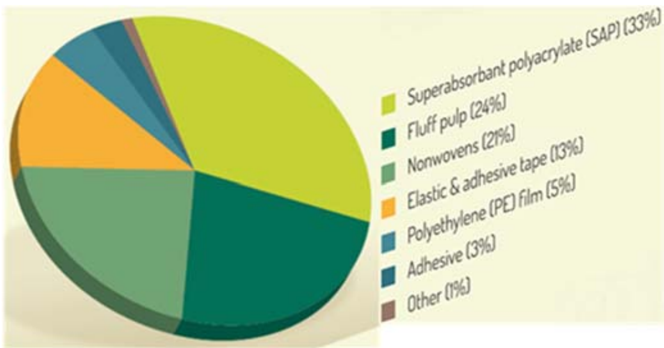


Figure 3 : Typical composition of a single-use baby diaper in 2004, 2011 and 2013 (Sources: EDANA, 2005, 2011 and 2015)

The average weight of the materials per unit of baby diaper is presented in the table below. (Cordella *et al.*, 2015). The data have been made available to the Dossier Submitter by EDANA and figures are considered to represent over 85% of the European market in Europe. While overall baby diapers weight has decreased over time, the following table shows that not all the composition materials have followed this general trend over 1987-2011.

Table 2 : Bills of materials (BOMs) for average units of single-use baby diapers sold in Europe in 1987, 2005 and 2011 and related LCI datasets (Cordella et al., 2015)

Material/component	Average weight per 1 unit of baby diaper (g)				LCI dataset modelled
	1987	1995	2005	2011	
Fluff pulp	52.8	37.4	14.1	13.2	Chemical pulp
Superabsorbent polymers (SAP)	0.7	5.1	13.2	11.1	Sodium polyacrylate
Polypropylene (PP)	4.1	4.5	7.0	5.8	PP nonwoven
Low density polyethylene (LDPE)	4.2	3.8	2.6	2.2	LDPE film
Elastic	1.3	1.6	1.7	1.0	TPU
Adhesives	0.8	0.4	0.6	0.1	SBR and Et–Nb copolymer
Others (e.g. tape, elastic back ear, other synthetic polymers)	1.1	3.2	1.8	2.6	PP tape
Total	65.0	56.0	41.0	36.0	–

A.2. The market of single-use baby diapers

A.2.1. Manufacture, import and export of single-use baby diapers

A.2.1.1. Global market

The global single-use baby diapers market is oligopolistic meaning that a small number of organizations or companies operate on the market with a high number of consumers.

The global single-use baby diapers market is anticipated to grow from $ 55,061 million in 2016 to $ 92,254 million by 2024(Figure 5), at a CAGR (compound annual growth rate)[3] of 6.86% between 2017 and 2024. Companies identified in this market include among others Kao Corporation, Kimberly-Clark Corporation (Huggies®, 26% of market shares[4]), Ontex International N.V, The Procter & Gamble Company (Pampers®, 36% of market shares); Svenska Cellulosa Aktiebolaget SCA (Up & Go, 3% of market shares); Unicharm Corporation (5% of market shares), Hengan International Group Company Limited, Essity AB, Bumkins[5,6,7](Figure 4).

[3] CAGR is a measure of an investment's annual growth rate over time, with the effect of compounding taken into account. It is often used to measure and compare the past performance of investments, or to project their expected future returns.
[4]https://www.nonwovens-industry.com/issues/2010-01/view_features/le-marche-des-couches-culottes-revolutionne-par-les-nouveaux-designs-croissance-ininterrompue-pour-les-principaux-acteurs-toujours-en-quete-de-nouveau/
[5] https://www.strategyr.com/market-report-baby-disposable-diapers-forecasts-global-industry-analysts-inc.asp
[6] https://www.transparencymarketresearch.com/baby-diapers-market.html
[7] https://www.researchandmarkets.com/reports/4191022/europe-baby-diaper-market-2016-2022

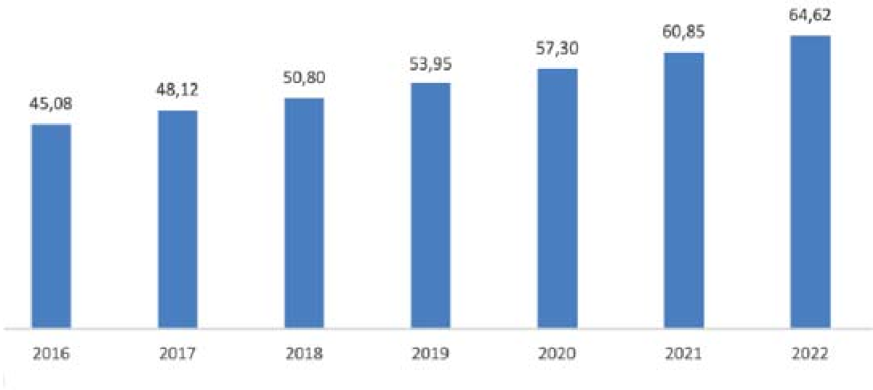


Figure 4 : Global turnover of single-use baby diapers sector 2016-2022 (Businesscoot, 2020)

Single-use baby diapers market is largely concentrated in Europe and North America (with 60% market share) but Pacific-Asia share is growing (Businesscoot, 2020).

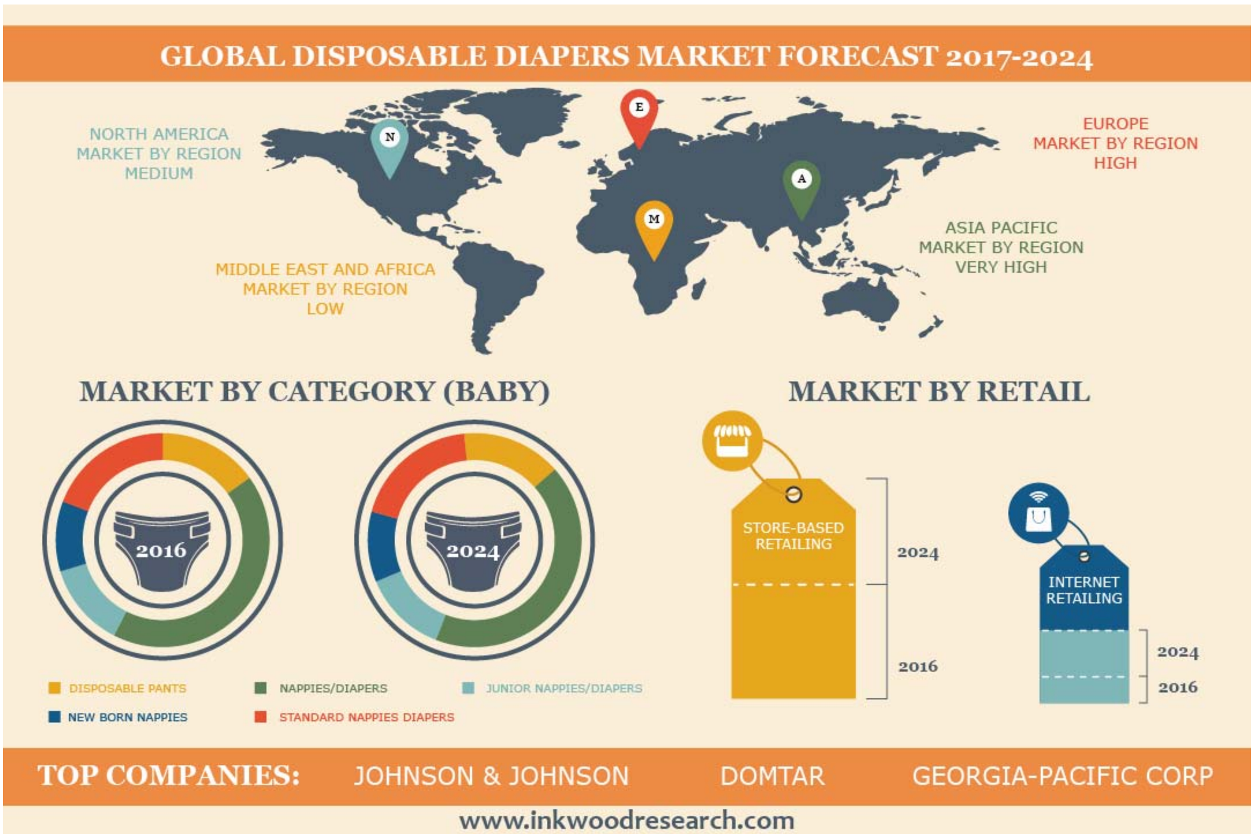


Figure 5 : Global single-use baby diapers market forecast 2017-2024

The store-based retailing is anticipated to dominate the global single-use baby diapers market. The store based diaper retailing incorporates the division of diapers reasonable for both infant and children. Assortments of diapers having different specifications are critical in the different retail shops which permits the client to buy diapers unmistakably. The easy task in store-based retailing is that the diapers can be assessed physically for any characteristics feature that the customer prefers. Mostly individuals' likes to go for the store-based retailers as they want to be specific about their buying, especially parents for their babies. At present, Internet is one of the most powerful domains. Many things can be done *via* the internet and so the use of internet retailing has come into play. Buyers discover a result of enthusiasm going by the site of the retailer specifically or *via* looking among alternative vendors utilizing a shopping search engine, which shows a similar item's accessibility and estimating at various e-retailers. The diaper market internet retailing is fundamentally broadening because of the developing on the online retailers and offering of a huge measure of items with the general specification that has given an edge to the Internet retailing.

Figure 6 : Global baby diapers market revenue, by product, 2016 (source : grandviewresearch.com)

This breakdown and the market domination of single-use baby diapers over other types of diapers is also representative of European market.

A.2.1.2. European market of single-use baby diapers for infants and young children

Like at global level, the European market of disposable baby diapers is oligopolistic. It is dominated by leader manufacturing companies which produce both under their own brands as well as for retailer brands[8]. There are also other manufacturers on the European market with their own brands or which supply distributors under different brands. Based on market

[8] https://www.statista.com/outlook/80050000/102/baby-diapers/europe?currency=eur

surveys and Dossier Submitter own knowledge, the number of manufacturing companies in Europe is between 10-15.

- Revenue in the single-use baby diapers segment amounts to €7,443 million in 2020. (Figure 7) The market is expected to grow annually by 1.1% (CAGR 2020-2023).
- Only for France, revenue in the single-use baby diapers segment amounts to €637.1 million in 2020.
- In global comparison, most revenue is generated in China (€7,872 million in 2020)[9].

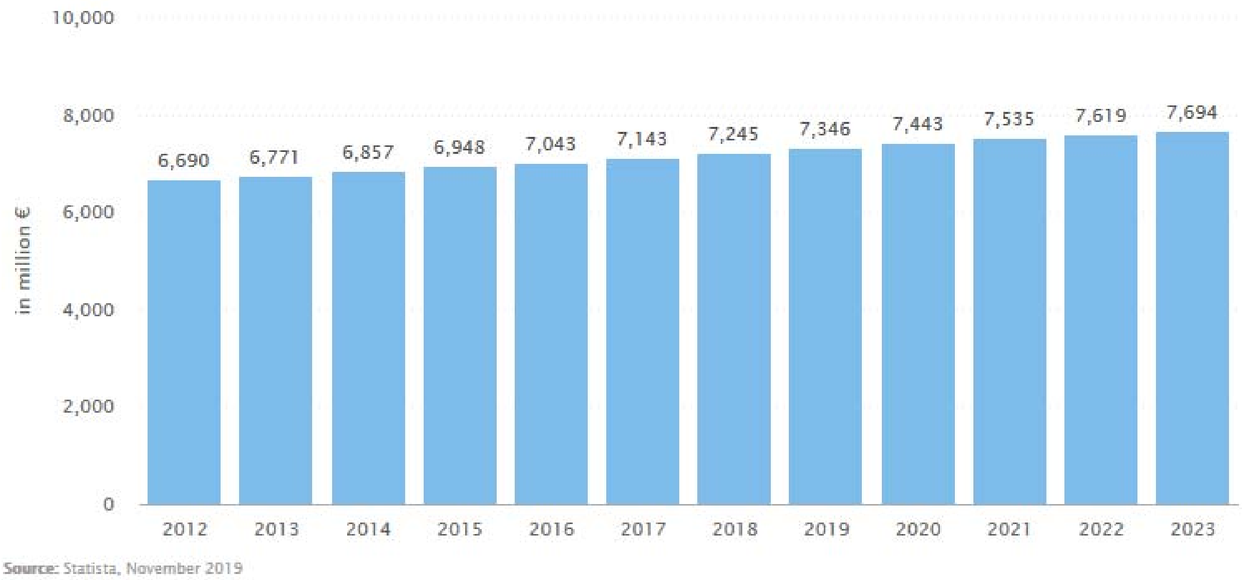


Figure 7 : Revenue in the Baby Diapers segment - European market (in million €)(source : www.Statista.com)

Different sizes of single-use baby diapers are produced depending of the child weight. The fit guide may vary from one brand to another:

- Size 0 / preemie (<3kg)
- Size 1 (2-5 kg)
- Size 2 (3-6 kg) or (5-8kg)
- Size 3 (4-9 kg) or (7-13 kg)
- Size 4 (7-18 kg) or size 4 (10-17 kg), some brands supply size 4+ (9-20 kg) with higher absorption capacity
- Size 5 (11-25 kg) or (14-18 kg), some brands supply size 5+ (13-27 kg) with higher absorption capacity
- Size 6 (16-30 kg)

One innovative brand now proposes connected disposable baby diapers.

A.2.2. Sales and consumption of single-use baby diapers

As mentioned above, single-use baby diapers are mainly purchased by families in big store-retailers (92% in sales value in France in 2018 for instance) but purchasing *via* the Internet

[9] https://www.statista.com/outlook/80050000/102/baby-diapers/europe?currency=eur

is increasing (7.6% in sales shares in 2018 in France for instance) (Businesscoot, 2020). Some brands now also propose Internet subscriptions to purchase baby diapers and home delivery. Distributors are far more numerous than manufacturers and are of various sizes and business models (online and physical shops, small and big retailers).

A.2.2.1. In Europe

The baby diapers can be categorised as disposable diapers, training diapers, cloth diapers, baby swim pants. Currently, single-use baby diapers account for the majority share of 68% to the total market share of baby diapers in Europe. Country-wise, UK is the market leader followed by France having higher birth rate as compared to other European countries[10].

According to EDANA, around 30 billion diapers and diaper pants are sold in the European Union (Figure 8).

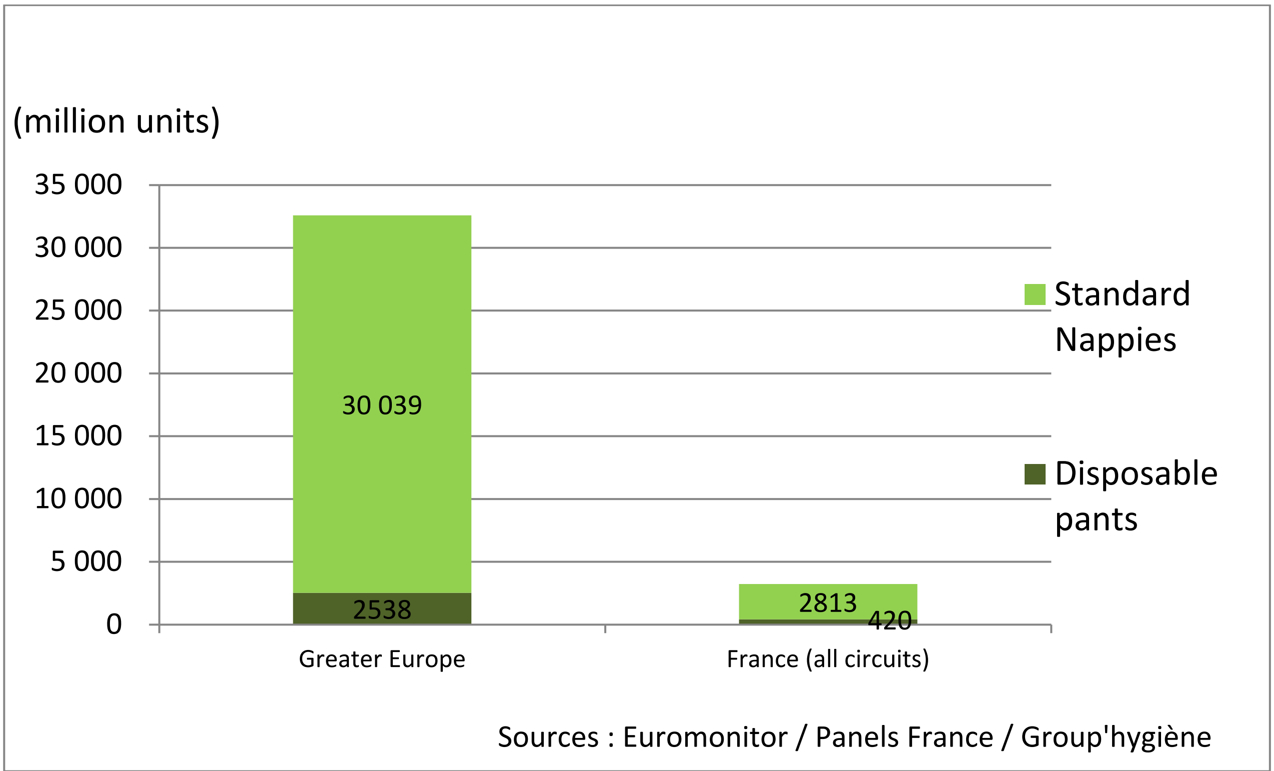


Figure 8 : European baby diapers retail market - Sales volumes in million units sold (EDANA hearing, 2015 figures-Euromonitor)

European internal market of single-use baby diapers is very dynamic with many imports and exports flows between European countries. For example, France exports single-use baby diapers to (among others) Belgium, Germany, Italy, the UK, Spain, Austria, Switzerland, Poland; and France imports single-use baby diapers from (among others) Germany, Czeck Republic, Belgium, Italy, Poland, Spain and the Netherlands (Businesscoot, 2020).

[10] https://www.prnewswire.com/news-releases/europe-baby--adult-diapers-market-outlook-2018-2023---market-is-expected-to-reach-usd-16-billion-300598595.html

Regarding imported diapers from outside Europe:

- In EU some diapers are imported as finished products (e.g. Vietnam). The amount of imported diapers in the EU is however not available to the Dossier Submitter's knowledge.
- In some european overseas territories, up to 50% of diapers are imported from Asia (e.g. Vietnam, China, South Korea, Malaysia…) and other countries (e.g. South Africa, USA) and importers claim to have no information about their composition. The amount of imported raw materials is not available to the Dossier Submitter's knowledge.

Regarding imported raw materials used in diapers manufacturing, most raw materials come from EU but some raw materials come from outside EU (see Annex A.3).

Demand for single-use baby diapers is largely driven by birth rate. Birth rate is slowly decreasing for several decades in the EU: in 2017, 5.075 million children were born in the EU-28, corresponding to a crude birth rate (the number of live births per 1 000 persons) of 9.9. For comparison, the EU-28 crude birth rate had stood at 10.6 in 2000, 12.8 in 1985 and 16.3 in 1970. As a consequence, the growth of single-use baby diapers market has slowed down.

Compared to re-usable baby diapers, demand for single-use baby diapers largely dominate the market. In France for instance, re-usable baby diapers represents 14% of sales (Businesscoot, 2020).

Even though the market for single-use baby diapers is oligopolistic, competition is high between retailers and distributors. As a consequence, the trend for the unit price of single-use baby diapers is slightly decreasing. More information about competition considerations on this market can be found in the main report in section 2.4.3.1.

According to NirYoav (2012) [11] price research, **the unit price for branded and store brands single-use baby diapers in Europe was 0.20€ on average: 0.23€** on average for branded diapers (0.20-0.25€) and 0.17€ for store brands (0.12-0.20€) (see Table 3 below).

Table 3: Average price for branded and store brands single-use baby diapers for Europe and 5 countries in 2012 (source : NirYoav, 2012)

Average price for branded								Average price for store brands						
	Europe	France	Germany	Italy	UK	Israel			Europe	France	Germany	Italy	UK	Israel
Premium	€ 0.24	€ 0.38	€ 0.26	€ 0.33	€ 0.26	€ 0.18		Premium	€ 0.20	€ 0.21	€ 0.14	N/A	€ 0.195	N/A
Standard	€ 0.25	€ 0.32	€ 0.21	€ 0.26	€ 0.23	€ 0.19		Standard	€ 0.18	€ 0.22	€ 0.14	€ 0.21	€ 0.180	N/A
Economy	€ 0.20	€ 0.23	€ 0.18	N/A	€ 0.18	€ 0.14		Economy	€ 0.12	€ 0.11	N/A	€ 0.17	€ 0.096	N/A

A.2.2.2. In France

The Dossier Submitter collected information from Group'Hygiène and other sources. According to Group'Hygiène, 3.2 billion diapers (accounting for 87% of sales volume) and

[11] https://www.slideshare.net/NirYoav/limited-european-baby-diaper-price-survey

diaper pants (13%) were sold in 2015 in metropolitan France. According to the same source, these figures have been stable since 2011 (see Figure 9).

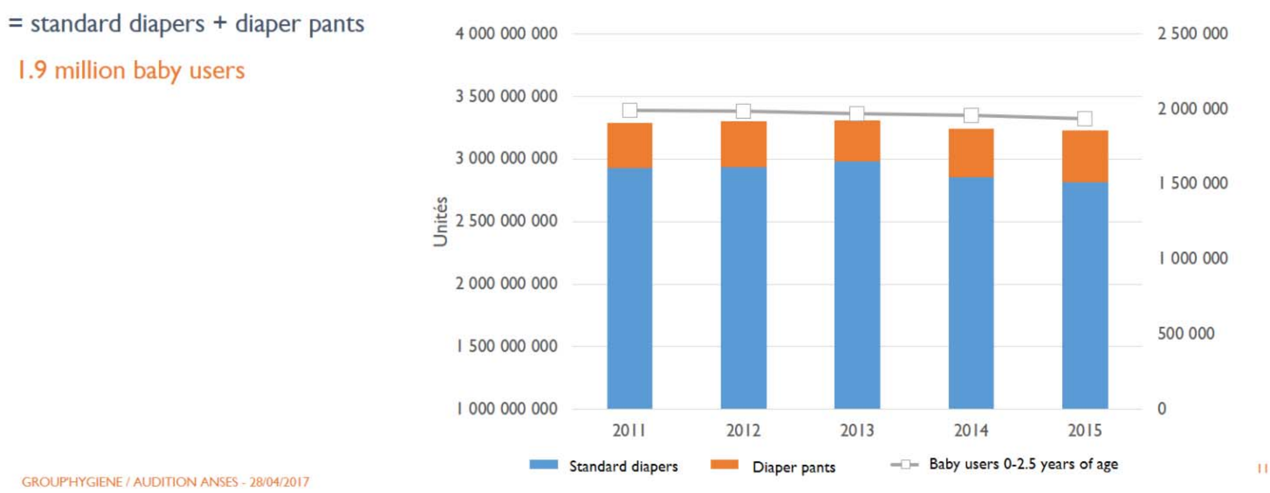


Figure 9: Sales volumes for diapers and diaper pants in metropolitan France (Group'Hygiène hearing, 2017 reported in ANSES, 2019)

As a comparison, in the United Kingdom, single-use and re-usable diapers represent around 2.47 billion units sold (UK Environment Agency, 2005b). In Italy, single-use baby diapers represent around 1.8 billion units produced in 2016 (Mendoza *et al.*, 2019b).

The French market is dominated by one leader company (more than 50% of markets shares), followed by distributors brands (24%) and other companies with smaller shares (between 0.2% and 13% each) (Businesscoot, 2020). The single-use baby diapers market in France represents around 729 million € in 2018, which is -3.5% compared to 2017. The market has been disturbed by some trust crises regarding the safety of baby diapers but the forecast are now indicating that the market keeps on growing from 2019 with a prevision value of 787 million € in 2023.

French imports of single-use baby diapers are much higher than its exports (factor of 25).

Regarding the unit price of single-use baby diapers in the French market, it is indicated to be 0.29€ on average (all brands and all quality) according to Businesscoot, 2020 (Table 4). **The average unit price for economy quality is 0.17€, for standard quality is 0.25 and for premium quality is 0.45€.** Businesscoot (2020) does not specify which types of diapers is included under each category.

Table 4: Single-use baby diapers unit price on the French market (2019)

Diaper size	Quality	Unit price	Average unit price
1	Standard	0.15 €	0.15 €
	Premium	0.25-0.40€	0.33 €
	Economy	0.13-0.14€	0.14 €
2	Standard	0.15-0.30€	0.23 €

	Premium	0.30-0.40€	0.35 €
	Economy	0.13 €	0.13 €
3	Standard	0.15-0.30€	0.23 €
	Premium	0.35-0.50€	0.43 €
	Economy	0.14-0.18€	0.16 €
4	Standard	0.15-0.45€	0.30 €
	Premium	0.45-0.50€	0.48 €
	Economy	0.14-0.20€	0.17 €
5	Standard	0.15-0.50€	0.33 €
	Premium	0.50-0.60€	0.55 €
	Economy	0.17-0.22€	0.20 €
6	Standard	0.15-0.45€	0.30 €
	Premium	0.50-0.60€	0.55 €
	Economy	0.20-0.26€	0.23 €
TOTAL AVERAGE			**0.29 €**

Source: own elaboration from Businesscoot, 2020

As a double-check, the Dossier Submitter carried out their own research in 2020 based on Internet prices in France for store brands and branded baby diapers. The results are presented in Table 5 and 6 below.

Table 5: Single-use baby diapers unit price on the French market in 2020 (store brands)

	Store brand A	**Store brand A - ecopack (>70 diapers)**	**Store brand A (ecologic)**	**Store brand B**	**Store brand B - ecopack (>70 diapers)**	**Store brand C (>70 diapers)**
size 1	0.11 €	NA	NA	0.14 €	NA	NA
size 2	0.18 €	NA	NA	0.16 €	NA	0.13 €
size 3	0.21 €	0.17 €	0.31 €	0.18 €	0.13 €	0.13 €
size 4	0.24 €	0.19 €	0.33 €	0.22 €	0.14 €	0.14 €
size 5	0.29 €	0.21 €	0.37 €	0.21 €	0.16 €	0.17 €
Average price[12]	0.21 €	0.19 €	0.34 €	0.18 €	0.14 €	0.14 €
TOTAL AVERAGE	**0.20€**					

Table 6: Single-use baby diapers unit price on the French market in 2020 (branded diapers)

	Leader Brand D - standard	**Brand E – month-pack**	**Brand F***	**Brand G***	**Brand H***	**Brand I***	**Brand J***	**Brand K***	**Brand L***	**Brand M***

[12] Prices are given without discount (based on Internet prices of march the 11th 2020) from 3 stores internet websites

size 1	0.13 €	0.24 €	0.27 €	0.22 €	0.29 €	0.29 €	0.27 €	0.26 €	0.34 €	0.26 €
size 2	0.22 €	0.24 €	0.31 €	0.31 €	0.30 €	0.36 €	0.27 €	0.33 €	0.32 €	0.37 €
size 3	0.25 €	0.26 €	0.34 €	0.35 €	0.37 €	0.39 €	0.33 €	0.38 €	0.41 €	0.40 €
size 4	0.36 €	0.29 €	0.41 €	0.39 €	0.43 €	0.44 €	0.36 €	0.41 €	0.45 €	0.43 €
size 5	0.40 €	0.39 €	0.44 €	0.42 €	0.51 €	0.52 €	0.44 €	0.46 €	0.53 €	0.50 €
Average price[13]	0.27 €	0.28 €	0.35 €	0.34 €	0.38 €	0.40 €	0.33 €	0.37 €	0.41 €	0.39 €
TOTAL AVERAGE	**0.276€**		**0.37€**							
GRAND TOTAL AVERAGE	**0.32€**									

*brands marked with an asterisk are sold as "ecologic by presentation" baby diapers

The average unit price for store brands is 0.20€ (table 5) and for branded diapers is 0.32€ **(table 6)** (from 0.276€ for standard brands to 0.37€ for "ecologic by presentation" diapers). "Ecologic by presentation" diapers unit price range from 0.33€ to 0.41€. In general, higher prices are observed for the biggest diaper sizes (up to 0.53€ for size 5, according to Table 6). As a comparison, Businesscoot (2020) indicates that the most expensive diapers are of premium quality which are sold from 0.33€ to 0.55€ / unit. The prices vary with the size of the diaper as well as with the brand, the number of diapers included in the pack (small pack, eco-pack, month-pack, jumbo-pack, etc.) and with regular discounts practiced by retailers and websites. The Dossier Submitter's research only includes regular single-use baby diapers and not night pants or training pants. **Moreover, this benchmark does not pretend to conclude about the exact price of a single-use baby diaper**. It aims at providing an order of magnitude of its average unit price based on a limited research.

These results are also consistent with NirYoav (2012) for France: the average price for branded diapers range from 0.23€ to 0.38€ (0.31€ on average) and for store brands from 0.11€ to 0.22€ (0.18€ on average).

As a comparison with European unit prices, based on NirYoav (2012), French single-use baby diapers seem more expensive that the European average (0.23€ / unit). However, NirYoav (2012) is based on their own research and no reference is given. A more recent, detailed and sourced European study of the unit price of single-use baby diapers country by country could help in getting a clearer view of the prices distribution within Europe. To the Dossier Submitter's knowledge, such a study is not available.

A.3. Supply chain and life cycle of single-use baby diapers

The typical value chain of nonwovens (including single-use baby diapers) is described in the following figure.

[13] Prices are given without discounts (based on Internet prices of march the 11th 2020 from 4 stores internet websites

Figure 10 : The value chain of non wovens (EDANA, 2011)

The typical life cycle of single-use baby diapers include the following steps: selecting and handling raw materials, manufacturing the diaper, packaging, transport and distribution, use, end-of-life (Figure 11).

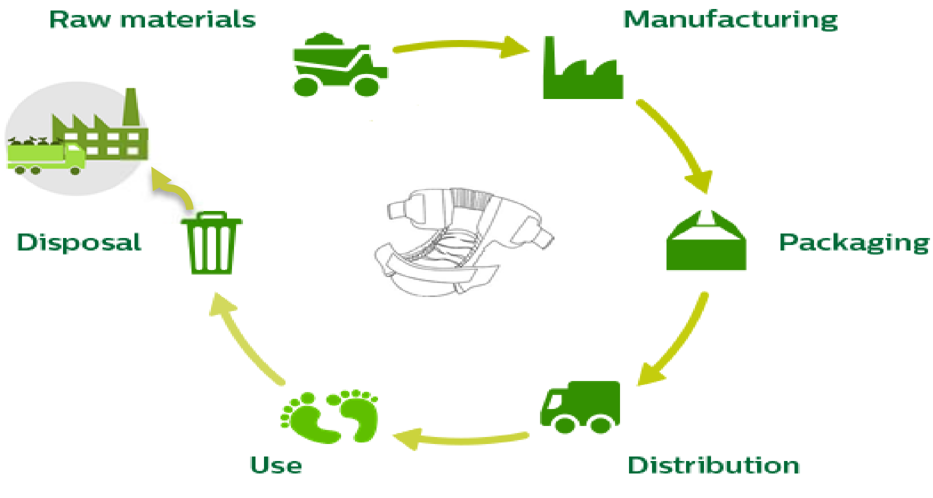


Figure 11 : Typical life cycle of a generic single-use baby diaper

The following does describe each step of the typical life cycle of single-use baby diaper. The information presented comes from the literature and from stakeholders consulted during the elaboration of the restriction proposal.

<u>Selecting and handling raw materials</u>

The raw materials used in diaper manufacturing are processed upstream and supplied to the diaper producer. According to Mendoza *et al.* (2019a), almost 700,000 tons of raw materials are consumed annually in the EU to manufacture single-use baby diapers, excluding packaging and wastes. These raw materials are elastic cuffs, topsheet, absorbent core (backsheet, acquisition layers, ATB (air-trough bonded) layer, fluff pulp, SAP), front and elastic back ears, composite backsheet with frontal tape, hot-melt adhesive (glue), fastening tapes of the back ears, waist and leg elastics and optional elements such as lotions, inks and dyes.

Details on the composition of those raw materials are provided in Annex A.1 and more information on how raw materials are processed by suppliers is provided in Annex E.2.

According to the information collected from producers of single-use baby diapers, most of the raw materials come from European countries but some come from outside EU:

- USA (fluff, ears, elastic waistband)
- China and India (elastics)
- Taiwan (ears)
- Japan and South Korea (SAP)
- Turkey (tapes)

The suppliers of raw-materials consist of an unknown number from inside and outside EU and they are hardly identifiable. According to industry, raw materials come from sources worldwide but undergo the same principles of evaluation before qualified for use for the production of AHP, irrespective of the country of origin of the raw material. Certain materials such as mineral oil and pigments come in different purity grades. The appropriate purity grade in the constituent is chosen as required for the intended use.

Most of the raw materials arrived at production site in the form of rolls (or blocks for glue or big bags for the beads of SAP up to one ton). Once received, the raw materials are stored in a temperature- and humidity-controlled environment. They are usually stored only for a short period of time (no more than a few hours) before being used. They are then cut, shaped and assembled to manufacture baby diapers.

As reported by Mendoza *et al.* (2019a), for the manufacturing of standard single-use baby diapers in Italy, the costs of the raw materials range from €0.95/kg (e.g. cellulose pulp) to €39/kg (e.g. frontal tape)[14], or in total around 90€/1000 diapers (i.e. 0.09€/diaper). It is assumed to be of the same range in all EU countries and to represent the most significant hot-spot.

<u>Manufacturing the diaper</u>

Typical manufacturing process in the EU is able to produce 1,000 diapers per minute (Mendoza *et al.,* 2019a). The fully automated, continuous[15] and mechanical manufacturing process is broken down into three main stages:

[14] In their assessment, Mendoza *et al.* (2019a) did not take into account raw materials such as fastening tapes of the back ears, waist and leg elastics and optional elements like lotions, inks and dyes. However they consider that these materials only represent 1% of the product weight.

15 Some manufacturers consulted indicated that manufacture occurs 24/7 and only stops for specific site closures. Closing times for cleaning, reloading and maintenance are scheduled and planned.

- Fiberisation of the fluff pulp, addition of SAP, and formation of the core,
- Lamination with films, nonwoven materials and elastic elements and gluing / thermowelding / ultrasound bonding in order to form the single-use baby diaper,
- Shaping, cutting, folding and packaging for shipping.

These different steps are represented in Figure 12. According to the information collected, diapers are assembled products and do not have any chemical treatment during their manufacturing. The circulation speed of the processed diapers into the manufacturing machine is high so that the contact of the product with each piece of the machinery is very short (fraction of a second).

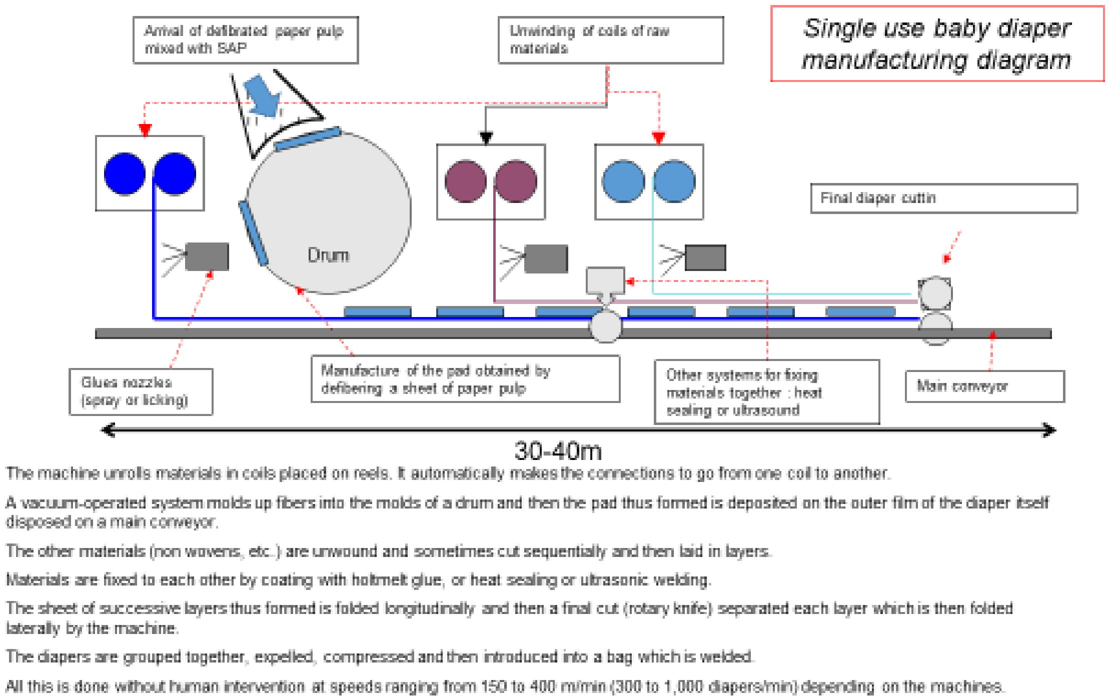


Figure 12 : Typical manufacturing diagram of a single-use baby diaper

As mentioned in Annex A.1, the different materials are glued together with polymer-based adhesives (UK Environment Agency, 2005a). Currently, almost all the material layers of a single-use baby diaper are bonded together using hot-melt adhesive, a petrol-based glue (Mendoza *et al.,* 2019b). For more information about the types of glues, please refer to Annex A.1. Unfortunately as explained in Annex A.1, the composition of any of these glues could not be obtained from suppliers due to confidentiality and business secret. To enable the bonding, the solid glue is first melted in a fuser at a temperature of 130-180°C. The hot-melt glue is then pumped through a system of tempered pipes to glue applicators placed in different production modules. Various equipment is used in the gluing process, including fusers, pumps, pipes and glue applicators. Chiller units are also needed to avoid glue contamination in some unit (Mendoza *et al.,* 2019b). Gluing process can be heat-sealing or ultrasound welding. Glue represents less than 3% (<1g) of the diaper weight (Mendoza *et al.* 2019a). Total adhesives are reported to weigh up to 2g. For some diapers however, the gluing process can be replaced by alternative bonding technologies such as a combination of thermo-mechanical and ultrasonic bonding technologies (Mendoza *et al.*, 2019a). For more details, please see Annex E.2.2.2.4.

Some manufacturers report that the glues used are compliant with FDA standard 175.105 on adhesives[16.]

Once assembled and glued, the finished diapers are then grouped and ejected from the machine and compressed to be packaged.

Figure 13 : Single-use baby diapers during manufaturing process (Drylock website)

Manufacturing costs include energy costs (electricity consumption by the industrial equipment), maintenance costs (periodic check-ups of equipment components, lubrication, replacement of parts and cleaning components, e.g. filters) and labor costs (time spent by the staff for loading and handling the raw materials as well as monitoring the equipment performance during the production shift). Mendoza *et al.* (2019b) estimate the total manufacturing cost at 2.5€/1000 diapers (i.e. 0.0025€/diaper) in the EU.

<u>Packaging</u>

Finished baby diapers are wrapped into a consumer pack and put in protective packaging during the transport to distributors. The manufacturers claimed that the bagging, filming and packaging steps are also fully automated. The ready-to-be-shipped packs are finally stored in separated room.

<u>Transport</u>

At the manufacturing stage, transport concerns raw materials upstream and finished products downstream.

[16] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=175.105

- Raw materials are transported from suppliers to manufacturing site. Distances largely depends on the countries and geographical situations. Cordella *et al.* (2015) report that, according to the manufacturers of fluff pulp, 90% of the production of this material takes place in North America. Mendoza *et al.* (2019b) report transport distances for raw materials from 50 km (e.g. nonwovens for the front and back ears) to 9000 km (fluff pulp shipped by ocean freighter from the USA) to Italy. The corresponding transport costs of the raw materials range from €100 to €3,100 (equivalent to €0.005 and €0.14 per kg material transported). It is assumed the same in all EU countries.
- Finished baby diapers are transported from the manufacturing plant to households. In Mendoza *et al.* (2019b) study, this transport cost is estimated at €0.07/kg in the EU.

Use of single-use baby diapers

Please see Annex A.4.

End-of-life of single-use baby diapers

Transport

At the end-of-life stage, diapers wastes from production and used diapers from households are collected and transported to waste management plants. This cost is estimated by Mendoza *et al.* (2019b) to 0.105 €/kg for Italy (based on a distance between 10 km and 100 km). It is assumed to be the same in all EU countries due to a lack of data for the EU.

In total, Mendoza *et al.* (2019b) estimate the total transportation cost (raw materials+final products+wastes) at 10€/1000 diapers (i.e. 0.001€/diaper) in the EU.

Recycling

Regarding single-use baby diapers, only part of the packaging waste produced in diaper manufacturing is recycled (36% of plastic film and 83% of cardboard) (Mendoza *et al.,* 2019b).

As reported in Mendoza *et al.* (2019b), AHP wastes can be efficiently recycled without external energy inputs. However, currently there is a low market penetration of AHP recycling technologies and some of these waste management plants are still under pilot testing. Likewise, there is a high level of uncertainty about the marketability and acceptability of recycled products. Further, the economic feasibility of the recycling process might be constrained by higher costs related to collection and sorting as individual waste fractions (EDANA, 2008).

In general, nowadays recycling and backfilling are not common disposal practices for single-use baby diapers. However, in Europe, a pilot project for recovering plastic and other materials from inside single-use diapers at the Fater’s AHP recycling plant, located in Treviso (Italy) is underway. However, the plant only addresses a very low proportion of the diapers being consumed in the country. The recycling plant is operating at about 10,000 tonnes annual capacity, addressing about 2% of the single-use diapers being consumed annually in Italy alone. Local waste management utility Contarina SpA collects used single-use diapers and other AHPs from curbside bins or large consumer hubs like hospitals from around 50 local towns and transports them to Fater’s plant. After dry cleaning the diapers using contact steam, and disposing of human waste in wastewater treatment plants, one ton of AHP waste can only yield 150 kg of cellulose, 75 kg of absorbing material, and 75 kg of mixed plastic, meaning that only 30% of the material is able to be recovered. As it is the case with Fater's recycling plant, many other single-use diaper recycling plants are facing limitations that challenge their ability to combat the single-use diaper problem. Collecting, cleaning and breaking diapers into their component parts is likely to remain a complex and expensive activity. This results in the vast majority of single-use diapers are being burnt in incinerators or landfilled[17].

Landfilling and incineration

In the EU, according to Mendoza *et al.* (2019a):

- 49% of the used diapers are sent to incineration with energy recovery,
- 45% of the used diapers are sent to landfill,
- 6% of the used diapers are sent to incineration without energy recovery,
- 30% of the packaging plastic film and 7% of the cardboard packaging are incinerated,
- 34% of the packaging plastic film and 10% of corrugated cardboard are landfilled.

Mendoza *et al.* 2019b estimate the total waste management cost for single-use baby diapers at 5.4€/1000 diapers in the EU (i.e 0.0054€/diaper).

As a comparison, Cordella *et al.* (2015) modelled that :

- 25% of the used diapers are incinerated with energy recovery,
- 63% of the used diapers are landfilled,
- 12% of the used diapers are incinerated without energy recovery.

In France, wasted single-use baby diapers are either incinerated (like 50% of ordinary households wastes) or landfilled (like 50% of other ordinary households wastes)[18]. The practice is similar all over Europe (ReZero *et al.*, 2019[19]).

As reported in literature, single-use baby diapers stand for about 3% of municipal solid wastes (Mendoza *et al.* 2019b). This represents around 6.7 million tons per year in EU28 (ReZero *et al.*, 2019). According to accepted statistics, the average weight of each of these diapers is around 200g (after being used). Each child can therefore be assumed to produce 438kg of dirty diapers annually - meaning that around 1 tonne of waste is produced for each child after two and a half years (ReZero *et al.*, 2019).

40,000 single-use baby diapers are used every minute in the EU, generating 1.3 ton/minute of waste (dry weight). Recycling or composting is not common disposal practice for diapers for the time being. However, creative innovations are ongoing to this respect such as DYCLE project. As reported in Mendoza *et al.* (2019b), the DYCLE project is developing a new business model for the diaper industry, which it is not only about substituting one type of diaper by another but about changing the way businesses operate through the application of natured-inspired creative solutions. DYCLE offers 100% compostable diapers (produced

[17] https://zerowasteeurope.eu/wp-content/uploads/2019/12/bffp_single_use_menstrual_products_baby_nappies_and_wet_wipes.pdf
[18] http://ekladata.com/cWHpI6VU7nOAmxASnXSKH_WffMk/2009-cniid-fiche-couches.pdf
[19] https://zerowasteeurope.eu/wp-content/uploads/2019/12/bffp_single_use_menstrual_products_baby_nappies_and_wet_wipes.pdf

locally) for free, through a forward and reverse collection system. In this system, parents collect new diapers and drop used diapers in a pre-defined place. Used diapers are blended with charcoal, kitchen waste and fungus to be converted into black earth (rich soil) by using the terra-preta method[20]. The resulting soil substrate can be used for fruit trees and plants. Fruit harvested from the trees could be used for baby food and juice production in order to close the nutrients and material cycle of baby diapers.

All in all, each step of the life cycle of a single-use baby diaper represents a cost which composes the unit cost of the finished product. The composition of this unit cost is presented in the main report, section 2.4.1.3.

A.4 The use of single-use baby diapers

Since the 1990s, single-use baby diapers have been used by more than 90% of families in most European countries (EDANA, 2011). In France, single-use baby diapers have been worn by over 95% of babies for almost 20 years (Group'Hygiène, 2015). Nonetheless, some parents choose to use re-usable diapers. The choice of diaper type is influenced by family members as well as by income disparity and methods of access to information (Thaman and Eichenfield, 2014).

In 1990, Shanon *et al.* published the results of a questionnaire-based study on diaper choices in 600 parents of young children under two years of age seen in a clinic or by paediatricians in Ottawa (Shanon *et al*., 1990). Single-use baby diapers were used by 82.3% of the parents. Only 2.7% of the parents exclusively used re-usable cloth diapers. The choice was driven by convenience for single-use baby diapers, rash prevention for single-use baby and reusable diapers, cost for diapers washed at home, and convenience for diapers washed by a diaper cleaning service.

In 2004, a study on diaper use (types of diapers used, number of diaper changes per day, age when children stop using diapers) was undertaken in the United Kingdom. Eight thousand households were surveyed between June 2002 and February 2003. Only those with a child who was in diapers or had worn diapers in the recent past (children under the age of 10) were interviewed (n=2,096). Of these families, 94.1% used only single-use baby diapers, 1.5% only re-usable diapers, 2.4% both types of diapers but primarily single-use diapers, and 2% both types of diapers but primarily reusable diapers (UK Environment Agency, 2005b). The people preferring re-usable diapers considered they were more eco-friendly and less expensive and contained fewer chemicals. In some cases, they had also been recommended by friends or family members or donated by a family that no longer needed them.

In Belgium, a pilot programm was implemented in 2002 and then in 2005 to encourage parents to use re-usable diapers for a period of 13 weeks. The parents were recruited in a maternity department. Seventy percent of the 436 women invited to take part in this programme declined. Only 23 participants (in 2002 or 2005) said they intended to continue using reusable diapers at the end of the 13 weeks, i.e. 5% of the women invited to participate. The main reasons for not wanting to continue were leakage, difficulty of use, extra work and cost (EDANA, 2010). Several other initiatives have been taken in France to promote reusable diapers (ADEME, 2012).

[20] https://dycle.org

Diapering habits vary according to country, income level, family practices and cultural norms. Single-use diapers are used in most countries except for example in India and China, where re-usable diapers are widely used. Diaper changing practices differ depending on the country. In Japan, for example, babies are changed while standing up rather than while lying on their back, which has resulted in babies in Japan frequently wearing training pants before they start toilet training. However, in Western Europe and North America, training pants are almost exclusively limited to the toilet-training period (Figure 14) (Thaman and Eichenfield, 2014).

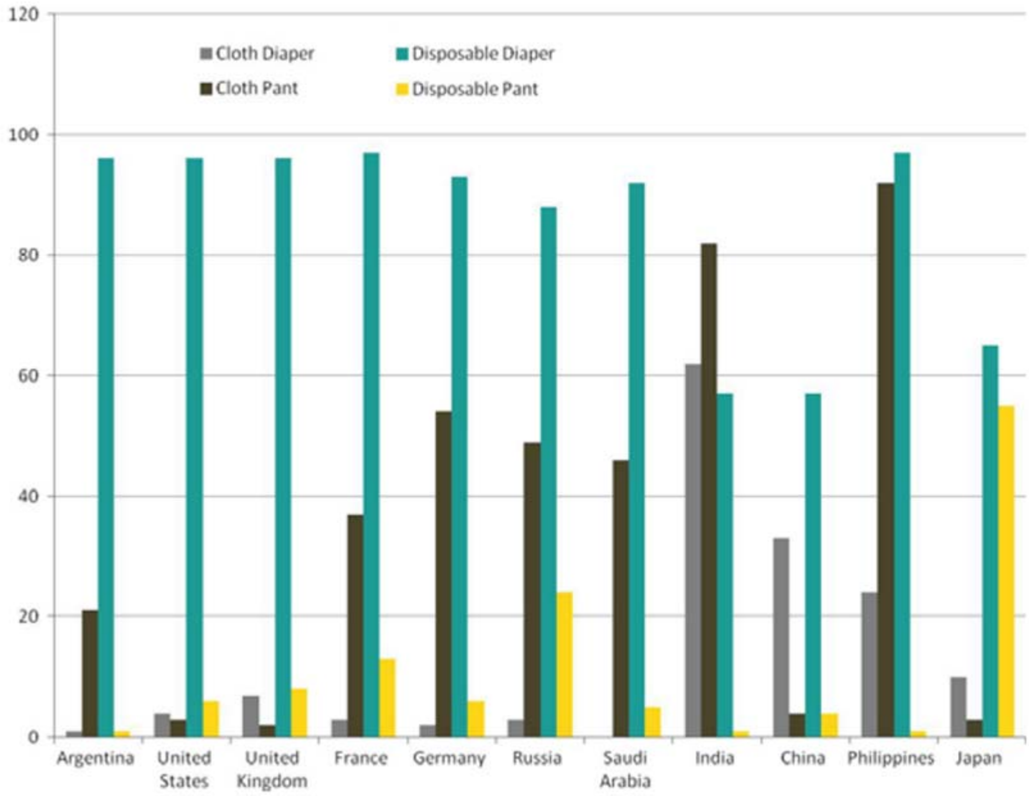


Figure 14: Use of the various types of diapers according to country in children between the ages of zero and 24 months (%) (source : Thaman and Eichenfield, 2014)

- **Number of diapers used before toilet training**

Estimates of the number of single-use baby diapers used by a baby before toilet training range from 3,800 to 4,800 (UK Environmental Agency, 2005b). These estimates vary depending on the age at which it is considered that children are fully toilet trained (between 2.5 and three years old).

- **Diaper wearing time**

Younger babies are changed more frequently than older babies (10 times/day versus 4-5 times/day). The average diaper wearing time for an older baby is four hours during the day and 10 to 12 hours at night (Thaman and Eichenfield, 2014). Indeed, as they reach one year of age, babies sleep an average of 14 to 15 hours per day, with most of their sleep occurring overnight (~10-12 hours) (UK Environmental Agency, 2005b).

A.5. Uses advised against by the registrants

Not relevant.

Annex B: Information on hazard and risk

B.1. Identity of the substance(s) and physical and chemical properties

B.1.1. Name and other identifiers of the substance(s)

Various substances or groups of substances fall within the scope of the restriction proposal.

The aim of this restriction proposal is to reduce the risk that can be shown due to the presence of hazardous chemicals in single-use baby diapers. This restriction proposal therefore covers chemical substances described here under:

- The polycyclic aromatic hydrocarbons (PAHs): benzo[c]fluorene, benz[a]anthracene, cyclopenta[*c,d*]pyrene, chrysene, 5-methylchrysene, benzo[*e*]acephenanthrylene, benzo[*k*]fluoranthene, benzo[*j*]fluoranthene, benzo[e]pyrene, benzo[*d,e,f*]chrysenebenzo[d,e,f]chrysene, dibenz[a,h]anthracene, Indeno[1,2,3-c,d]pyrene, benzo[*g,h,i*]perylene, dibenzo[*def,p*]chrysene dibenzo[def,p]chrysene, naphtho[1,2,3,4-*def*]chrysenenaphtho[1,2,3,4-def]chrysene, benzo(*r,s,t*)pentaphenebenzo[r,s,t]pentaphene, dibenzo[*b,def*]chrysenedibenzo[b,def]chrysene

- The following polychlorinated dibenzo-p-dioxins (PCDDs): 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD

- The following Polychlorinated dibenzofurans (PCDFs): 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, OCDF

- The polychlorobiphenyls PCBs (NDL-PCBs and DL-PCBs: PCB 81, PCB 77, PCB 123, PCB 118, PCB 114, PCB 105, PCB 126, PCB 167, PCB 156, PCB 157, PCB 169, PCB 189 and the PCBs),

- Formaldehyde.

Justification for inclusion of substances

According to the comments received from the consulted stakeholders during earlier stages of the assessment, none of these substances are intentionally added to diapers during the manufacturing process, but rather they are residues or contaminants. Indeed, these chemicals have been found in various studies performed in Europe these last few years (Danish EPA, 2009 ; VITO, 2008 ; OSAV, 2018 ; Wiberg *et al.,* 1989 ; Schecter *et al.,* 1998 ; DeVito et Schecter, 2002 ; Shin *et al.*, 2005). Moreover, in ANSES 2019, health thresholds have been exceeded when a QHRA was performed (ANSES, 2019). Therefore, the Dossier Submitter suggests to include all the above mentioned chemicals to discard from european market all articles that are not free of hazardous chemicals and hereby reduce health impact.

B.1.2. Composition of the substance(s)

Please refer to Annexes A.1 and D for description of the composition of single-use baby diapers. The list of substances covered by this restriction proposal is available in section 1.1.5 of the main report.

B.1.3. Physicochemical properties

Physical and chemical properties are gathered in the table below.

Table 7 : Chemical and physica[21]l properties of the substances included in the restriction proposal

Substances (CAS Number)	**EC Number**	**Harmonised Classification under CLP**	**Density**	**Vapour pressure (Pa)**	**Melting point**	**Boiling point (°C)**	**Water solubility (mg/L)**	**Log Kow**
PAH								
Benzo[g,h,i]perylene (191-24-2)	205-883-8	No harmonised classification	1.3-1.32	79.99	278	500	0.26µg/L at 25°C	6.18-7.23
Benzo[e]acephenanthrylene (205-99-2)	205-911-9	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	-	79.99	166	481	0.0012 mg/L at 20°C	5.78-6.6
Benz[a]anthracene (56-55-3)	200-280-6	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.27	66.7	158	437.6	0.014 mg/L at 25°C	5.5-5.76
Indeno[1,2,3-c,d]pyrene (193-39-5)	205-893-2	No harmonised classification	-	79.99	163	536	-	4.19-6.7
Chrysene (218-01-9)	205-923-4	Muta. 2 Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.27	66.7	255	448	0.002 mg/L at 25°C	5.7-6.64
Benzo[*k*]fluoranthene (207-08-9)	205-916-6	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.28	66.7	217	480	0.00076 mg/L at 25°C	6.11
Benzo[*j*]fluoranthene (205-82-3)	205-910-3	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.3	66.7	166	480	0.0025 mg/L at 25°C	5.96
Benzo[*e*]pyrene (192-97-2)	205-892-7	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.3	66.7	177	467	0.0051 mg/L at 23°C	5.96
Benzo[*d*,*e*,*f*]chrysene (50-32-8)	200-028-5	Skin Sens. 1 Muta. 1B	1.3	66.7	176	495	0.0038 mg/L at 25°C	5.96

[21] The sources consulted to retrieve chemical and physical properties are, among others, the following : ECHa website, former HSDB website, IPCS INCHEM website, chemicalland21 website, CSST website, INERIS website

Substances (CAS Number)	**EC Number**	**Harmonised Classification under CLP**	**Density**	**Vapour pressure (Pa)**	**Melting point**	**Boiling point (°C)**	**Water solubility (mg/L)**	**Log Kow**
		Carc. 1B Repr. 1B Aquatic Acute 1 Aquatic Chronic 1						
Dibenz[a,h]anthracene (53-70-3)	200-181-8	Carc. 1B Aquatic Acute 1 Aquatic Chronic 1	1.28	93.3	269	524	5.10^{-4}mg/L at 27°C	6.65
Cyclopenta[c,d]pyrene (27208-37-3)	-	No harmonised classification	1.358	66.7	-	438	-	-
5-methylchrysene (3697-24-3)		No harmonised classification	1.165	66.7	118	449	0.062 mg/L at 27 °C	5.9 - 6.07
Benzo[c]fluorene (205-12-9)	205-908-2	No harmonised classification	1.185	53.3	125-127	398	-	4.9
Dibenzo[def,p]chrysene (191-30-0)	205-886-4	Carc. 1B Muta.2	1.313	93.3	162	552	$3.62.10^{-3}$ mg/L at 25 °C	7.1
Naphtho[*1*,*2*,*3*,*4*-*def*]chrysene (192-65-4)	205-891-1	No harmonised classification	1.313	93.3	234	552	$1.6.10^{-4}$ mg/L at 25 °C	7.1
Benzo[*r*,*s*,*t*]pentaphene (189-55-9)	205-877-5	No harmonised classification	1.313	93.3	282	552	$7.4.10^{-5}$ mg/L at 25 °C	7.1
Dibenzo[*b*,*def*]chrysene (189-64-0)	205-878-0	No harmonised classification	1.313	93.3	308	552	$3.5.10^{-5}$ mg/L at 25 °C	7.1
Formaldehyde								
Formaldehyde (50-00-0)	200-001-8	Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* Skin Corr. 1B Skin Sens. 1	1.03 - 1.06	$440\ 10.^{3}$	-92	-19.1	4.10^{5} mg/L at 20°C	0.35

Substances (CAS Number)	**EC Number**	**Harmonised Classification under CLP**	**Density**	**Vapour pressure (Pa)**	**Melting point**	**Boiling point (°C)**	**Water solubility (mg/L)**	**Log Kow**
		Muta. 2 Carc. 1B						
PCDDs								
2,3,7,8-tetrachlorodibenzo[*b*,*e*][1,4]dioxin (2,3,7,8 TCDD) (1746-01-6)	-	No harmonised classification	1.6	133.32	305	418	2.10^{-4} mg/L at 25 °C	7.01
1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (1,2,3,7,8 PeCDD) (40321-76-4)	-	No harmonised classification	1.7	133.3	240	448.5	-	7.39
1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin (1,2,3,4,7,8 HxCDD) (39227-28-6)	-	No harmonised classification	1.8	146.7	273	475	4.10^{-6} mg/L at 20 °C	7.71
1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (1,2,3,6,7,8 HxCDD) (57653-85-7)	-	No harmonised classification	1.8	146.7	285	478	-	7.78
1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin (1,2,3,7,8,9 HxCDD) (19408-74-3)	-	No harmonised classification	1.8	146.7	243	478	-	7.78
1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (1,2,3,4,6,7,8-HpCDD) (35822-46-9)	-	No harmonised classification	1.8	160	264	503.3	$1.9.10^{-3}$ mg/L	8.1
octachlorodibenzo-*p*-dioxin (OCDD) (3268-87-9)	-	No harmonised classification	1.9	173.3	300-330	527.8	4.10^{-7} mg/L at 20 °C	8.41
PCDFs								
2,3,7,8-tetrachlorodibenzofuran (2,3,7,8 TCDF) (51207-31-9)		No harmonised classification	1.6	133.3	227	421.2	$6.92.10^{-4}$ mg/L at 26 °C	6.45
1,2,3,7,8-pentachlorodibenzofuran (1,2,3,7,8 PeCDF) (57117-41-6)		No harmonised classification	1.7	146.7	225	450.6	-	6.73

Substances (CAS Number)	EC Number	Harmonised Classification under CLP	Density	Vapour pressure (Pa)	Melting point	Boiling point (°C)	Water solubility (mg/L)	Log Kow
2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8 PeCDF) (57117-31-4)		No harmonised classification	1.7	146.7	196	450.6	$2.35.10^{-4}$ mg/L at 23 °C	6.80
1,2,3,4,7,8-hexachlorodibenzofuran (1,2,3,4,7,8 HxCDF) (70648-26-9)		No harmonised classification	1.8	146.7	-	475.5	-	7.01
1,2,3,6,7,8-hexachlorodibenzofuran (1,2,3,6,7,8 HxCDF) (57117-44-9)		No harmonised classification	1.8	159.9	-	478.7	-	6.95
2,3,4,6,7,8-hexachlorodibenzofuran (2,3,4,6,7,8 HxCDF) (60851-34-5)		No harmonised classification	1.8	159.9	239.5	478.7	-	7.19
1,2,3,7,8,9-hexachlorodibenzofuran (1,2,3,7,8,9 HxCDF) (72918-21-9)		No harmonised classification	1.8	159.9	-	478.7	-	6.90
1,2,3,4,6,7,8-heptachlorodibenzofuran (1,2,3,4,6,7,8 HpCDF) (67562-39-4)		No harmonised classification	1.8	159.9	233	502.7	$3.3.10^{-12}$ mol/L	7.26
1,2,3,4,7,8,9-heptachlorodibenzofuran (1,2,3,4,7,8,9 HpCDF) (55673-89-7)		No harmonised classification	1.8	159.9	-	502.7	-	7.04
octachlorodibenzofuran (OCDF) (39001-02-0)		No harmonised classification	1.9	173.3	258	525.9	$2.61.10^{-12}$ mol/L	7.22
DL-PCB								
3,4,4′,5-tetrachloro-1,1′-biphenyl; PCB 81 (70362-50-4)		No harmonised classification	1.4	106.7	-	379.7	-	6.01
3,3′,4,4′-tetrachloro-1,1′-biphenyl ;PCB 77 (32598-13-3)		No harmonised classification	1.4	106.7	182-184	380.7	18.10^{-2} mg/L	6.00

Substances (CAS Number)	EC Number	Harmonised Classification under CLP	Density	Vapour pressure (Pa)	Melting point	Boiling point (°C)	Water solubility (mg/L)	Log Kow
2,3′,4,4′,5′-pentachloro-1,1′-biphenyl; PCB 123 (65510-44-3)		No harmonised classification	1.5	120	-	390.2	-	6.50
2,3′,4,4′,5-pentachloro-1,1′-biphenyl; PCB 118 (31508-00-6)		No harmonised classification	1.5	120	110	388.2	-	6.42
2,3,4,4′,5-pentachloro-1,1′-biphenyl; PCB 114 (74472-37-0)		No harmonised classification	1.5	120	98	388.4	$4.9.10^{-8}$ mol/L	6.30
2,3,3′,4,4′-pentachloro-1,1′-biphenyl; PCB 105 (32598-14-4)		No harmonised classification	1.5	120	117	392.2	$1.04.10^{-8}$ mol/L	6.36
3,3′,4,4′,5-pentachloro-1,1′-biphenyl; PCB 126 (57465-28-8)		No harmonised classification	1.5	120	-	409.2	-	6.45
2,3′,4,4′,5,5′-hexachloro-1,1′-biphenyl; PCB 167 (52663-72-6)		No harmonised classification	1.6	120	-	416	$6.17.10^{-9}$ mol/L	6.87
2,3,3′,4,4′,5-hexachloro-1,1′-biphenyl; PCB 156 (38380-08-4)		No harmonised classification	1.6	120	-	417.1	$1.48.10^{-8}$ mol/L	6.74
2,3,3′,4,4′,5′-hexachloro-1,1′-biphenyl; PCB 157 (69782-90-7)		No harmonised classification	1.6	133.3	-	420	-	6.82
3,3′,4,4′,5,5′-hexachloro-1,1′-biphenyl; PCB 169 (32774-16-6)		No harmonised classification	1.6	133.3	-	436.6	$1.41.10^{-9}$ mol/L	6.9
2,3,3′,4,4′,5,5′-heptachloro-1,1′-biphenyl; PCB 189 (39635-31-9)		No harmonised classification	1.7	133.3	-	443.9	$1.9.10^{-9}$ mol/L	7.2

B.1.4. Justification for grouping

The justification for targeting the substances in this restriction proposal is explained under 1.1.4 in the main report and in Annex B.1.1.

B.2. Manufacture and uses (summary)

Data about manufacture and uses are provided in Annex A.

B.3. Classification and labelling

B.3.1. Classification and labelling in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

The classifications of the substances in the scope are included in Annex B.1 and in section 1.2.2 of the main report.

B.3.2. Classification and labelling in classification and labelling inventory/ Industry's self classification(s) and labelling[1]

The self-classifications of the substances in the scope are included in section 1.2.2 of the main report.

B.4. Environmental fate properties

4 PAHs, PCBs like PCDD/Fs are also among the first 12 POPs covered by the Stockholm Convention in 2001 (meaning they are known to be Persistent Organic Pollutants and regulated as such).

B.5. Human health hazard assessment

B.5.1 PAHS

Hazards and risks of PAHs were reviewed within various risk assessment frameworks and by various international committees (ATSDR,1995; EFSA, 2008; IARC, 2010, 2012b; WHO, 1998, 2003; Health Council of the Netherlands, 2006; EU, 2008). Furthermore, ECHAs Risk Assessment Committee (RAC) established a dose-response relationship for the carcinogenicity of coal tar pitch - high temperature (CTPHT) (ECHA, 2018) and an Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019).

These reports have assessed the animal and human toxicological data on PAHs in detail and it is not the goal of the Dossier Submitter to re-do those assessments.

Given the targeting, primarily mutagenicity (section B.5.1.7.) and carcinogenicity (section B.5.1.8.) will be addressed, as well as irritation (section B.5.1.3), sensitisation (section B.5.1.5) endocrine disruting effects (section B.5.1.10) and toxicokinetics (section B.5.1.1.).

B.5.1.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

B.5.1.1.1 Absorption

- **Oral**

Recently, ECHA (2019) evaluated in the restriction report 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications, the available data on oral absorption. Based on this, ECHA (2019) selected **an oral absorption fraction of 0.3 (30%)**. It is noted that this value will only be applied for route-to-route extrapolation to derive an internal DNEL (see section B.5.1.11.), and the risk assessment will be based on an internal dose metric. Below, a justification for this value is described (taken from ECHA 2019).

*"For experimental animals, the gastro-intestinal absorption of PAHs, especially BaP, is well documented. Absorption of (unbound) PAHs from the gastro-intestinal tract appears to vary per animal species. Table 8 provides an overview of studies on oral bioavailability of PAH in different species. Oral absorption of BaP was reported to be 35-99 % in rats, 12 % in goats and 30.5 % in pigs. It is known that the use of rodent models for human exposure assessment is limited by the physiological differences between rodents and primates (Zhang et al., 2013). In fact, no single animal can mimic the gastro-intestinal tract characteristics of humans. However, pig and human colon morphology appears similar (Zhang et al., 2013, Kararli, 1995). Furthermore, in the pig study the PAHs were administered orally via milk, which is considered a relevant vehicle because it is likely that children playing outside and people playing sports are (semi-) fed rather than fasted. For these reasons, **an oral absorption fraction of 0.3 (30 %) was assumed**, based on the report by Cavret et al. (2003)."* The Dossier Submitter chose to apply this oral absorption fraction to all PAHs although oral absorption varies between PAHs (Table 8) (for example, Carvet *et al*. showed that the oral absorption of phenanthrene was 86.1%).

The Dossier Submitter notes that the selected value for oral absorption differs from the one used by ECHA (2017, 2018b). In their evaluation of the possible health risks of recycled rubber granules, ECHA (2017) applied an oral absorption fraction of 0.5. Recently, ECHAs (RAC), in their evaluation of a dose-response for carcinogenicity for CTPHT, assumed an default absorption from oral exposure of 100% for lack of quantitative data on the absorption of PAHs from CTPHT and coal tar pitch volatiles after oral exposure for humans (ECHA, 2018b). The oral absorption fraction will be used to derive the internal DNEL (see section B.5.1.11.). As in the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019), the Dossier Submitter considers that an oral absorption fraction of 0.3 would result in a realistic risk assessment.

Table 8 : Overview of oral bioavailability studies (taken from: RIVM, 2016)

PAH	Animal	Route of administration	Bioavailability %	Reference
BaP (benzo[d,e,f]chrysene /benzo[a]pyrene)	rat	Oral gavage	35-99 %	Ramesh *et al.*, (2004); as cited by EFSA (2008)
Chrysene	Rat	Oral gavage	75-87 %	Ramesh *et al.* (2001)

BaP	Pig	Orally *via* milk	30.5 %	Cavret *et al.* (2003)
BaP	Goat	Oral gavage	12 %	Grova *et al*. (2002)
BaP	Rat	Intraduodenal infusion	30 %	Foth *et al.* (1988)
BaP	Rat	Oral gavage	10 %	Foth *et al.* (1988)
BaP	Rat	Oral gavage	40 %	Ramesh *et al*. (2001)

- **Dermal**

PAHs are lipophilic substances which allow them to easily penetrate cell membranes and be stored in the body. However, the metabolism of PAHs within the epidermis by cytochrome P450 mono-oxygenase, which is also present in the skin, converts them into more hydrosoluble compounds and therefore more excretable. Furthermore, PAHs metabolic activation is responsible for the formation of highly mutagenic and carcinogenic metabolites in the skin (Shimada 2006 as cited in Bourgart et al., 2019).

A dermal absorption study in 4 workers exposed to tar ointment showed absorption rates between 0.036 and 0.135 L/hour depending on the anatomical sites for a 45-minute exposure, suggesting that 20-56% of the dose would be absorbed within 6 hours (VanRooij *et al.*, 1993). Dermal absorption rates varied by 69% between different anatomical sites (shoulder > neck, forearm, groin > wrist and ankle) and by only 7% between individual volunteers (VanRooij *et al.,* 1993). In an in vitro study, the total amount of BaP absorbed (10 µg/cm²) in viable explant skin samples from donors was approximately 3% of the dose after 24 hours of exposure (Kao *et al*., 1985). Similar penetration rates were measured in skin samples from other species, including marmots, rats and rabbits (Kao *et al*., 1985). Mouse skin penetrated a greater proportion of the dose (>10%), while guinea pig skin penetrated only a negligible percentage of the dose (0.1%) (Kao *et al.,* 1985). In a study on human cadaver skin, Wester *et al*. (1990) showed that 23.7 ± 9.7% of the applied dose of BaP penetrated the skin (US EPA, 2017). These results suggest that metabolism is also an important determinant of permeation.

Dermal penetration rates of BaP and PAHs vary depending on the species, individual, type of study (*in vivo, in vitro*, site of application) and matrix used (Table 9). The vehicle is an important factor in skin penetration. Studies investigating the dermal absorption fraction of PAHs in animals and humans have used soil or a solvent like acetone or ethanol as vehicle. Topical exposure of female Sprague-Dawley rats and female rhesus monkeys to BaP in crude oil or *via* acetone resulted in 4 to 5 times greater absorption than that of BaP in soil (Wester *et al*., 1990; Yang *et al*., 1989 as cited in ATSDR, 1995 and US EPA, 2017). *"In general, animal studies report percentages between 7-100 % or 0-65 % in solvent and soil respectively. Human studies report percentages between 4-78 % or 0-27 % in solvent and soil respectively (*Figure 15*). In the current assessment, it is assumed that after diffusion to the skin, the PAHs are present on the skin in an unbound state, i.e. not bound to soil, rubber or any other particles. Implicitly, it follows that absorption of unbound PAHs is more efficient compared to absorption of PAHs from soil, which first need to partition from the soil before they can be absorbed. Hence, the actual absorption fraction is probably larger than those empirically derived with soil as vehicle. On the other hand, it is assumed that applying PAHs in the presence of a solvent enhancing the* *absorption, overestimates the required absorption fraction. This is in agreement with BAuA (2010), who report that the use of these highly lipophilic solvents may result in an overestimation of PAH migration rates"* (ECHA 2019).

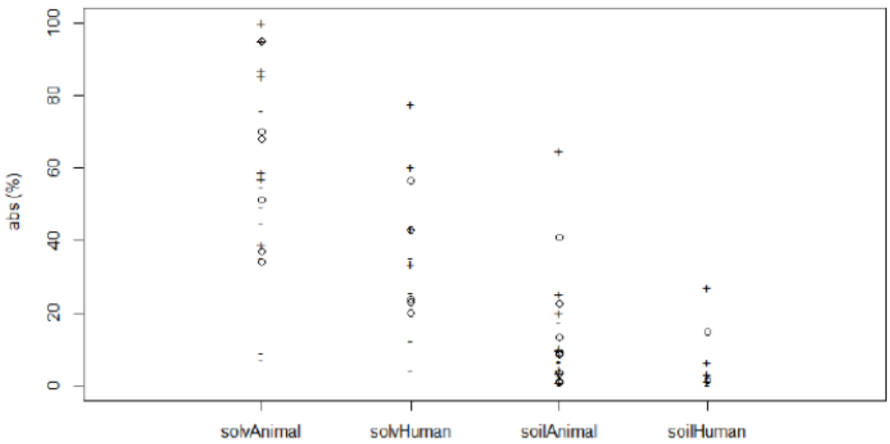


Figure 15: Dermal absorption data based on literature in vitro and in vivo data in soil or solvent (acetone/ethanol). Circles indicate mean, -/+ indicate reported minimum and maximum values or are an approximation of the range obtained by taking mean -/+ 2SD (taken from: RIVM, 2016).

Table 9: Detailed information on the dermal absorption data (this refers to BaP unless otherwise stated) as used for setting a dermal absorption fraction (adapted from: RIVM, 2016).

In vivo/in vitro study		Vehicle	Value %	Reference
In vivo	Workers (n = 12)	/	20 to 56% (variation of 69% depending on the site of exposure)	VanRooij *et al.* (1993)
	Rat SD mâle	Ethanol	52,7 ± 1,3%	Payan *et al.* (2009)
	Hairless guinea pig	Acetone	37% (± 0.9)	Ng *et al.* (1992)
	Hairless guinea pig	Acetone	26,4 ± 5,5% (skin levels included) 16,9 ± 2,5% (skin level not included)	Chu *et al.* (1996)
	Rat SD	1) BaP in crude petroleum 2) Soil fortified with BaP in crude petroleum 3) Acetone	@24h 1) 5.5% (se=1.4) 2) 1.1% (se=0.3) 3) 35-48%	Yang *et al.* (1989)
	Rat and guinea pig	Acetone	Rat : 70 ± 7.6% Hairless guinea pig : 68 ± 9.3%	Moody *et al.* (1995)
	Rhesus monkey	1) Soil 2) Acetone	1) 13.2% (± 3.4) 2) 51% (± 22)	Wester *et al.* (1990)
Ex vivo	Human Skin	Ethanol	20%	Bartsch *et al.* (2016)
	Human Skin	Acetone	3%	Bourgart *et al.* (2019)

In vitro	Rat	1) BaP in crude petroleum 2) Soil fortified with BaP in crude petroleum 3) Acetone	@24h 1) ~12% 2) ~1%	Yang *et al.* (1989)
	Human skin (female Breast Skin)	1) Soil 2) Acetone	1) 14.8% (± 6.17) 2) 56,4% (± 10.59) @24h	Moody *et al*. (2007)
	Viable skin excised sample from viable human skin (leg); Marmoset; CDF rat, NZ rabbit ; C3H, C57BL/6 and DBA/2 mouse ; Guinea pig	Acetone	man, marmouset, CDF rat, NZ rabbit: 1 - 3% C3H, C57BL/6 and DBA/2 mouse : >10% Guinea pig : 0.1%	Kao *et al*. (1985)
	Human skin	Soil	Between ~0.3% and ~1.1%	Roy and Singh (2001)
	Human skin	Soil aged	0.14 - 1.1 %	Stroo *et al*. (2005)
	Pig skin	Pure, soil and aged soil	Pure: 76±3.2% Soil:8.5±0.9% Soil : 3.5±0.5% Aged soil: 3.7±0.5% Aged soil: 1.8±0.2%	Turkall *et al*. (2010)
	Pig skin	Sand or Clay, pure BaP	9.0% (± 0.4) to 22.7% (± 1.3)	Abdel-Rahman *et al*. (2000)
	Human skin	Soil	0.2-6.5 %	Roy *et al.* (1998)
	Rat; hairless guinea pig; human Test skin; human skin (abdominal) (n = 2)	Acetone	Rat: 95 % (± 9.6) hairless guinea pig: 51% (± 3.0) human Testskin: 34% (±12.4) human: 23% (± 5,3) - 43% (± 8,7)	Moody *et al*. (1995)
	Human cadaver skin	1) Soil 2) Acetone	1) 1.4% (± 0.9) 2) 23.7% (± 9.7)	Wester *et al*. (1990)
	Hairless guinea pig	Acetone	10.6% @24h	Ng *et al.* (1992)

B.5.1.1.2 Distribution

The distribution of PAHs is taken from the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications.

Extensive summaries of the available data on distribution have been provided a.o. by ATSDR (1995), WHO (1998 or 2003), or EFSA (2008).

A summary is provided by WHO (2003):
"In laboratory animals, PAHs become widely distributed in the body following administration by any one of a variety of routes and are found in almost all internal organs, particularly those rich

in lipid (WHO, 1997). Maximum concentrations of BaA in perfused tissues (e.g. liver, blood, brain) were achieved within 1–2 hours after administration of high oral doses (76 and 152 mg/kg of body weight). In lesser perfused tissues (e.g. adipose and mammary tissue), maximum levels of this compound were reached in 3–4 hours (Bartosek et al., 1984). In male Wistar rats receiving a gavage dose of 2–15 mg of [$_{14}$C]-pyrene per kg of body weight, the fat had the highest levels of radioactivity, followed by the kidney, liver, and lungs (Withey et al., 1991). Orally absorbed DBAhA in rats was also widely distributed to several tissues. After continuous oral administration of 0.5 µg of [$_{3}$H]BaP daily to male rats for up to 7 days, the radioactivity persisted in liver, kidney, lung, and testis (Yamazaki & Kakiuchi, 1989). Orally administered BaP (200 mg/kg of body weight) has been shown to cross the placental barrier and has been detected in fetal tissues (2.77 µg/g) (Shendrikova & Aleksandrov, 1974). Using ^{14}C-tagged BaP, a BaP concentration 1–2 orders of magnitude lower in embryonic than in maternal tissues was determined after oral administration in mice (Neubert & Tapken, 1988). Differences in concentrations in the fetus among the various PAHs appeared to be highly dependent on the gastrointestinal absorption of the compound."

B.5.1.1.3 Metabolism

The metabolism of PAHs is taken from the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications:

A short summary is provided in WHO (2003):

"The metabolism of PAHs is complex. Generally, the process involves epoxidation of double bonds, a reaction catalysed by the cytochrome P-450-dependent monooxygenase, the rearrangement or hydration of such epoxides to yield phenols or diols, respectively, and the conjugation of the hydroxylated derivatives. Reaction rates vary widely, and interindividual variations of up to 75-fold have been observed, for example, with human macrophages, mammary epithelial cells, and bronchial explants from different donors. Most metabolism results in detoxification, but some PAHs in some situations become activated to DNA-binding species, principally diol-epoxides, that can initiate tumours (WHO, 1997). Although the PAHs are similar, they have structural differences that are the basis for differences in metabolism and relative carcinogenicity. The metabolism of the more carcinogenic, alternant (equally distributed electron density) PAHs, such as BaP, BaA, and DBAhA, seems to differ in some ways from that of non-alternant (uneven electron density distribution) PAHs, such as FA, BbFA, BkFA, BjFA, IP [Indeno[1,2,3-cd]pyrene], BghiP [Benzo[ghi]perylene], and PY (Phillips & Grover, 1994; ATSDR, 1995). In general, little is known about the metabolism of most PAHs, particularly in non-rodent species. It should be noted that there appear to be species differences in the enzymes that activate PAHs (Michel et al., 1995) and in the formation of DNA adducts (Kulkarni et al., 1986)."

It should be noted that metabolic activation is seen as a prerequisite for the carcinogenic potential of the PAHs covered by this restriction proposal, as has been extensively discussed in other reviews of PAH toxicity. See also section B.1.7. on mutagenicity below.

B.5.1.1.4 Elimination

The elimination of PAHs is taken from the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications, based on in various risk assessment frameworks and by various international committees, e.g. ATSDR (1995), EFSA (2008), or WHO (1998, 2003).

A summary is provided by WHO (2003):

"PAH metabolites and their conjugates are excreted predominantly via the faeces and to a lesser extent in the urine. Conjugates excreted in the bile can be hydrolysed by enzymes of the gut flora and reabsorbed. It can be inferred from available data on total body burdens in humans that PAHs do not persist for long periods in the body and that turnover is rapid. This excludes those PAH moieties that become covalently bound to tissue constituents, in particular to nucleic acids, and are not removed by repair (WHO, 1997). The excretion of urinary metabolites is a method used to assess internal human exposure of PAHs."

B.5.1.2. Acute toxicity

Not relevant for this restriction proposal.

B.5.1.3. Irritation

Of the seventeen PAHs evaluated in this restriction proposal, none has a harmonised classification for irritation in Annex VI of CLP (see section 1.2.3. main report).

B.5.1.4. Corrosivity

Not relevant for this restriction proposal.

B.5.1.5. Sensitisation

Of the seventeen PAHs evaluated in this restriction proposal, only BaP has a harmonised classification for skin sensitisation in Annex VI of CLP (see section 1.2.3. main report).

B.5.1.6. Repeated dosed toxicity

Not relevant for this restriction proposal.

B.5.1.7. Mutagenicity

Of the 17 PAHs evaluated in this restriction proposal, only BaP and chrysene are classified for germ cell mutagenicity in category 1B and 2, respectively, according to Regulation (EC) No 1272/2008. In addition, several international committees discussed the mutagenicity of these PAHs. The table below presents an overview.

Table 10: Mutagenicity/carcinogenicity of polycyclic aromatic hydrocarbons: overall overview of regulatory evaluations (adapted from ECHA 2019)

Chemical (CAS number)	Mutagenicity				Carcinogenicity	
	EC 1272/2008	WHO/IPCS (1998)	EC (2002)	FAO/WHO (2006)	EC 1272/2008	IARC
Benzo[d,e,f]chryseneBenzo[d,e,f]chrysene (50-32-8)	Muta. 1B (H340)	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple end-points; positive also at germ cell level)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 1
Benzo[e]pyrene (192-97-2)	No	Genotoxic	Equivocal (mixed results in vitro, inconsistent results in vivo)	-	Carc. 1B (H350)	Group 3
Benz[a]anthracene (56-55-3)	No	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple end-points; positive also at germ cell level)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2B
Dibenz[a,h]anthracene (53-70-3)	No	Genotoxic	Genotoxic (positive results in assays in vitro and in vivo for multiple end-points)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2A
Benzo[e]acephenanthrylene (205-99-2)	No	Genotoxic	Genotoxic (positive results in assays in vitro and in vivo for different end-points)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2B
Benzo[j]fluoranthene (205-82-3)	No	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2B
Benzo[k]fluoranthene (207-08-9)	No	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2B
Chrysene (218-01-9)	Muta. 2 (H341)	Genotoxic	Genotoxic (positive results in vitro and in vivo for multiple	Genotoxic, both in vitro and in vivo	Carc. 1B (H350)	Group 2B

			end-points; positive also at germ cell level)			
Benzo[g,h,i]perylene (191-24-2)	No	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	-	No	Group 3
5-methylchrysene (3697-24-3)	No	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No	Group 2B
Indeno[1,2,3-cd]pyrene (193-39-5)	No	Genotoxic	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No	Group 2B
Dibenzo[def,p]chrysene (191-30-0)	No*	Genotoxic (result derived from small database)	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No*	Group 2A
Naphtho[1,2,3,4-def]chrysene (192-65-4)	No	Genotoxic	Genotoxic (positive results assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No	Group 3
Benzo[r,s,t]pentaphene (189-55-9)	No*	Genotoxic	genotoxic (positive in assays in vitro and in vivo)	Genotoxic, both in vitro and in vivo	No*	Group 2B
Dibenzo[b,def]chrysene (189-64-0)	No*	Genotoxic (result derived from small database)	Genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No*	Group 2B
Benzo[c]fluorene (205-12-9)	No	-	-	-	No	Group 3
Cyclopenta[c,d]pyrene (27208-37-3)	No	Genotoxic	genotoxic (positive results in assays in vitro and for DNA binding in vivo)	Genotoxic, both in vitro and in vivo	No	Group 2A

*: these 3 chemicals have adopted RAC opinions that deal with harmonised classifications as Muta.2; H341 and Carc.1B; H350

As noted above, metabolic activation is seen as a prerequisite for the carcinogenic potential of the PAHs covered by this restriction proposal.

The following description is taken from IARC (2010):

"PAHs are metabolized by phase I enzymes and peroxidases, which produce DNA-reactive metabolites, and phase II enzymes, which form polar conjugates. Phase I enzymes, such as cytochrome P450s, catalyse the mono-oxygenation of PAHs to form phenols and epoxides. Specific cytochrome P450 isozymes and epoxide hydrolase can form reactive diol epoxides that comprise one class of ultimate carcinogenic metabolites of many PAHs. Both cytochrome P450s and peroxidases can form radical cations by one electron oxidation that comprise another class of ultimate carcinogenic metabolites. Further oxidation of PAH phenols leads to the formation of PAH quinones. The major cytochrome P450s that are involved in the formation of diol epoxides are 1A1, 1A2 and 1B1, while 2C9 and 3A4 play a minor role in the activation of PAHs. PAHs induce increased expression of activating cytochrome P450s via enhanced aryl hydrocarbon receptor-mediated transcription. Polymorphisms in human cytochrome P450s have been identified, some of which may be associated with increased susceptibility. Additional enzymes that may play a role in the further activation of some PAH diols include members of the aldo-keto reductase family, among which polymorphisms that influence susceptibility have been identified. Nicotinamide adenine dinucleotide phosphate:quinone oxidoreductase 1 catalyses the reduction of PAH quinones to hydroquinones which may be re-oxidized and generate reactive oxygen species. Polymorphisms in this gene have also been described.

The major phase II enzymes include the glutathione S-transferases, uridine 5'-diphosphate glucuronosyltransferases and sulfotransferases. The major glutathione S-transferases involved in the conjugation of PAH metabolites are M1, P1 and T1. Multiple polymorphisms of these as well as polymorphisms in both uridine 5'-diphosphate glucuronosyl- and sulfotransferases have been identified, some of which can modulate susceptibility to cancer.

The current understanding of the carcinogenesis of PAHs in experimental animals is almost solely based on two complementary mechanisms: those of the diol epoxide and the radical cation. Each provides a different explanation for the data observed in experimental animals.

The diol epoxide mechanism features a sequence of metabolic transformations of PAHs, each of which leads to potentially reactive genotoxic forms. In general, PAHs are converted to oxides and dihydrodiols, which are in turn oxidized to diol epoxides. Both oxides and diol epoxides are ultimate DNA-reactive metabolites. PAH oxides can form stable DNA adducts and diol epoxides can form stable and depurinating adducts with DNA through electrophilic carbonium ions. The inherent reactivities of oxides and diol epoxides are dependent on topology (e.g. bay regions, fjord regions, cyclopenta rings), and the reactivity of diol epoxides is further dependent on factors such as stereochemistry and degree of planarity. Both stable and depurinating adducts are formed primarily with guanines and adenines, and induce mutations (e.g. in ras proto-oncogenes) that are strongly associated with the tumorigenic process. Some mutagenic PAH diols, oxides and diol epoxides are tumorigenic in experimental animals.

One-electron oxidation creates radical cations at a specific position on some PAHs. The ease of formation and relative stabilities of radical cations are related to the ionization potential of the PAH. Additional important factors in the radical cation mechanism are localization of charge in the PAH radical cation and optimal geometric configuration, particularly the presence of an angular ring. The radical cation mechanism results in the formation of depurinating DNA adducts with guanines and adenines, which generate apurinic sites that can induce mutations in ras proto-oncogenes, which are strongly associated with tumorigenesis.

There is strong evidence that the diol epoxide mechanism operates in the mouse lung tumorigenesis of many PAHs evaluated in this monograph. For some PAHs, there is strong *evidence that both radical cation and diol epoxide mechanisms induce mouse skin carcinogenesis. Many of the pathways that lead to PAH carcinogenesis involve genotoxicity, and the genotoxic effects of PAHs and their metabolites were included in the overall evaluation of each PAH discussed.*

The genotoxic effects of exposure to complex mixtures that contain PAHs have been studied in some populations exposed in industrial settings and in patients who undergo coal-tar therapy. Measured end-points include mutagenicity in urine and the presence of aromatic DNA adducts in the peripheral lymphocytes of exposed workers. In some studies, specific benzo[a]pyrene–DNA adducts have been measured. Cytogenetic effects such as micronucleus formation have also been reported.

Other mechanisms of carcinogenesis have been proposed for PAHs, but these are less well developed. The ortho-quinone/reactive oxygen species mechanism features enzymatic oxidation of non-K-region PAH diols to ortho-quinones by aldo-keto reductases, and has been studied only in in-vitro systems. These PAH ortho-quinones are highly reactive towards DNA; they yield DNA adducts and damage DNA. PAH ortho-quinones induce mutations in the p53 tumour-suppressor gene in vitro; they can also undergo repetitive redox cycling and generate reactive oxygen species, which have been associated with oxidative DNA-base damage as well as the induction of pro-oxidant signals that may have consequences on growth. Reactive oxygen species can also be produced by other mechanisms such as the formation of PAH quinones through peroxidase reactions. Thus, this pathway has the potential to contribute to the complete carcinogenicity of a parent PAH.

The mechanism of meso-region biomethylation and benzylic oxidation features biomethylation of parent PAHs to methyl PAHs. Methyl PAHs are further metabolized by cytochrome P450s to hydroxymethyl PAHs that are converted into reactive sulfate ester forms that are capable of forming DNA adducts. Studies on this mechanism have been limited to subcutaneous tissues in rats that are susceptible to PAH tumorigenesis.

Several of the biological effects of PAHs, such as enzyme induction of xenobiotic metabolizing enzymes, immunosuppression, teratogenicity and carcinogenicity, are thought to be mediated by activation of the aryl hydrocarbon receptor. This receptor is widely distributed and has been detected in most cells and tissues. There is also evidence that the aryl hydrocarbon receptor acts through a variety of pathways and, more recently, that cross-talk with other nuclear receptors enables cell type-specific and tissue-specific control of gene expression. Translocation of the activated aryl hydrocarbon receptor to the nucleus may require threshold concentrations of the ligand. Various oxidative and electrophilic PAH metabolites are also known to induce enzyme systems via anti-oxidant receptor elements. The biological effects of aryl hydrocarbon receptor and anti-oxidant receptor element signalling involve a variety of cellular responses, including regulation of phase I and II metabolism, lipid peroxidation, production of arachidonic acid-reactive metabolites, decreased levels of serum thyroxine and vitamin A and persistent activation of the thyroid hormone receptor. Aryl hydrocarbon receptor signalling may result in adaptive and toxic responses or perturbations of endogenous pathways. Furthermore, metabolic activation of PAHs produces cellular stress. This in turn activates mitogenmediated protein kinase pathways, notably of Nrf2. The Nrf2 protein dimerizes with Mafoncoproteins to enable binding to an anti-oxidant/electrophilic response element, which has been identified in many phase I/II and other cellular defence enzymes and controls their expression. Therefore, cellular stress may be regulated independently of aryl hydrocarbon receptor-mediated xenobiotic metabolizing enzymes."

"PAHs must be metabolically activated in order to induce tumours. However, individuals differ in their ability to metabolize PAHs: people who are deficient in particular enzymes that activate PAHs to reactive metabolites may be at a lower risk for chemical carcinogenesis, whereas deficiencies in enzymes that detoxify reactive metabolites may increase this risk. Some of the

epidemiological studies that have been conducted to date have shown positive relationships between genetic polymorphisms of drug-metabolizing enzymes and susceptibility to cancer, while others have been inconclusive. Many factors, including race, age, sex, tobacco smoking, alcohol intake and genetic factors, could induce or inhibit drug-metabolizing activities which indicates that a complex interaction exists. Multi-gene and exposure interactions may also play a complex role in the interpretation of any increases in risk."

In conclusion, given the ability to induce genotoxic effects, there is no threshold value below which no health risk exists for mutagenic PAHs.

B.5.1.8. Carcinogenicity

Eight PAHs covered by this restriction proposal (benzo[d,e,f]chrysene (BaP), benzo[e]pyrene (BeP), benz[a]anthracene (BaA), dibenz[a,h]anthracene (DBAhA), Benzo[e]acephenanthrylene(BbFA), benzo[j]fluoranthene (BjFA), benzo[k]fluoranthene (BkFA) and chrysene (CHR)) have harmonised classifications for carcinogenicity (category 1B) according Regulation (EC) No 1272/2008.

Three PAHs (dibenzo[def,p]chrysene ; benzo[r,s,t]pentaphene ; dibenzo[b,def]chrysene) have adopted RAC opinions that deal with harmonised classifications for carcinogenicity (category 1B) according Regulation (EC) No 1272/2008.

The other six PAHs (benzo[g,h,i]perylene, 5-methylchrysene, indeno[1,2,3-cd]pyrene; naphtho[1,2,3,4-def]chrysene, benzo[c]fluorine, cyclopenta[c,d]pyrene) have no classification for carcinogenicity according Regulation (EC) No 1272/2008. However, some of these PAHs have been classified by the International Agency for Research on Cancer (IARC 2010, 2012), see for details Table 10 in previous section.

Within the purpose of current restriction proposal it is not intended to re-evaluate the carcinogenic potential of the already classified PAHs. Based on reviews by various international committees (ATSDR, 1995; EFSA, 2008; IARC, 2010, 2012; WHO, 1998, 2003; Health Council of the Netherlands, 2006; EU, 2008), the previous Annex XV restriction reports for 8 PAHs in consumer products prepared by BAuA (BAuA, 2010) and for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019) and the note on CTPHT by ECHAs RAC (ECHA, 2018), key studies were selected and presented in the table below. Summaries of the key oral and dermal carcinogenicity studies are presented in sections B.5.8.1. and B.5.8.2., respectively.

Table 11 : Overview of key studies for PAH-mixtures for the endpoint carcinogenicity (taken from ECHA 2019

Species, strain, sex, no/group	Test substance, duration of exposure	Reference
ORAL		
Rat, Wistar 52/sex/group	BaP Vehicle: soybean oil *Via* gavage: 5 d/wk for 104 wk	Kroese *et al*. (2001); Wester *et al.* (2012)
Mouse, B6C3F1, female 48/group	1. BaP 2. two coal tar mixtures containing various PAHs including BaP *Via* diet for 104 weeks	Culp *et al.* (1998)
Mouse, A/J, female 30/group	1. BaP 2. PAH-rich manufactured gas plant residu *Via* diet for 104 weeks	Weyand *et al*. (1995)
DERMAL		
Mouse, NMRI, female 100/group	1. BaP 2. a mixture of known carcinogenic PAHs ('C PAH', including BaP) 3. a mixture of PAHs not considered carcinogenic by the study authors ('NC PAH') 4. a combination of the latter two ('C PAH + NC PAH'). Dermal (back area), twice weekly during entire lifespan	Schmähl *et al*. (1977)
Mouse, NMRI, female 40/group	BaP and other PAHs tested individually Dermal (dorsal skin in the interscapular area), twice weekly, during entire lifespan	Habs *et al.* (1980)
Mouse, NMRI, female 20/group	BaP and a condensate containing various PAHs Dermal, twice weekly, during entire lifespan	Habs *et al.* (1984)
Mouse, C3H/HeJ, male 50/group	BaP Dermal, twice weekly, 99 weeks	Warshawsky and Barkley (1987)
Mouse, SENCAR, male and female 40/sex/group	BaP and extracts of soot from various sources Dermal 1×/week, 50-52 weeks	Nesnow *et al.* (1983)

B.5.1.8.1 Carcinogenicity: animal data - oral

The assessment of carcinogenic oral studies is taken from the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications:

"Three oral carcinogenicity studies were identified as key studies: one in rats with BaP exposure via gavage (Kroese et al., 2001; Wester et al., 2012) and two in mice, each with both BaP- as well as PAH-mixture exposure via the diet (Culp et al., 1998; Weyand et al., 1995)."

B.5.1.8.1.1 Lifetime gavage study in rats: Kroese *et al*. (2001); Wester *et al*. (2012)

"A combined chronic and carcinogenicity study in Wistar rats clearly showed BaP to be a potent carcinogen upon chronic oral administration. Groups of male and female Wistar rats (n = 52/group) were administered oral doses of 0, 3, 10, or 30 mg BaP/kg bw/d by gavage (vehicle: soybean oil) on 5 days per week for 104 weeks. The most potent carcinogenic effects of BaP under these testing conditions were observed in the liver and forestomach, while for both organs a low spontaneous incidence was noted in this rat strain. Papillomas and carcinomas were observed in the forestomach, and adenomas and carcinomas in the liver of both female and male rats. Tumours were found at the lowest dose tested (3 mg/kg bw/d), though at a (borderline) non-significant incidence. Statistically significant incidences were observed at 10 mg/kg bw/d and above. Other tumours observed in this study were tumours of the auditory canal, skin and appendages, oral cavity, small intestine, kidney and soft tissue sarcomas.

Liver tumours were also responsible for morbidity and the high mortality rate at the highest dose level in both sexes (100 % after about 70 weeks). Mortality was mainly due to sacrifice for humane reasons when rats became emaciated, often with distended abdomen in which frequently one or more palpable masses were present in the cranial area (liver). In control animals, survival after 104 weeks was about 65 % and 50 % in males and females, respectively. The main cause of death in these animals was tumour development in the pituitary, which was consistent with earlier findings in historical controls of this laboratory (Kroese et al., 2001; Wester et al., 2012)."

It is noted that these studies of Kroese *et al.* (2001) and Wester *et al.* (2012) were used by RIVM (2001) as basis for the construction of the virtually safe dose (VSD) (see section B.5.1.11.1).

Table 12 : Incidences of tumours in liver and forestomach in male and female Wistar rats following treatment with pure BaP (5 days per week, for 104 weeks) (Kroese et al. 2001; Wester et al. 2012) (taken from: ECHA, 2019)

		Dose (mg/kg bw/d)			
		0	**3**	**10**	**30 [a]**
Females					
Forestomach	*examined*	*52*	*51*	*51*	*52*
Squamous cell papilloma		1	3	20***	25***
Squamous cell carcinoma		0	3	10**	25***
Liver	*examined*	*52*	*52*	*52*	*52*
Hepatocellular adenoma		0	2	7*	1
Hepatocellular carcinoma		0	0	32***	50***
Auditory canal [b]	*examined*	*0*	*1*	*0*	*20*
Squamous cell papilloma		0	0	0	1
Carcinoma [c]		0	0	0	13**
Males					
Forestomach	*examined*	*52*	*52*	*52*	*52*
Squamous cell papilloma		0	7*	18***	17***
Squamous cell carcinoma		0	1	25***	35***
Liver	*examined*	*52*	*52*	*52*	*52*
Hepatocellular adenoma		0	3	15***	4

Hepatocellular carcinoma		0	1	23***	45***
Auditory canal [b]	*examined*	*1*	*0*	*7*	*33*
Squamous cell papilloma		0	0	0	4
Carcinoma [c]		0	0	2	19***

[a] note that this group had a significantly shorter lifetime
[b] these tissues were examined only when abnormalities were observed upon macroscopic examination
[c] composite tumours of squamous and sebaceous cells apparently arisen from the pilosebaceous units / "Zymbal glands"
* $p<0.01$; ** $p<0.001$; *** $p<0.00001$, Fisher's exact test, analyses of tumour incidence of the auditory canal was based on n = 52

B.5.1.8.1.2: Lifetime feeding study in mice: Culp *et al*. (1998)

"*In a 2-year carcinogenicity study, female B6C3F1 mice (n= 48/group) were fed pure BaP or two different coal tar mixtures containing high amounts of several PAHs (Culp et al., 1998). Two additional groups of 48 mice each served as controls, one group was fed the standard diet, while the other was fed the standard diet treated with acetone in a manner identical to the BaP diets. The BaP diets were prepared by dissolving the appropriate amount of BaP in acetone and mixing the solution with the standard animal diet. The coal tar diets were prepared by freezing the coal tar mixtures in liquid nitrogen and blending with the appropriate amount of standard animal diet. The homogeneity of the coal tar diets was determined by measuring the amount of BaP in the sample by HPLC. Coal tar (CAS No 8007-45-2) mixture 1 was a standardised composite from seven manufactured gas plant waste sites and coal tar mixture 2 was a composite from two of the seven waste sites plus a third site having a very high BaP content. The PAH composition of the coal tar mixtures was assessed by gas chromatography/mass spectroscopy (Table 13). The BaP content was also analysed by high performance liquid chromatography (HPLC) with fluorescence detection and found to be 2240 ± 51 (mean ± SD, n = 2) mg BaP per kg coal tar for coal tar Mixture 1 and 3669 ± 134 (n = 4) mg BaP per kg coal tar for coal tar mixture 2.*"

Table 13 : Polycyclic aromatic hydrocarbon composition of coal tar mixtures [a] (taken from: ECHA, 2019)

Compound	Coal tar mixture 1 (mg/kg)	Coal tar mixture 2 (mg/kg)
Acenapthene	2049	1270
Acenaphtylene	3190	5710
Anthracene	2524	2900
Benz[*a*]anthracene	2374	3340
Benzo[*b*]fluoranthene	2097	2890
Benzo[*k*]fluoranthene	699	1010
Benzo[*g,h,i*]perylene	1493	2290
Benzo[d,e,f]chrysene	1837	2760
Chrysene	2379	2960
Dibenz[*a,h*]anthracene	267	370
Dibenzofuran	1504	1810
Fluoranthene	4965	6370
Fluorene	3692	4770
Indan	1133	490
Indeno[1,2,3-cd]pyrene	1353	1990
1-methylnaphtalene	6550	5660
2-methylnaphtalene	11289	10700
Naphthalene	22203	32300
Phenanthrene	7640	10100
Pyrene	5092	7220

"The BaP-treated animals (n = 48/group) received BaP via the diet in concentrations of 0, 5, 25 or 100 ppm (equivalent to doses of 0, 0.7, 3.6 or 14 mg/kg bw/d; assuming 1 mg/kg bw/d corresponds to 7 ppm for mice, cf. EFSA, 2008) for 2 years. In the same experiment, groups of 48 female B6C3F1 mice were fed diets containing 0, 0.01, 0.03, 0.1, 0.3, 0.6 or 1.0 % coal tar mixture 1, which contained benzo[a]pyrene at a concentration of 2240 mg/kg (equivalent to BaP doses 0.032, 0.09, 0.3, 0.96, 1.92 or 3.2 mg/kg bw/d, cf. EFSA, 2008), or 0, 0.03, 0.1 or 0.3 % of coal tar mixture 2, which contained benzo[a]pyrene at a concentration of 3669 mg/kg (equivalent to BaP doses of 0.16, 0.52 or 1.1 mg/kg bw/d, cf. EFSA, 2008).

Body weight and food consumption were evaluated. All mice, including those that died during the experiment, were examined grossly at necropsy. Organ weights were noted. A histopathological examination was made on the liver, lungs, small intestine, stomach, tongue and esophagus from all mice. In addition, a full histopathological examination was conducted on all animals in the following groups: 0.1, 0.3, 0.6 and 1.0 % coal tar mixture 1; 0.03, 0.1 and 0.3 % coal tar mixture 2; 5, 25, and 100 ppm BaP and both control groups. All gross lesions found in mice in the other dose groups were also examined histopathologically.

Food consumption, body weight and organ weights:

Food consumption was monitored every week for the first 12 weeks on dose and every 4 weeks thereafter. Mice fed 1.0 % coal tar Mixture 1 ate significantly less feed (~30 % less) than the control mice. Similarly, a significant decrease in food consumption was observed for mice fed 0.6 % coal tar Mixture 1 (~25 % less) and 0.3 % coal tar Mixture 2 (~20 % less). Intermittent decreases in food consumption were observed in the other groups fed coal tar Mixtures 1 and 2, with the effect occurring more frequently as the dose was increased. The food consumption of mice fed only BaP differed only sporadically from that of the control group.

Mice fed 0.6 % and 1.0 % coal tar Mixture 1 weighed significantly less than the control group after two weeks of treatment. The body weights of the other groups of mice fed coal tar Mixture 1 differed only sporadically from the control group throughout the entire experiment. Significant decreases in body weight were also observed in mice fed 0.3 % coal tar Mixture 2 and 100 ppm benzo[a]pyrene.

Liver, kidney and lung weights were determined in mice surviving to the end of the experiment. The livers of mice fed 0.3 % coal tar Mixture 1 or 0.3 % coal tar Mixture 2 weighed ~40 % more than the control group, a difference that was significant. None of the other treatment groups showed significant differences in liver weights. Mice fed 0.1 % coal tar Mixture 1 had decreased kidney weights compared to the controls. This trend was not evident at higher doses. Likewise, mice fed 0.03 % coal tar Mixture 1 had a significant decrease in lung weight. None of the other groups showed significant differences in lung weights.

Morbidity and mortality:
None of the mice fed 1.0 % coal tar Mixture 1 survived the treatment period. The early mortality rate for the mice fed 0.6 % coal tar Mixture 1 was also 100 %. Only 10 mice (21 %) in the 0.3 % coal tar Mixture 1 group survived to the end of the 2-year treatment, a difference that was significant (P = 0.00006) from the control group. The survival for the mice in the 0.0, 0.01, 0.03 and 0.1 % coal tar Mixture 1 dose groups was 65, 71, 69 and 63 %, respectively.

In mice fed coal tar Mixture 2, there was significantly (P = 0.00003) lower survival in the 0.3 % dose group (15 %) as compared to the control group (65 %). The survival in the remaining two dose groups was similar to the control group.

All of the mice fed 100 ppm BaP were removed from study due to morbidity or death. A significant (P = 0.0009) number of mice in the 25 ppm BaP dose group also died early. The percentage survival of mice fed 5 ppm BaP (56 %) was similar to the control group.

Tumorigenicity:
<u>BaP</u>

Significantly increased incidences of papillomas and carcinomas were observed in the forestomach, oesophagus, and tongue. The increase in incidence of neoplasms was related to dose, with high statistical significance in the 25 and 100 ppm groups. See further Table 14 for details on the tumour incidences in the BaP-treated mice."

Table 14 : Incidences of neoplasms in female B6C3F1 mice fed BaP for 2 years (Culp et al., 1998) (taken from: ECHA, 2019)

	BaP concentration (ppm) in diet				*P*-value for dose-related trend
	0	**5**	**25**	**100**	
	Corresponding BaP dose (mg/kg bw/d) [a]				
	0	*0.7*	*3.6*	*14*	
	incidences (%)				
Liver (hepatocellular adenomas)	2/48 (4)	7/48 (15)	5/47 (11)	0/45 (0)	NS [c]
Lung – alveolar/bronchiolar adenomas and/or carcinomas	5/48 (10)	0/48 (0)	4/45 (9)	0/48 (0)	NS
Forestomach – papillomas and/or carcinomas	1/48 (2)	3/47 (6)	36/46 [b] (78)	46/47 [b] (98)	<0.00001
Esophagus – papillomas and/or carcinomas	0/48 (0)	0/48 (0)	2/45 (4)	27/46 [b] (59)	0.0014
Tongue - papillomas and/or carcinomas	0/48 (0)	0/48 (0)	2/46 (4)	23/48 [b] (48)	0.0003
Larynx - papillomas and/or carcinomas	0/35 (0)	0/35 (0)	3/34 (9)	5/38 (13)	0.014
Hemangiosarcomas [d]	1/48 (2)	2/48 (4)	3/47 (6)	0/48 (0)	NS
Histiocytic sarcomas [e]	2/48 (4)	2/48 (4)	1/47 (2)	0/48 (0)	NS
Sarcomas	1/48 (2)	2/47 (4)	7/47 (15)	0/48 (0)	NS

a BaP doses are calculated assuming 1 mg/kg bw/d = 7 ppm in the diet for a mouse (cf. EFSA (2008))
b Significantly different (*P*<0.05) from control group
c NS=not significant
d organs involved include liver, mesentery and spleen
e organs involved include forestomach, glandular stomach, skin and skeletal muscle

<u>Coal tar mixtures</u>

"*Both coal tar mixtures induced a dose-dependent increase in tumours at various locations, i.e. in the liver: hepatocellular adenomas and carcinomas, in the lung: alveolar/bronchiolar adenomas and carcinomas, in the forestomach: squamous epithelial papillomas and carcinomas, in the small intestine: adenocarcinomas, histiocytic sarcomas, and, furthermore, haemangiosarcomas in multiple organs, and sarcomas. See further* Table 15 *for details on the tumour incidences in the coal tar mixture-treated mice.*
Lowest concentrations resulting in a statistically significantly increased tumour incidence was 0.3 % for mixture 1 and 0.1 % for mixture 2.

Schneider et al. (2002) used the original, unpublished raw data from Culp and co-workers in order to establish the total number of tumour-bearing animals at each dose level for the coal tar mixture-treated animals. The results can be found in Table 16*.*
This study indicated that BaP alone induced only tumours of the alimentary tract, whereas the coal tar mixtures also induced liver and lung tumours."

Table 15 : Incidences of neoplasms in female B6C3F1 mice fed coal tar mixtures I and II for 2 years (Culp et al., 1998) (taken from: ECHA, 2019)

	Mixture	**Coal tar concentration (%)**							***P*-value for dose-related trend**
		0.0	**0.01**	**0.03**	**0.1**	**0.3**	**0.6**	**1.0**	
		Incidences (%):							
Liver - hepatocellular adenomas and/or carcinomas	1	0/47 (0)	4/48 (8)	2/46 (4)	3/48 (6)	14/45 [a] (31)	1/42 (2)	5/43 (12)	0.007
	2	0/47 (0)	_ [b]	7/47 (15)	4/47 (9)	10/45 [a] (22)	_	_	0.0004
Lung –alveolar/bronchiolar adenomas and/or carcinomas	1	2/47 (4)	3/48 (6)	4/48 (8)	4/48 (8)	27/47 [a] (57)	25/47 [a] (53)	21/45 [a] (47)	<0.00001
	2	2/47 (4)	_	4/48 (8)	10/48 [a] (21)	23/47 [a] (49)	_	_	<0.00001
Forestomach – papillomas and/or carcinomas	1	0/47 (0)	2/47 (4)	6/45 (13)	3/47 (6)	14/46 [a] (30)	15/45 [a] (33)	6/41 (15)	<0.00001
	2	0/47 (0)	_	3/47 (6)	2/47 (4)	13/44 [a] (30)	_	_	<0.00001
Small intestine - adenocarinomas	1	0/47 (0)	0/46 (0)	0/45 (0)	0/47 (0)	0/42 (0)	22/36 [a] (61)	36/41 [a] (88)	<0.00001
	2	0/47 (0)	_	0/47 (0)	0/47 (0)	1/37 (3)	_	_	NS [c]
Hemangiosarcomas [d]	1	1/48 (2)	0/48 (0)	1/48 (2)	1/48 (2)	11/48 [a] (23)	17/48 [a] (35)	1/45 (2)	<0.00001
	2	1/48 (2)	_	1/48 (2)	4/48 (8)	17/48 [a] (35)	_	_	<0.00001
Histiocytic sarcomas	1	1/48 (2)	0/48 (0)	0/48 (0)	1/48 (2)	7/48 (15)	5/48 (10)	0/45 (0)	<0.00001
	2	1/48 (2)	_	3/48 (6)	2/48 (4)	11/48 [a] (23)	_	_	0.00003
Sarcomas [e]	1	1/48 (2)	4/48 (8)	3/48 (6)	2/48 (4)	7/48 (15)	1/48 (2)	2/45 (4)	0.006
	2	1/48 (2)	_	0/48 (0)	4/48 (8)	5/48 (10)	_	_	0.003

[a] significantly different (*P*<0.05) from control group
[b] not tested
[c] NS=not significant
[d] organs involved include skin, mesentery, mesenteric lymph nodes, heart spleen, urinary bladder, liver, uterus, thoracic cavity, ovary and skeletal muscle
[f] organs involved include mesentery, forestomach, skin and kidney

Table 16: Number of tumour-bearing animals in coal tar mixture treated groups (A: coal tar mixture 1, B: coal tar mixture 2). Analysis by Schneider et al. (2002), based on the study of Culp et al. (1998) (taken from: ECHA, 2019)
A

Coal tar mixture concentration in food (%)	0	0.01	0.03	0.1	0.3	0.01	1
BaP daily dose per animal (mg/kg bw/d) [a]	0	0.032	0.096	0.32	0.96	1.92	3.2
Tumour-bearing animals (%) [b]	5/48 (10)	12/48 (25)	14/48 (29)	12/48 (25)	40/48 (83)	42/48 (88)	43/48 (90)

[a] as calculated assuming 1 mg/kg bw/d corresponds to 7 ppm for mice
[b] calculated using individual animal data for tumours of the liver, lung, forestomach, small intestine, hemangiosarcomas, histiocytic sarcomas and sarcomas of the mesentery, forestomach, skin and kidney.

B

Coal tar mixture concentration in food (%)	0	0.03	0.1	0.3
BaP daily dose per animal (mg/kg bw/d)[a]	0	0.16	0.52	1.1
Tumour-bearing animals (%) [b]	5/48 (10)	17/48 (35)	23/48 (48)	44/48 (92)

[a] as calculated assuming 1 mg/kg bw/d corresponds to 7 ppm for mice
[b] calculated using individual animal data for tumours of the liver, lung, forestomach, small intestine, hemangiosarcomas, histiocytic sarcomas and sarcomas of the mesentery, forestomach, skin and kidney.

It is noted that this study of Culp *et al*. (1998) and the analysis of Schneider *et al*. (2002) were used by EFSA (2008) as basis for dose response modelling (BMDL calculation). BMD modelling was performed on the total number of tumour-bearing animals. The two tested coal tar mixtures did not produce significantly different dose-response curves and therefore the data were combined by EFSA (2008). However, the results for the animals receiving the two highest doses of coal tar mixture 1 were omitted due to premature death of all animals in these dose groups. In addition to using only BaP as marker for the carcinogenic PAHs, EFSA explored additionally the use of PAH2 (benzo[d,e,f]chrysene and chrysene), PAH4 (benzo[d,e,f]chrysene, chrysene, benz[a]anthracene, benzo[b]fluoranthene) and PAH8 (benzo[d,e,f]chrysene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, dibenz[ah]anthracene, indeno[1,2,3-cd]pyrene). The US EPA BMD software (BMDS) was used for modelling the total tumour-bearing animals and BMD10 and BMDL10 values were calculated. The Table 17 below presents the BMDL10-values for BaP, PAH2, PAH4 and PAH8.

Table 17 : $BMDL_{10}$ for BaP, PAH2, PAH4 and PAH8 (calculated by EFSA, 2008) based on total tumour-bearing animals in the 2-year carcinogenicity study on coal tar mixtures by Culp et al. (1998)

Marker	$BMDL_{10}$ (mg/kg bw/d)
BaP	0.07
EFSA PAH2	0.17
EFSA PAH4	0.34
EFSA PAH8	0.49

This study of Culp *et al*. (1998) was also used by OEHHA (2010) and US EPA (2017) as basis for dose response modelling (BMDL calculation) for BaP. BMD modelling was performed on the forestomach and oral cavity tumours in females mouse for OEHHA and on the forestomach, esophagus, tongue, larynx (alimentary tract) tumors for US EPA (see Annex B.5.1.11.1).

B.5.1.8.1.3. Lifetime feeding study in Weyand *et al*. (1995)

"Groups of female A/J mice (n=30/group) were used for a feeding experiment with pure BaP and a PAH-rich manufactured gas plant residue. This mouse strain was chosen because of its sensitivity to chemical induction of pulmonary adenomas. A negative control group was fed the basal gel diet. In addition, a non-treated group of mice and a group dosed with vehicle only were fed with a NIH-07 pellet diet and used as negative controls. A further group served as positive control and was administered pure BaP (100 mg/kg) by i.p. injection in 0.25 mL of tricaprylin. After the last exposure day (= after 260 days of diet administration), the animals were sacrificed and their lungs and stomach removed for histology (Weyand et al., 1995).

In this study, the test item was denominated as 'Manufactured Gas Plant Residue' (MGP). MGPs, commonly also referred to as coal tar, are waste by-products formed in large quantities during coal gasification. It is noted that the BaP-content of MGP is similar to the BaP-content of the one designated 'coal tar mixture 2' by Culp et al. (1998, cf. above).

<u>BaP</u>

BaP was fed at concentrations of 16 or 98 ppm in the diet, resulting in an ingested amount of 40.6 or 256.6 µg BaP/day/mouse (according to study authors), respectively (equivalent to doses of 1.624 or 10.264 mg BaP/kg bw/d, respectively, assuming a 25 g body weight). The survival rate for both treatment groups was 25/30 and 27/30, respectively. In the control group 21/30 mice survived to the end of the study. Increased numbers of tumours in the forestomach and the lung were induced after treatment with pure BaP in feed for 260 days at both concentrations. In Table 18, the incidence of forestomach and lung tumours is presented.

Table 18 : Incidences of forestomach and lung tumours in female A/J mice fed pure BaP for 260 days (Weyand et al., 1995) (taken from: ECHA, 2019)

	BaP conc in food (ppm)		
	0	**16**	**98**
	BaP intake (mg/kg bw/d)		
	0	*1.624*	*10.264*
Forestomach	0/21 (0 %)	5/25 (20 %) *	27/27 (100 %) *
Lung	4/21 (19 %)	9/25 (36 %) *	14/27 (52 %) *

*significantly different ($p<0.05$) from control, determined by x_2 test

<u>MGP</u>

MGP, which contained BaP at a concentration of 2760 mg/kg (as determined by GC-MS), was given at concentrations of 0.1 or 0.25 % in the diet, resulting in ingested amounts of 6.9 or 16.3 µg BaP/mouse/d (according to study authors), respectively, (equivalent to doses of 0.276 or 0.652 mg BaP/kg bw/d, assuming a 25 g bodyweight). The survival rate for both treatment groups was 27/30 and 29/30, respectively. Treatment with MGP induced development of tumours in the lung. No local tumours in the forestomach were noted. The effect of MGP ingestion on the development of lung tumours is given in Table 19."

Table 19 : Incidences of lung tumours in female A/J mice fed MGP for 260 days (Weyand et al., 1995) (taken from: ECHA, 2019)

	MGP conc in food (%)		
	0	**0.10**	**0.25**
	BaP intake (mg/kg bw/d)		
	0	*0.276*	*0.652*
Lung	4/21 (19 %)	19/27 (70 %) *	29/29 (100 %) *

*significantly different ($p<0.05$) from control, determined by x_2 test

B.5.1.8.2. Carcinogenicity: animal data - dermal

The assessment of carcinogenic oral studies is taken from the Annex XV restriction report for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019):

"*Five dermal carcinogenicity studies were identified as key studies: one in NMRI mice using BaP and PAH-mixtures (Schmahl et al., 1977), two studies in NMRI mice using pure BaP and individual PAHs or a condensate containing various PAHs, respectively (Habs et al., 1980+1984), a study in C3H/HeJ mice using pure BaP (Warshawsky and Barkley, 1987) and finally a study in SENCAR mice using pure BaP and extracts of soot from various sources (Nesnow et al., 1983).*"

B.5.1.8.2.1. Dermal lifetime study in mice (Schmähl *et al.*, 1977)

"*The carcinogenic action of PAH mixtures predominantly found in condensates of automobile exhaust were studied in this study. A total of four different test items was administered: pure BaP, a mixture of known carcinogenic PAHs ('C PAH', including BaP), a mixture of PAHs not considered carcinogenic by the study authors ('NC PAH'), and a combination of the latter two ('C PAH + NC PAH').*
Female NMRI mice were dermally exposed (back area) to these test items (dissolved in 0.02 mL acetone) twice weekly for their entire lifespan. Concentrations were adjusted in a way that treated animals of the BaP, C PAH, and C PAH + NC PAH groups received 1.0, 1.7, or 3.0 µg BaP (corresponding to 0.04, 0.068, or 0.12 mg BaP/kg bw/d, assuming a 25 g bodyweight) regardless of the test item used. For the NC PAH group, concentrations were used which corresponded to the proportions (by weight) of the respective PAHs relative to BaP as encountered in real-life exhaust gas condensates. In order to be able to register possible weak effects, higher doses of NC PAH were given. In addition, a concurrent control group was treated with the vehicle acetone alone. Table 20 presents an overview of the doses applied."

Table 20 : Doses (in µg) applied in skin dropping experiments, in relation to benzo[a]pyrene (Schmähl et al., 1977) (taken from: ECHA, 2019)

Controls					
Acetone		as solvent			
Benzo[d,e,f]chrysene		1.0	1.7	3.0	
C PAH					
Benzo[d,e,f]chrysene		1.0	1.7	3.0	
Dibenz[a,h]anthracene		0.7	1.2	2.1	
Benz[a]anthracene		1.4	2.4	4.2	
Benzo[e]acephenanthrylene		0.9	1.5	2.7	
	total	*4.0*	*6.8*	*12.0*	
NC PAH					
*(benzo[d,e,f]chrysene		1.0	3.0	9.0	27.0)
Phenanthrene		27.0	81.0	243.0	729.0
Anthracene		8.5	25.5	76.5	229.5
Fluoranthene		10.8	32.4	97.2	291.5
Pyrene		13.8	41.4	124.2	372.6
Chrysene		1.2	3.6	10.8	32.4
Benzo[e]pyrene		0.6	1.8	5.4	16.2
Benzo[ghi]perylene		3.1	9.3	27.9	83.7
	total	*65.0*	*195.0*	*585.0*	*1755.0*
C PAH + NC PAH					
*(benzo[d,e,f]chrysene		1.0	1.7	3.0)	
Total C PAH		4.0	6.8	12.0	
Total NC PAH		65.0	110.5	195.0	
Total C PAH + NC PAH		69.0	117.3	207.0	
Relation of C PAH: NC PAH is constantly 1:16.25					

*used as reference substance

"*The test articles were administered to the shaved skin of mice until the natural death of the animals or until the animals developed a tumour. At the start of the study, each dose group consisted of 100 animals, but spontaneous deaths and autolysis reduced the total number of animals examined in each group (Schmähl et al., 1977).*

Lifetime exposure of female NMRI mice to 1.0, 1.7, and 3.0 µg BaP/animal from various mixtures produced a dose-related increase in carcinomas and other tumours of the skin at the site of application. In Table 21 the findings are presented in detail."

Table 21 : Incidences of skin tumours (percentages in brackets) in female NMRI mice topically administered PAHs 2 d/wk for their entire lifespan (Schmähl et al., 1977) (taken from: ECHA, 2019)

Pure BaP:					
dose (µg)	**0**	**1.0**	**1.7**	**3.0**	
Skin carcinoma	0/81 (0 %)	10/77 (13 %)	25/88 (28 %)	43/81 (53 %)	
Any skin tumour	1/81 (1 %)	11/77 (14 %)	25/88 (28 %)	45/81 (56 %)	
C PAH:					
dose (µg)[a]	**0**	**4.0**	**6.8**	**12.0**	
Skin carcinoma	0/81 (0 %)	25/81 (31 %)	53/88 (60 %)	63/90 (70 %)	
Any skin tumour	1/81 (1 %)	29/81 (36 %)	57/88 (65 %)	65/90 (72 %)	
NC PAH:					
dose (µg)[a]	**0**	**65.0**	**195.0**	**585.0**	**1755.0**
Skin carcinoma	0/81 (0 %)	1/85 (1 %)	0/84 (0 %)	1/88 (1 %)	15/86 (17 %)
Any skin tumour	1/81 (1 %)	1/85 (1 %)	0/84 (0 %)	1/88 (1 %)	16/86 (19 %)
C PAH + NC PAH:					
dose (µg)[a]	**0**	**69.0**	**117.3**	**207.0**	
Skin carcinoma	0/81 (0 %)	44/89 (49 %)	54/93 (58 %)	64/93 (69 %)	
Any skin tumour	1/81 (1 %)	46/89 (52 %)	57/93 (61 %)	65/93 (70 %)	

[a] dose refers to the complete PAH mixture

The results given in the above table show clearly that PAH mixtures containing BaP and certain other PAHs will cause a higher incidence of neoplasms when administered at the same BaP exposure level. At very high doses (almost 10 times higher than the highest doses selected in the rest of the trial) the group of substances which were supposed to be non-carcinogenic also proved to be biologically effective. The whole mixture (C PAH + NC PAH)appears to be more effective than the C PAH group alone.

In this study, induction of local tumours was observed at all tested concentrations for BaP, carcinogenic PAHs and the whole mixture (C PAH + NC PAH). The lowest tested concentration of 1.0 µg BaP/animal was equivalent to 0.04 mg BaP/kg bw/d (assuming a 25 g bodyweight).

B.5.1.8.2.2 Dermal lifetime study in mice (Habs *et al*., 1980)

"*In a dermal lifetime study, pure BaP and other PAHs (benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fuoranthene, indeno[1,2,3-cd]pyrene, cyclopentadieno-[cd]pyrene, coronene) were tested with regard to local carcinogenicity by topical application to mouse skin. Groups of female NMRI mice (n=40) were topically administered 2d/wk for up to 130 weeks (except for coronene wit a 4d/wk frequency), with the individual PAHs dissolved in acetone (or DMSO in case of coronene). Table 22 presents an overview of the applied dose levels. Controls received the vehicle alone. The solutions were applied by topical dropping to the clipped dorsal skin in the interscapular area. Each application comprised 0.02 mL. All experimental animals were checked twice daily and the occurrence of tumours at the site of application was recorded. Animals at an advanced stage of macroscopically clearly infiltrative tumour growth were killed prior to their natural death (Habs et al., 1980).*"

Table 22 : Dose levels of the individual PAHs tested topically on mice (Habs et al., 1980) (taken from: ECHA, 2019)

PAH	solvent	Individual dose (µg/animal/day)			Frequency of application
		I	II	III	
Benzo[d,e,f]chrysene	acetone	1.7	2.8	4.6	2d/wk
Benzo[e]acephenanthrylene	acetone	3.4	5.6	9.2	2d/wk
Benzo[j]fluoranthene	acetone	3.4	5.6	9.2	2d/wk
Benzo[k]fuoranthene	acetone	3.4	5.6	9.2	2d/wk
Indeno[1,2,3-cd]pyrene	acetone	3.4	5.6	9.2	2d/wk
Cyclopentadieno-[cd]pyrene	acetone	1.7	6.8	27.2	2d/wk
Coronene	DMSO	5.0	15.0	4d/wk	

"A clear dose-response relationship could be established for the carcinogenic activity of pure BaP at the site of application. Control animals did not develop tumours at the site of application. Study results are summarised in Table 23. "

Table 23 : Incidence of skin tumours in female NMRI mice topically administered with various PAHs (Habs et al., 1980). See Table B 15 for details on the applied dose levels (taken from: ECHA, 2019)

		Animals with local tumours		
		incidence	percentage	Age standardized tumour frequencies (%)
Acetone		0/35	0	0.0
DMSO		0/36	0	0.0
Benzo[d,e,f]chrysene	I	8/34	23.5	24.8
	II	24/35	68.6	89.3
	III	22/36	61.1	91.7
Benzo[b]fluoranthene	I	2/38	5.3	4.6
	II	5/34	14.7	14.0
	III	20/37	54.1	65.4
Benzo[j]fluoranthene	I	1/38	2.6	1.6
	II	1/35	2.9	2.6
	III	2/38	5.3	3.5
Benzo[k]fuoranthene	I	1/39	2.6	1.7
	II	0/38	0.0	0.0
	III	0/38	0.0	0.0
Indeno[1,2,3-cd]pyrene	I	1/36	2.8	1.4
	II	0/37	0.0	0.0
	III	0/37	0.0	0.0
Cyclopentadieno-[cd]pyrene	I	0/34	0.0	0.0
	II	0/35	0.0	0.0
	III	3/38	7.9	11.0
Coronene	I	1/39	2.6	3.1
	II	2/40	5.0	6.1

"It is noted that the lowest tested concentration of 1.7 µg BaP/animal topically administered (2d/wk) for up to 130 weeks was associated with a significant increase in local tumours in female NMRI mice. Also benzo[b]fluoranthene induced local tumour formation. The dose of 1.7 µg BaP/animal is equivalent to 0.068 mg/kg bw/d (assuming a body weight of 25 g)."

B.5.1.8.2.3 Dermal lifetime study in mice (Habs *et al*., 1984)

"In a third life-time study, the carcinogenicity of condensates of the seed of Citrullus colocynthis was examined. See Table 24 for details on the PAH-content of this condensate. BaP was used as positive control. Groups of female NMRI mice were treated 2d/wk with 2 or 4 µg BaP/mouse in acetone or 15 or 60 µg condensate/mouse (corresponding to 78 or 312 pg BaP/mouse) and one solvent–treated control, each group containing 20 animals. The individual dose in the control group was 0.01 mL acetone. The solutions (0.01 mL) were applied by topical dropping to the clipped dorsal skin in the interscapular area twice a week for life. All animals were monitored twice daily and the occurrence of skin tumours was recorded. Animals in an advanced stage of macroscopically clearly invasive tumour growth were killed, all other animals were observed until their natural death (Habs et al., 1984)."

Table 24 : Concentration of PAHs in a condensate of Citrullus colocynthis seed used (Habs et al., 1984) (taken from: ECHA, 2019)

PAH	Concentration (µg/g)
Benz[a]anthracene	9.2
Chrysene and triphenylene	13.0
Fluoranthene	28.1
Pyrene	30.4
Benzofluoranthene (b+j+k)	6.7
Benzo[e]pyrene	3.8
Benzo[d,e,f]chrysene	5.2
Perylene	1.0
Indeno[1,2,3-cd]pyrene	1.6
Benzo[ghi]perylene	1.7
Anthanthrene	0.6

"*Treatment was tolerated without signs of acute or subacute toxicity. Weight development in test compound-treated mice did not differ from that in controls. Mean survival time was 691 (95 % CI: 600-763) days in the acetone control, 648 (440-729) days in the 2 µg BaP/mouse, 528 (480-555) days in the 4 µg BaP/mouse groups, 572 (407-644) in the low dose condensate group and 611 (430-673) in the high dose condensate group.*
BaP was found to be clearly carcinogenic in both tested concentrations. No skin tumours were seen in vehicle controls. The carcinogenic activity of BaP and the tested condensate after chronic epicutaneous application to female NMRI mice is presented in Table 25.*"*

Table 25 : Incidences of skin tumours in female NMRI mice topically administered with BaP for 2d/wk (Habs et al., 1984) (taken from: ECHA, 2019)

Treatment	Number (%) of animals with skin tumours		
	total	papillomas	Carcinomas
Control	0 (0)	0 (0)	0 (0)
BaP- low dose	9 (45)	2 (10)	7 (35)
BaP – high dose	17 (85)	0 (0)	17 (85)
Condensate – low dose	1 (5)	0 (0)	1 (5)
Condensate - high dose	5 (25)	2 (10)	3 (15)

"*In summary, the lowest topically administered concentration of 2 µg BaP/mouse to female NMRI mice throughout their lifetime induced statistically significant skin tumours in 9/20 animals (45 %). The concentration of 2 µg BaP/animal is equivalent to 0.08 mg/kg bw/d (assuming 25 g bodyweight).* "

B.5.1.8.2.4 Dermal lifetime study in mice (Warshawsky and Barkley 1987)

"*In a further study, relative carcinogenic potencies of three combustion products of fossil fuels (including BaP and two N-heterocyclic compounds 7H-dibenzo[cg]carbazole and dibenz[aj]acridine) were compared in carcinogenicity mouse skin bioassays (skin painting studies). In the exposure groups, 50 male C3H/HeJ mice were treated twice a week with a 0.025 % solution of the tested compounds (12.5 µg compound/animal delivered in 50 µl of acetone) applied to the interscapular region of the back for up to 99 weeks. The animals of the control group were treated with 50 µL of distilled acetone twice weekly. Hair from the backs of mice was removed with electric clippers at least two days before the first treatment and every two weeks after the first treatment. During the course of the experiment animals were observed twice daily (Warshawsky and Barkley 1987).* "

Table 26 : Incidences of skin tumours in male C3H/HeJ mice (Warshawsky and Barkley, 1987) (taken from: ECHA, 2019)

	No. mice examined	No. mice with malignant tumours	No. mice with benign tumours (only)	Average latency period (wks)
No treatment	50	0	0	-
Acetone	50	0	0	-
0.025 % dibenz[aj]acridine	50	22	3	80.3
0.025 % 7H-dibenzo[cg]carbazole	50	47	1	36.6
0.025 % BaP	50	47	1	32.4

"*Male C3H/HeJ mice administered with 12.5 µg BaP/animal for 99 weeks produced skin tumours in 48/50 mice. While in one instance a benign tumour was found, tumours were malignant in all other cases. The mean latency period in the BaP-group was 32.4 weeks.*

Assuming a body weight of 30 g/male mouse, the concentration of 12.5 µg BaP/animal is equivalent to 0.417 mg/kg bw/d."

B.5.1.8.2.5 Dermal 52-week mouse study (Nesnow *et al.*, 1983)

"*Nesnow et al. (1983) studied carcinogenic risks following skin exposure of mice to extracts of soots of various sources, namely coal chimney soot, coke oven materials, industrial carbon black, oil shale soot, and gasoline vehicle exhaust materials. Also pure BaP was tested. This study also addressed tumour initiation and tumour promotion activity of the extracts and BaP. Below only the data of the complete carcinogenesis protocol (i.e. evaluation of the production of tumours after repeated application of a carcinogen of up to 1 year) are described.*

Male and female SENCAR mice (40/sex/group) were treated topically 1/week (or twice weekly for the highest dose level). Samples of soot extracts or BaP were administered in 0.2 ml acetone for 50 to 52 weeks. Four agents were examined for their ability to act as complete carcinogens, i.e. BaP, coke over main extract, roofing tar extract, and gasoline vehicle exhaust extract.

Weekly application of 50.5 µg BaP produced a carcinoma incidence of greater than 93 %, with almost one carcinoma per mouse. Higher doses did not increase the tumour multiplicity. No carcinomas were observed in the control animals. The coke oven main sample also produced a strong complete carcinogen response in both male and female mice. Male mice seemed to be more sensitive; 98 % of the males bore approximately one carcinoma, while only 75 % of the *females responded. The roofing tar sample produced a significant response only at the highest dose applied (4 mg/mouse/week), with 25 % to 28 % of the mice bearing tumours. The gasoline vehicle exhaust extract was essentially inactive as a complete carcinogen at the doses applied. The results are presented in Table 27. "*

Table 27 : Tumours observed following administration of BaP to SENCAR mice in the complete carcinogenesis protocol (Nesnow et al., 1983) (taken from: ECHA, 2019)

Dose BaP (µg/mouse/week)	sex	Mice with carcinomas (%)a
0	M	0
0	F	0
12.6	M	10
12.6	F	8
25.2	M	63
25.2	F	43
50.5	M	93
50.5	F	98
101	M	80
101	F	90
202	M	80
202	F	93

Table 28 : Tumours observed following administration of coke oven main extract, roofing tar extract, and gasoline vehicle exhaust extract to SENCAR mice in the complete carcinogenesis protocol (Nesnow et al., 1983) (taken from: ECHA, 2019)

Dose extract (µg/mouse/week)	sex	Mice with carcinomas[a]		
		Coke over main	Roofing tar	Gasoline vehicle
100	M	5	0	0
100	F	5	0	0
500	M	36	0	0
500	F	30	0	0
1000	M	48	3	0
1000	F	60	0	0
2000	M	82	3	0
2000	F	78	8	0
4000	M	98	25	3
4000	F	75	28	5

"It is noted that this skin painting experiment with BaP (in acetone as solvent) of Nesnow et al. (1983) and the analysis of Knafla (2011) were used by ECHAs RAC as basis for establishing a dose-response relationship for the dermal route for the carcinogenicity of coal tar pitch - high temperature (ECHA 2017c)."

B.5.1.8.3. Carcinogenicity: human data

Information as presented below is taken primarily from the EU (2008), the IARC evaluation (2010), the RAC note on CTPHT (ECHA, 2017c),the previous Annex XV restriction reports for 8 PAHs in consumer products prepared by BAuA (BAuA, 2010) and for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019).

In the RAC note on CTPHT (ECHA, 2018b), ECHA concluded that "*dermal exposure may be significant to both local (skin) and systemic cancers in occupational settings. For local cancers from direct dermal contact with CTPHT in articles, BaP may again be chosen as the relevant indicator of exposure.*"

Evidence that mixtures of PAHs are carcinogenic to humans is primarily derived from occupational studies of workers following inhalation and dermal exposure. No data were located regarding cancer in humans following inhalation of individual PAH compounds. Exposure of humans to PAHs is characterised by a mixture of these compounds and other substances in either occupational or environmental situations. Therefore, it is difficult to ascertain the carcinogenicity of a single PAH component or a given mixture of PAHs, as presumably amplification of carcinogenicity may have occurred through the presence of other carcinogenic substances in the mixtures. According to IARC (2012b), no epidemiological data on benzo[d,e,f]chrysene alone were available. For oral exposure to single PAHs or PAH mixtures in humans no adequate long-term data are available.

There is a large body of epidemiological studies of PAH-exposed workers, especially in coke ovens and aluminium smelters supporting a clear excess of lung cancer, and highly suggestive of an excess of bladder cancer. Skin cancer in man is well known to have occurred following exposure to poorly refined lubricating and cutting oils.

The epidemiological studies include cohort and case-control studies with various PAH-rich sources. Exposure–response relationships for occupational PAH exposure and cancer in humans have been reviewed by several working groups of IARC (2010), US EPA (1984), WHO (1987, 1998, 2000, and 2003), and by the UK Health and Safety Executive (HSE, Armstrong *et al*., 2003, 2004). In addition to these evaluations by international committees, several additional studies have been published (Armstrong *et al*., 2009; Boffetta *et al*., 1997; Bosetti *et al*., 2007; Costantino *et al*., 1995; Mastrangelo *et al*., 1996; Moolgavkar *et al*., 1998). All of them confirm that heavy occupational exposure to mixtures of PAHs entails a substantial risk of lung, skin, or bladder cancer. The main route of occupational exposure is inhalation in most industries. However, in many cases, skin exposure represents an important route.

In the 1980s, IARC reviewed numerous epidemiological studies on PAH-exposed workers whose occupational exposure was assessed on the basis of type of employment or industrial process involved. Given the long latency between first exposure and cancer, these workers were exposed mainly during the first half of the century, when data on industrial hygiene were scarce. A definite risk of cancer was found in workers employed in the coke (lung cancer), aluminium (lung and bladder cancer), and steel industries (lung cancer), which were subsequently considered Group 1 carcinogens along with coal tar pitch, untreated and mildly treated mineral oils, and soot. On the other hand, inconsistencies between studies, lack of control of confounding factors, potential bias, and uncertainty regarding a dose-response relationship precluded any definitive conclusions for other occupational settings: roofers and asphalt workers, mechanics exposed to engine exhaust, bus and truck drivers, railroad workers, and excavator operators exposed to diesel exhaust in mines and tunnels (IARC 1983, 1984, 1985, 1989). These evaluations were updated in 2010 and further confirmed in 2012 and included also occupational exposure during coal gasification, coal tar distillation, paving and roofing with coal-tar pitch, and occupational exposure as a chimney sweep as Group 1 carcinogens (IARC 2010, 2012b).

In the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (IARC, 2010), more than 40 case-control and case-cohort studies dealing with various cancers are discussed. Their results brought a number of point estimates indicating the relation between PAH exposure and different types of cancer, and also confirmed trends between duration of exposure and/or the level of exposure and specific cancer. But when looking at interval estimates, a lot of these results were not statistically significant (e.g. Blot *et al*., 1983; Schoenberg *et al*., 1987), the 95% confidence intervals were wide (e.g. Zahm *et al*., 1989), and some of the results were based on small study samples (e.g. 3 exposed cases in the study of Grimsrud *et al*., 1998). It does not mean that the associations do not exist.

Only 1 out of 2 occupational studies confirmed skin cancer risk related with the PAH exposure from coal dust (Gallagher *et al*., 1996 cited in IARC,2010). The risk detected reached OR 1.6 (95% CI: 1.0 – 2.4) and related to squamous-cell carcinoma (Table 29).

Table 29 : Case-control studies of skin cancers and exposure to PAHs (taken from IARC, 2010)

Reference, location	Effective no. of subjects	Job/exposure category	Skin cancer subtype	No. of exposed cases	Odds ratio (95% CI)	Comments
Kubasiewicz *et al.* (1991), Poland	374 cases (1983–88), 752 population and 752 hospital controls	*Exposure to PAHs*	Any	216	1.15 [NA, *p* >0.05]	Lifetime occupational history. [poor description of study population; the results should be interpreted with caution].
		Tar		28	1.09 [NA, *p* >0.05]	
		Pitch		15	0.93 [NA, *p* >0.05]	
		Soot		29	1.22 [NA, *p* >0.05]	
		Coke		32	1.29 [NA, *p* >0.05]	
Gallagher *et al.* (1996), Canada	226 BCC cases and 180 SCC cases (1983–84), 406 population controls	Pitch tar and tar products	BCC	32	1.2 (0.7–2.1)	Lifetime occupational history; adjusted for skin and hair colour and mother's ethnicity
			SCC	27	0.9 (0.5–1.7)	
		Coal dust	BCC	67	1.4 (0.9–2.1)	
			SCC	69	1.6 (1.0–2.4)	

BCC, basal-cell carcinoma; CI, confidence interval; NA, not applied; SCC, squamous-cell carcinoma

In a review, several industries and occupations were included of which data were published before 1997 (Boffetta *et al*., 1997). Heavy exposure to PAHs entails a substantial risk for lung, skin and bladder cancer, which is not likely to be due to other carcinogenic exposure present in the same industries. The major target organ of PAH carcinogenicity was found to be the lung. The increased risk for lung cancer was present in most industries and occupations. An increased risk for skin cancer was related to high dermal exposure. However, increased risk for bladder cancer was less consistent; positive associations were mainly found in industries where workers were exposed to coal tars and coal tar pitch volatiles (e.g., aluminium production, coal gasification and tar distillation).

B.5.1.8.4. Carcinogenicity: summary, discussion and conclusion

Animal data

In numerous animal studies, the carcinogenic effects of PAHs, as single compounds or as various complex PAH-containing mixtures to which humans may be exposed, were examined by various routes of exposure. Of the PAHs under evaluation, BaP is the best-studied PAH. It is carcinogenic by all routes tested in a number of animal species. The majority of carcinogenicity studies in experimental animals were conducted as skin painting studies and a limited number of studies following ingestion were available. Oral studies with pure BaP or PAH mixtures resulted in increased tumour incidences in the gastrointestinal tract, liver, and respiratory tract in rats and mice. Dermal exposure to relative low BaP or various PAH concentrations induced benign and malign skin tumours in various strains of mice. It is noted that experimental data on the combined carcinogenicity of exact these 17 PAHs under current evaluation are not available. However, most of the 17 PAHs under current evaluation have implicitly been tested as part of the PAH mixtures in the various studies.

Human data

No data are available on the carcinogenic effects of single PAHs in humans. Most of the human studies have addressed the carcinogenicity of PAH mixtures with BaP as marker compound. A considerable number of epidemiological studies have demonstrated that occupational exposure to soot, coal tar, and other PAH-containing mixtures is carcinogenic to humans. The main route of occupational exposure is inhalation in most industries. However, in many cases, skin exposure represents an important route. However, interpretation and comparison of these data is partly hampered due to differences in study design (case control versus cohort); differences in exposure measurements; not taking into account lifestyle factors; unawareness of co-exposure; and, incomplete data presentation. Nevertheless, despite these confounding factors, the majority of the epidemiological data on PAH-exposed workers, especially in coke ovens and aluminium smelters support a clear excess of lung cancer, and are highly suggestive of an excess of bladder cancer. Skin cancer in man is well known to have occurred following exposure to poorly refined lubricating and cutting oils .

B.5.1.9. Toxicity for reproduction

BaP is classified for effects on fertility and developmental toxicity, according to Regulation (EC) No 1272/2008. However, the observed effects are threshold effects and it is considered that these thresholds will be orders of magnitude higher than potential DMELs for carcinogenicity.

Data on developmental toxicity of PAH are not relevant for this dossier.

Information as presented below is taken primarily from several evaluations from the Scientific Committee on Food (2002), WHO(1998) and EFSA (2008).

In its criteria document, the WHO discussed the reproductive toxicity of several individual PAHs, among which benzo[d,e,f]chrysene. It was concluded that this PAH had adverse effects on female fertility and reproduction (WHO, 1998).

According to Scientific Committee on Food evaluation (2002):

"There is limited or no evidence in animals on the reproductive toxicity of individual PAH, other than benzo[a]pyrene and naphthalene. In oral studies, benzo[a]pyrene was without effects on reproductive capacity in a single generation study in mice up to 133 mg/kg bw/day via the diet, but impaired fertility was seen in the offspring of female mice given >10 mg/kg bw/day by gavage. A NOAEL for this effect has not been established. A single, poorly reported study in the rat, in which benzo[a]pyrene was given in the diet at a level of 1000 mg/kg diet (corresponding to an intake of 50 mg benzo[a]pyrene/kg bw/day), reported an effect on fertility. Intraperitoneal administration of benzo[a]pyrene resulted in toxicity to the ovary (destruction of primordial

oocytes, reduced ovarian weight). An oral study with acenaphthene has shown reduced ovarian weight at a high dose of 700 mg/kg bw/day."

B.5.1.10. Other effects

Immunosuppressive effects

According to Scientific Committee on Food (2002) :

"The immunotoxicity of PAH has been known for a number of years (Malmgren et al., 1952). The immunotoxic effect most often reported following exposure to PAH is immunosuppression. A few reports also deal with immunopotentiation (stimulation) either in vitro or following inhalation or topical exposure. Immunosuppression is associated with an increased susceptibility of the exposed individuals to the development of cancers or infectious diseases, whereas immunopotentiation results in an increased secretion of cytokines by immune cells, thus leading to inflammation which in turn and under specific circumstances may facilitate tumour development or expression of hypersensitivity (allergy, contact hypersensitivity) or auto immunity (Burchiel and Luster, 2001). It should be noted that most studies on the immunotoxicity of PAH have used parenteral administration and that most of the available data consider only a few selected substances, benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene being most widely used.

Two main mechanisms have been suggested as promoting PAH-induced immunosuppression. One involves the reactivity of PAH with the Ah receptor and the other their capacity to increase the intracellular calcium concentration in immune cells possibly due to protein tyrosine kinase activation by PAH. In any case, antigen and mitogen receptor signaling pathways are altered leading to proliferation and/or death (apoptosis) of immune cells (Burchiel and Luster, 2001; Near et al., 1999; Krieger et al., 1994; Davila et al., 1995; Mounho et al., 1997)."

Endocrine disruptor

DHI Water and Environment for European Commission (2007) evaluated endocrine-related disrupting effects on humans and wildlife. This evaluation has resulted in categorisation of the substances based on the following screening criteria : relevance of test parameter, test reliability, dose-response relationship or indications of effect thresholds, endocrine disruption potency, endocrine disruption structure-activity relationship, comparison with systemic toxicity.

The presence of PAHs on the following lists was also considered :

- The Endocrine Disruption Exchange Inc (TEDX[22]): The purpose of this list is to present chemicals for which at least one study showing an effect on the endocrine system has been published in order to improve information for scientists, managers and the public. As of September 2018, nearly 1,400 substances were listed as EDs on the TEDX list.
- The Sin List[23] (Substitute It Now). The NGO ChemSec has identified substances that meet the criteria for Substances of Very High Concern (SVHC) as defined in the REACH

[22] https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list

[23] http://sinlist.chemsec.org/

regulation. Among them, 3 categories of substances are included: CMR substances, substances that are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) and substances of equivalent concern including EDs (last update: November 2019). The inclusion of a substance on the SIN list as an ED is based on a converging set of arguments (in vivo and/or in vitro toxicology and/or ecotoxicology studies, the EU classification of the substance, etc.). As of November 201, 991 substances were listed on the TEDX list ans 127 as suspected EDs.

Table 30: Endocrine disrupting effect of polycyclic aromatic hydrocarbons: overview of evaluations (website consulted 28/08/2020)

Chemical (CAS number)	CE (2007) [a]	TEDX list	SIN list
Benzo[d,e,f]chrysene (50-32-8)	Cat. 1 (cat. 1 for human health and cat. 2 for wildlife)	Yes	No
Benzo[e]pyrene (192-97-2)	N	Yes	No
Benz[a]anthracene (56-55-3)	Cat. 2 (cat. 2 for Human health and cat. 2 for Wildlife)	Yes	No
Dibenz[a,h]anthracene (53-70-3)	-	Yes	No
Benzo[e]acephenanthrylene(205-99-2)	-	Yes	No
Benzo[j]fluoranthene (205-82-3)	-	Yes	No
Benzo[k]fluoranthene (207-08-9)	-	Yes	No
Chrysene (218-01-9)	-	Yes	No
Benzo[g,h,i]perylene (191-24-2)	-	No	No
5-methylchrysene (3697-24-3)	-	Yes	No
Indeno[1,2,3-cd]pyrene (193-39-5)	-	Yes	No
Dibenzo[def,p]chrysene (191-30-0)	-	Yes	No
Naphtho[1,2,3,4-def]chrysene (192-65-4)	-	Yes	No
Benzo[r,s,t]pentaphene (189-55-9)	-	Yes	No
Dibenzo[b,def]chrysene (189-64-0)	-	Yes	No
Benzo[c]fluorine (205-12-9)	-	No	No
Cyclopenta[c,d]pyrene (27208-37-3)	-	Yes	No

- : Not studied

[a] Cat 1 : at least one in-vivo study providing clear evidence for endocrine disruption in an intact organism; cat. 2 : potential for endocrine disruption . *In-vitro* data indicating potential for endocrine disruption in intact organisms. Also includes effects *in-vivo* that may, or may not, be ED-mediated; Cat 3a : No scientific basis for inclusion in list; cat. 3b : substances with no or insufficient data gathered

B.5.1.11. Derivation of DMELs

For PAHs, only the HRVs of the reference compound, benzo[def]chrysene (BaP), were identified. Indeed, the toxicity of only a limited number of PAHs is currently known. Some PAHs, primarily those with a low molecular weight, induce systemic non-carcinogenic threshold effects (mainly kidney, liver and blood disorders) for which HRVs have been established. Other PAHs, in particular those with a high molecular weight, appear to be carcinogenic and genotoxic. BaP was considered as a marker of PAH exposure and carcinogenic effects (WHO-IPCS, 1998) (see section B.5.1.8.4).

B.5.1.11.1. Dermal DMEL

Taking into account the close contact of single-use baby diapers with the buttocks, the use of dermal HRVs seemed appropriate. It is noted that selecting the oral study of Culp *et al*. (1998)

for evaluation of the dermal (systemic) route may introduce uncertainty to the risk assessment as route-to-route extrapolation is needed. Further, it is noted that dermal (systemic) exposure is reflected in the dose-response relationship derived from the epidemiological studies (see section B.1.5.8.3.).

With respect to dermal-local exposure, carcinogenicity data on PAHs are available and several dermal DMEL was derived: Sullivan *et al.* (1991 cited by Knafla *et al*., 2011), LaGoy and Quirck (1994), Hussain *et al.* (1998), Knafla *et al.* (2006), Knafla *et al*. (2011) and BAuA (2010) (Table 31).

Table 31: No threshold dermal HRV and DMEL for BaP or PAHs

Substances	**BaP**	**BaP**	**BaP**	**BaP**	**BaP**	**PAHs**	
Organism/reference	**Sullivan *et al.***	**LaGoy and Quirk**	**Hussain *et al.***	**Knafla *et al.***	**Knafla *et al.***	**BAuA**	
year	1991	1994	1998	2006	2011	2010	
Type of value	Slope factor					DMEL	
Value	$6.6x10^3$ (mg/cm²/day)$^{-1}$	0.76 (µg/animal/day)$^{-1}$	37,47 (mg/ kg/day)$^{-1}$	25 (mg/kg/day)$^{-1}$	3.5 (µg/cm²/day)$^{-1}$	0.1 – 30 ng/kg bw/d	10^{-5} risk level: 0.03 – 10 ng/kg bw/d 10^{-6} risk level: 0.004 – 1 ng/kg bw/d
critical effect	Skin tumors (carcinomas)			Skin tumors		Tumors (skin, lung, any site)	
Species	NMRI mouse			mouse	mouse	Rat or mouse	
Exposure time	2 x/wk; entire lifespan			1 or 2×/wk; between 52 to lifetime depending on the studies	1 or 2 x/wk; 50-52 wks	Oral : 7 d/wk; 104 wk or 260 d Dermal : 2/wk; lifetime or 78 wk Inhalation : 17h/d, 5 d/w, 10 or 20 months; 16 h/d, 5 d/wk 44 wk	
Exposure route	Mouse skin-paiting bioassay			Dermal	Dermal	Dermal, oral and inhalation	
Dose descriptor, adjustment and construction	No information available	Low-dose linear extrapolation (LMS) → $2.3x10^4$ (mg/cm²/day)$^{-1}$ → 30 cm²	Low-dose linear extrapolation (Model-Free Extrapolation (MFX) computer model (Krewski *et al.*, 1991))	$BMD_{05}L_{95}$ = Low-dose linear extrapolation (LMS) Average slope factor = 0.55 (µg/animal day)$^{-1}$ → dose-equivalent slope factor	$BMD_{05}L_{95}$ = Low-dose linear extrapolation slope factor = 0.58 (µg/animal day)$^{-1}$ → 6 cm²	BMDL ou T25 Large assessment factor	BMD10, $BMDL_{10}$ ou T25 Low-dose linear extrapolation (probit model and LMS)
Key study	Schmähl *et al*. (1977)			Levin et *al.* (1977) ; Habs *et al*. (1980, 1984) ; Schmahl *et al*. (1977) ; Nesnow *et al.* (1983) ; Grimmer *et al.* (1983, 1985)	Nesnow *et al.* (1983)	Culp *et al.* (1998) ; Weyand *et al*. (1995) ; Schneider *et al.* (2002) ; Schmähl *et al.* (1977) ; FhI (1997); Heinrich *et al*. (1994); Schulte *et al*. (1994)	

LMS : linearized multistage model

Sullivan *et al*. (1991), LaGoy and Quirck (1994) and Hussain *et al*. (1998) proposed dermal slope factor derived from the Schmähl *et al*. (1977) mouse skin painting study. In this study, three groups of 100 mice per group were dermally exposed to BaP at doses of 1.0, 1.7, and 3.0 µg/cm² (0.0064; 0.0109 and 0.0191 mg/kg bw/day) twice weekly for their entire lifespan. A group of 100 mice, treated with acetone, served as the controls. The following incidence of skin tumors (carcinomas) was observed in the study at each of the treatment doses : 0/81 at 0; 10/77 at 0.0064; 25/88 at 0.0109 and 43/81 at 0.0191 mg/kg bw/day). Sullivan *et al*. derived a slope factor of $6.6x10^3$ (mg/cm²/day)$^{-1}$. "*Hussain et al. (1998) converted the Schmähl et al. (1977) dataset to a mg/kg day dose basis using an assumed mouse body weight of 45 g and applied the Krewski et al. (1991) model free extrapolation approach to derive a cancer slope factor of 0.0375 (µg/kg/day)$^{-1}$. LaGoy and Quirk (1994) calculated a cancer slope factor of 0.76 (µg/animal day)$^{-1}$ based on an amortized dose and the linearized multistage model (LMS)*" (Schnafla *et al*., 2006).

Knafla *et al*. (2006) proposed a dermal slope factor of 25 (mg/kg bw/day)$^{-1}$ for BaP. This slope factor was based on seven relevant animal studies. "*The studies identified in the literature were evaluated for goodness of design (i.e., use of control groups, adequate dose spacing, clear identification of dose levels, presence of a dose-response relationship, statistically significant differences compared to controls). Those which met these criteria were selected for evaluation of their suitability for derivation of a dermal cancer slope factor that can be used to assess human risk from carcinogenic PAHs. […] Studies based on a two stage model of carcinogenesis (i.e., initiation–promotion) were not considered, since they typically involved application of a powerful tumour promoting agent […] to which humans are not typically exposed dermally in the environment, and thus complete carcinogenicity studies were preferentially used*. *This selection criterion eliminated a substantial portion of the BaP skin cancer database from further consideration. Finally, studies that considered only a single dose in addition to the control were not considered, which also eliminated a significant portion of th available database. The studies selected for analysis also involved the application of BaP to skin in an acetone or acetone/DMSO vehicle. These vehicles will increase the solubility of BaP and thus may lead to greater dermal penetration than might occur for environmentally exposed humans. This may lead to an overestimation of potential human health risks from dermal exposures to BaP"* (Knafla *et al.,* 2006) (Table 32).

This cancer slope factor was developed using the benchmark dose approach and the linearised multistage model. The upper 95th CI at the 5% effect level above background incidence (BMR) was used as the point of departure for low-dose linear extrapolation. "*US EPA (2000) stated typical convention for calculating a BMDL is to use the upper 95th confidence interval of the 10% effect level for a dichotomous cancer endpoint (e.g., 10% of the animals in an exposed group demonstrating skin carcinomas above the background incidence)*. Knafla *et al.* choose a Benchmark response (BMR) of 5% instead of the 10% used usually by US EPA. Indeed, "*the background incidence of skin carcinomas was zero in all cases. Thus, use of a BMDL incidence lower than 10% from data in these studies will be readily distinguishable from background incidence (which is zero) and is not expected to result in any additional confounding factors."* The following table summarises key parameters of the studies upon which the dermal cancer slope factor was derived, BMD modelling and slope factors. An average dermal cancer slope factor of 0.55 (µg/animal/day)$^{-1}$ was then converted to a dose-equivalent slope factor of 25 (mg/kg bw/day)$^{-1}$ based on an adult mouse body weight of 45 g.

Table 32 : Dermal studies of BaP considered for calculation of dermal cancer slope factor, Benchmark dose calculations and slope factors (adapted Knafla et al., 2006)

Reference	Tested material	Mouse strain and sex	Application rate	Dosing Duration	BMD_5 (µg/animal /day)$^{-1}$	BMD_5L (µg/animal /day)$^{-1}$	Slope factor (µg/animal /day)$^{-1}$
Levin *et al.* (1977)	BaP and several benzo-ring derivatives of BaP	C57BL/6J (Female)	1×/2 weeks	60 weeks	not used, due to the limited number of dose levels (i.e., two levels in addition to the control) reported		
Habs *et al.* (1980)	BaP, benzo[*b*]- (BbF), benzo[*j*]- (BjF), and benzo[*k*]-fluoranthene (BkF), indeno[1,2,3,-*cd*] pyrene (IP), cyclopentadieno(*cd*)pyrene (CP), and coronene (COR)	NMRI (Female)	2×/week	130 weeks (lifetime)			
Habs *et al.* (1984)	Condensate from coloquint seeds (*Citrullus colocynthis*)	NMRI (Female)	2×/week	130 weeks (lifetime)			
Schmahl *et al.* (1977)	Automobile exhaust gas condensates	NMRI (Female)	2×/week	Lifetime	0.127	0.0693	0.72
Nesnow *et al.* (1983)	Extracts of soot from various sources	SENCAR (Female)	1×/week	50 – 52 weeks	1.49	0.691	0.58*
		SENCAR (Male)			0.949	0.457	n.c.
Grimmer *et al.* (1985)	Flue gas condensate from briquet-fired residential furnaces	CFLP (Female)	2×/week	104 weeks (lifetime)	0.0866	0.0743	n.c.
Grimmer *et al.* (1983)	Automobile exhaust gas condensates	CFLP (Female)	2×/week	104 weeks (lifetime)	0.234	0.143	0.35
Average							0.55

n.c. : not calculated due to a poor model fi with measured tumor incidence data.* Adjusted for less than lifetime exposure by multiplying by (730/365).

"Knafla et al. (2011) extended the earlier work to develop another dermal slope factor for BaP of 3.5 (µg BaP/cm_2/day)$^{-1}$ derived as a per-unit skin surface area, based on a mouse skin painting study of Nesnow et al. (1983). Another two complete carcinogenicity assay studies on mice were

considered (Schmahl et al., 1977; Grimmer at al., 1983), but these did not report the surface area to which BaP was applied (Knafla et al., 2011).

Table 33 : Summary of Cancer Bioassay Studies used to determine dermal slope factor of B[a]P (adapted from Knafla et al., 2011)

Study	Slope factor[a] (µg/animal)$^{-1}$	Surface area (cm²)	Slope factor[b] (µg/cm²/d)$^{-1}$
Schmahl *et al*. (1977)	0.72	nr	nc
Grimmer *et al*. (1983)	0.35	nr	nc
Nesnow *et al.* (1983)	0.58	6[b]	3.5

[a] From Knafla *et al*. (2006) – dose is on a per day basis; [b] Estimed surface area of application based on pers. comm., Nesnow, S.

Nesnow et al. (1983) studied carcinogenic risks following skin exposure of mice to samples of soot of various sources, namely coal chimney soot, coke oven materials, industrial carbon black, oil shale soot, and gasoline vehicle exhaust materials. Compositional similarity of these materials to CTPHT can hardly be determined, however, it is still regarded as relevant as these materials contain significant levels of various PAHs (reported e.g. for coke oven materials by Kirton and Crisp, 1989) which may be rapidly absorbed into the epidermis and further metabolized into reactive BaP metabolites that form stable adducts. Thus, BaP (and other PAHs) have the potential to exert carcinogenic activity in the epidermis – a portal of entry effect for dermal exposure, where the epidermis is the target tissue (Knafla et al., 2011).

The available skin painting studies in mice suggest that skin metabolism of BaP leading to adduct-forming metabolites is equivalent between humans and mice. An adjustment was made for differences in epidermal thickness between humans and mice. The skin cancer slope factor was derived from studies where a mouse either exhibited a tumour or did not, a function oftumour incidence (Knafla 2011).

It is noted that ECHA's committee (RAC) choose the dermal slope factor derived by Knafla *et al.* (2011) for the dermal-local route a dose-response relationship for the carcinogenicity of CTPHT (ECHA 2018).

In the restriction of PAHs in consumer products, BAuA (2010) derived several dermal DMEL for BaP using T25 or BMD calculations:

" For the calculations based on T25 as dose descriptor, a total of 11 dose-response relationships from as many different experiments were evaluated, including 5 studies with oral, 3 with dermal, and 3 with inhalation application. The three inhalation studies could not be used for the calculations based on BMD_{10}/$BMDL_{10}$, as for these descriptors, a study design using 3 treated groups + control is required."

"The following criteria were then applied to further limit the number of selectable studies and – within these studies, endpoints - for DMEL calculation:

1. *Only studies, in which BaP was administered as the component of a mixture of PAHs, were considered for the following two reasons: a) As regards the carcinogenic potential of PAH mixtures of varying composition, studies with BaP alone are not considered representative of the problems addressed in this dossier, aiming at regulating a total of*

eight PAHs in articles which even contain a multitude of other PAHs (some of which may be even more potent carcinogens); b) T25 or BMD values obtained from carcinogenicity studies performed with BaP alone tended to be clearly higher than those from studies using mixtures (mostly tar preparations of different origin), even when both were based on BaP content

2. *Studies with strong deficits in experimental design and/or reporting were only considered, if meaningful results could be obtained in spite of these flaws.*
3. *Within a study that had been selected in step 1 only endpoints were considered, for which a 'meaningful' dose-response relationship could be established, which was assumed to be the case if: a) at least 3 dose levels in addition to a concurrent control could be obtained. Studies with only two dose levels + control were ruled out for BMD calculation by definition and were only used for T25 calculations, if the range of net tumour incidences observed included the net 25 increase, i. e. when an experimental value was obtained above the potential T25. Studies with only one dose level in addition to control were not used; b) ideally, response increased monotonously with dose ; c) ideally, if the highest observed substance-related net increase in incidence was above 50 %".*

"For each of the selected studies (where appropriate) T25, BMD_{10}, and $BMDL_{10}$ estimates were used as dose descriptors. For all of these descriptors (thus, for each of the studies) DMELs were calculated applying both the 'Large Assessment Factor' and the 'Linearised' approach (the latter at both the 10^{-5} and 10^{-6} risk levels and using the 'Probit' as well as the 'Multistage Cancer' algorithms for curve fitting). A commonly used approach would have been to derive a final DMEL from that study considered the most sensitive (or otherwise most relevant), i. e. the 'key study'." The following table summarises T25, BMD_{10}, and $BMD_{10}L$ estimates and dermal DMELs obtained by using these different dose descriptors. Because BAuA (2010) excluded Probit calculations[24], BMD_{10} and $BMD_{10}L$ using the Probit model are not included in the following table because BAuA (2010).

[24] "*In the particular case of the calculations using the BMDL10 dose descriptor and the Probit fitting model, even values from the upper fg/kg bw/d range up to about 30 ng/kg bw/d were obtained (4 orders of magnitude). However, as the Multistage Cancer model is the approach recommended by the REACH IR/CSA guidance, the very low values obtained by the Probit approach are not considered further in this dossier*." (BAuA, 2010)

Table 34: Dermal DMELs obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All dose levels in mg BaP/kg bw/d, DMEL in ng BaP/kg bw/d (adapted from BAuA, 2010)

Reference	Test item	Route	Species	Site/type of tumour	Modifications factors		Assessment factor		T25					BMD – multi stage cancer				BMDL – multi stage cancer			
					Lifetime	Schedule	AS*	BA**	Dose level used for T25 calculation	T25	Linearised DMEL 10^{-5}	Linearised DMEL 10^{-6}	Large AF DMEL	BMD_{10}	Linearised DMEL 10^{-5}	Linearised DMEL 10^{-6}	Large AF DMEL	$BMDL_{10}$	Linearised DMEL 10^{-5}	Linearised DMEL 10^{-6}	Large AF
Culp *et al*. (1998)	CMT 1	Oral	Mouse	Lung	1	1	7	1/2.5	0.858	0.386	5.512	0.552	15.44	0.298	10.629	1.063	29.761	0.238	8.511	0.851	23.829
	CMT 1								0.481	0.694	9.921	0.992	27.780	0.0282	10.081	1.008	28.228	0.183	6.552	0.655	18.347
Weyand *et al*. (1995)	MGP				260/730	1			0.276	0.108	0.554	0.055	1.551	/				/			
Schneider *et al*. (2002)	CTM 1			Any site	1	1			0.086	0.103	1.467	0.147	5.109	0.102	3.639	0.364	10.189	0.083	2.977	0.298	8.336
	CTM2								0.143	0.128	1.830	0.183	5.124	0.084	2.984	0.298	8.356	0.057	2.031	0.203	5.687
Schmähl *et al.* (1977)	C PAH	dermal		Skin carcinoma	1	2/7			0.068	0.028	0.115	0.012	0.323	0.010	0.098	0.010	0.275	0.008	0.085	0.009	0.239
	C PAM + NC PAH								0.040	0.020	0.083	0.008	0.231	0.009	0.088	0.009	0.246	0.008	0.077	0.008	0.216
FhI (1997)	Creosote			Skin – any tumour	78/104	2/7			0.009	0.016	0.047	0.005	0.133	0.006	0.046	0.005	.0129	0.005	0.035	0.004	0.099
Heinrich *et al.* (1994)	CTP	Inhalation	Rat	Lung	1/3	5/7	4		0.034	0.022	0.130	0.013	0.209	/				/			
	CTP				2/3	5/7	4		0.034	0.009	0.104	0.01	0.167	/				/			
Schulte *et al.* 1994)	CTP		Mouse	Lung adenoma	44/104	5/7	7		0.077	0.019	0.083	0.008	0.232	/				/			

* Allometric scaling; ** Bioavailability factor in order to account for the assumption of 50 % absorption across all routes in animal experiments using organic solvents as vehicle vs. 20 % absorption in the human exposure situation (dermal absorption from a sweat matrice

Table 35 above "*shows, that of the two main approaches presented in the REACH IR/CSA guidance R.8, i. e. the T25-based linearised approach at the 10^{-6} risk level and the BMD_{10}-based large assessment factor (or 'EFSA') approach using the Multistage Cancer model, the latter leads to estimates which are less conservative by a factor of ca. 30 in the present case (when comparing the upper limits of the corresponding DMEL ranges).*

Conversely, the choice of dose descriptor (T25/BMD_{10}/$BMDL_{10}$) did not impact significantly on the outcome of the calculations."

"*The following DMEL results ranges (excluding the Probit calculations) were obtained:*

Large Assessment Factor approach: 0.1 – 30 ng/kg bw/d

Linearised Approach, 10^{-5} risk level: 0.03 – 10 ng/kg bw/d

Linearised Approach, 10^{-6} risk level: 0.004 – 1 ng/kg bw/d

The boundaries of these ranges roughly represent the results from the most (lower boundaries) and least (upper boundaries) sensitive studies, respectively. Instead of taking the most sensitive DMEL from a single study forward to quantitative risk characterisation, the whole range of DMELs using different approaches were accounted for."

Table 35 : Overview of dermal DMEL ranges obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All values in ng/kg bw/d (adaptaed from BAuA, 2010)

		All studies			Only dermal studies		
Method		**Lowest valur**	**Highest value**	**Hig/Low ratio**	**C PAH (Schmälh *et al.*, 1977)**	**C PAH + NC PAH (Schmälh *et al.*, 1977)**	**Creosote (Fhi, 1997)**
T25	linearised approche, 10^{-5} risk level	0.047	9.921	211	0.115	0.083	0.047
	linearised approche, 10^{-6} risk level	0.005	0.992	198	0.012	0.008	0.005
	large assessment factor	0.133	27.780	209	0.323	0.231	0.133
BMD_{10} (LMS)	linearised approche, 10^{-5} risk level	0.046	10.629	231	0.098	0.088	0.046
	linearised approche, 10^{-6} risk level	0.005	1.063	213	0.01	0.009	0.005
	large assessment factor	0.129	29.761	231	0.275	0.246	0.129
$BMD_{10}L$ (LMS)	linearised approche, 10^{-5} risk level	0.035	8.511	243	0.085	0.077	0.035
	linearised approche, 10^{-6} risk level	0.004	0.851	213	0.009	0.008	0.004
	large assessment factor	0.099	23.829	241	0.239	0.216	0.099
All calculations		$1.3x10^{-5}$	29.761	229			

Taking into account the unit of the slope factor and the exposure data available, using slope factor derived by Sullivan *et al*. (1991), Laroy and Quirck (1994) and Knafla *et al*. (2011) was not possible in the current restriction proposal. The Dossier submitter did not choose the slope factor derived by Hussain *et al*. (1998) because of the lack of information on the derivation.

Because the dermal route is a relevant exposure route in this restriction proposal, the Dossier Submitter gives preference to the derivation of DMEL from dermal studies for PAHs mixture. If only dermal studies were considered, the following DMEL results ranges for PAHs mixture derived by BAuA were obtained (Table 35):

Range for linearised approche, 10^{-5} risk level: 0.035 – 0,115 ng/kg bw/d

Range for linearised approche, 10^{-6} risk level: 0,004 - 0.012 ng/kg bw/d

Range for large assessment factor : 0,099 – 0.323 ng/kg bw/d

The Dossier Submitter choose BMD approach because this approach is based on a modeling of the experimental data taking into account all available information on the dose response curve whereas T25 is calculated from one data point on the dose-response curve. The Dossier submitter choose BMDL as dose descriptor because the BMDL is the lowest statistically significant increased incidence that can be measured in most studies, and would normally require little or no extrapolation outside the observed experimental data.

The Dossier submitter used BMDL derived by Knafla *et al*. (2006) to propose DMELs for BaP alone following REACh guidance R8 (ECHA 2012) (Table 36). DMEL ranges are 0.004 – 0.009 ng/kg bw/day for PAHs mixture and 0.006 – 0.029 ng/kg bw/day for BaP.

The Dossier Submitter selected two DMELs (10^{-6} risk level) to assess health risks:

- **for PAH mixture, a DMEL of 0.004 ng/kg bw/d (BAuA, 2010, considering only dermal studies) (most conservative DMEL but all DMELs are in the order of magnitude),**
- **for BaP alone, a DMEL of 0.006 ng/kg bw/d (derived from Knafla *et al.*, 2006) (most conservative DMEL).**

Table 36 : Overview of dermal DMEL ranges obtained by using the different calculation methods featured in the REACH Guidance on Information Requirements. All values in ng/kg bw/d (adaptaed from BAuA, 2010)

		All studies			Only dermal studies		
Method		**Lowest valur**	**Highest value**	**Hig/Low ratio**	**C PAH (Schmälh *et al.*, 1977)**	**C PAH + NC PAH (Schmälh *et al.*, 1977)**	**Creosote (Fhi, 1997)**
T25	linearised approche, 10^{-5} risk level	0.047	9.921	211	0.115	0.083	0.047
	linearised approche, 10^{-6} risk level	0.005	0.992	198	0.012	0.008	0.005
	large assessment factor	0.133	27.780	209	0.323	0.231	0.133
BMD_{10} (LMS)	linearised approche, 10^{-5} risk level	0.046	10.629	231	0.098	0.088	0.046
	linearised approche, 10^{-6} risk level	0.005	1.063	213	0.01	0.009	0.005
	large assessment factor	0.129	29.761	231	0.275	0.246	0.129
$BMD_{10}L$ (LMS)	linearised approche, 10^{-5} risk level	0.035	8.511	243	0.085	0.077	0.035
	linearised approche, 10^{-6} risk level	0.004	0.851	213	0.009	0.008	0.004
	large assessment factor	0.099	23.829	241	0.239	0.216	0.099
All calculations		1.3×10^{-5}	29.761	229			

Table 37 : Dermal DMEL derived for BaP from Knafla et al. (2006)

Reference	Species	Site/type of tumour	BMR	Multi stage cancer; BMDS software				Modifications factors		HBMDL (mg/kg bw/day)	Assessment factor		High to low dose risk extrapolation factor	DMEL 10^{-6} (ng/kg bw/d)
				BMD (µg/animal/day)	**BMDL (µg/animal/day)**	**BMD (mg/kg bw/day)*** **	**BMDL (mg/kg bw/day)**	**Lifetime**	**Schedule**		**AS***	**BA*** *		
Schmähl *et al.* (1977)	Mouse	Skin carcinoma	5%	0.127	0.0693	0.005	0.003	1	2/7	0.0008	7	1/ 2.5	50.000	0.006
Nesnow *et al.* (1983)	Mouse (Female data only)			1.49	0.691	0.059	0.028	52/104	1/7	0.004				0.029
Grimmer *et al.* (1983)	Mouse			0.234	0.143	0.009	0.006	1	2/7	0.002				0.014

- * Allometric scaling; ** Bioavailability factor in order to account for the assumption of 50 % absorption across all routes in animal experiments using organic solvents as vehicle vs. 20 % absorption in the human exposure situation (dermal absorption from a sweat matrix); *** assuming a 25 g bodyweight

B.5.1.11.2. Age-dependent adjustment factor (ADAF)

An additional factor when using an animal study to calculate cancer risks for young children is that a standard carcinogenicity study only exposes the laboratory animals to the substance starting from the age of around 6-8 weeks. This corresponds approximately to the period of adolescence in the case of humans. The consequence is that such a study does not provide any information about exposure in the preceding period. In the US, OEHHA and US EPA apply a specific factor to calculate carcinogenic risks in children (age-dependent adjustment factor or ADAF for the US EPA, age-sensivity factor or ASF for OEHHA) (US EPA, 2005; OEHHA, 2009). The value of the ADAF should preferably be determined based on substance-specific information; otherwise it is, by default , 10 for the 0 to 2 years old group and three for the 2 to 16 years old group. The default ADAF for people aged 16 and up is one (US EPA, 2005; OEHHA, 2009). This factor does not apply when establishing the TRV but rather when calculating the risk. For BaP, OEHHA (2000) recommend to apply this factor for all carcinogens, including BaP, unless chemical-specific data exist that could be used to make more specific adjustments to risk. Furthermore, in 2017, US EPA chose also to apply this ADAF. “ *The oral slope factor for benzo[a]pyrene is derived with the intention that it will be paired with EPA’s relative potency factors for the assessment of the carcinogenicity of PAH mixtures. In addition, regarding the assessment of early life exposures, because cancer risk values calculated for benzo[a]pyrene were derived from adult animal exposures, and because benzo[a]pyrene carcinogenicity occurs via a mutagenic mode of action, exposures that occur during development should include the application of ADAFs”.*

This issue has also been noted by the EU Scientific Committees in their evaluation of the existing risk assessment methodologies and approaches for genotoxic carcinogens (SCHER/SCCP/SCENIHR, 2009), though no clear decision or recommendation was presented. EFSA (2005) has also taken this issue into consideration in their opinion on the Margin of Exposure (MoE)-approach (EFSA, 2005) and concludes that the usual default factor for inter- and intra-species differences of 10×10 for non-genotoxic substances would also be relevant for substances which are both genotoxic and carcinogenic. According to EFSA, these default factors could be reduced or increased when appropriate chemical specific data are available. The MOE approach does however not lead to explicit conclusions (quantitatively) about the excess cancer risk. However, EFSA does assert that an MOE of 10,000 or higher would indicate a ‘low concern from a public health point of view’.

When using the linear extrapolation method, it is generally assumed that applying the high-to-low dosage factor results in an assessment which is sufficiently conservative to cover intraspecies differences as well. Some doubts have been expressed on this assumption. For example, the high-to-low dosage factor is argued to only correct for a 10 % risk in animals to e.g. a 0.0001 % risk in animals. Recommendations have therefore been made to apply the interspecies and intraspecies factors to carcinogenic substances by default, similarly to the risk assessment of non-carcinogenic substances, in addition to the high-to-low dosage factor (Slob *et al*., 2014). As is the case for non-carcinogenic substances, the default intraspecies factor of 10 should in that case be included to cover also any differences in sensitivity as a consequence of “early-life exposure”.

However, within Europe, there is no general agreement (based on any regulatory framework, including REACH) on how to deal with the issue of 'early-life exposure' in the quantitative risk assessment of carcinogenic substances based on an animal study. For that reason, it was decided to follow the approach as described in the ECHA Guidance (ECHA, 2012) and not to apply ADAF in the risk calculation. It is further considered that a broad and general discussion on these assessment factors is urgently needed. That discussion should focus on the question whether and in which cases AFs for inter- and intraspecies may need to be applied for non-threshold carcinogens. It is considered that this discussion should not be limited to REACH but should also include other risk assessment frameworks.

B.5.1.11.3. Carcinogenicity: markers of exposure -TEF approach

In contact with consumer articles and mixtures, consumers are exposed to a multitude of PAH mixtures of different composition. A main issue in the risk assessment of PAHs is the quantification of the carcinogenic potency of PAH mixtures. The composition of the PAH mixtures encountered in food, consumer products, mixtures such as rubber granules and the environment varies, resulting in varying carcinogenic potencies. Each of the (sometimes up to several hundred) different PAH mixture components possesses its own toxicity profile, absorption behaviour, and may potentially be carcinogenic. For risk assessment of PAH mixtures, various approaches have been described such as the Toxicity Equivalence Factor (TEF) approach, or the marker approach.

EFSA (2008) concluded that "*the TEF approach to the risk characterisation for PAHs in food was not considered to be scientifically valid because of the lack of data from oral carcinogenicity studies on different PAHs, their different modes of action and the evidence of poor predictability of the carcinogenic potency of PAH mixtures based on the currently proposed TEF values*". Indeed, because there is a total lack of adequate data from oral carcinogenicity studies on individual PAHs other than benzo[d,e,f]chrysene, TEF values for PAHs in food have been suggested based on studies using skin application, pulmonary instillation and subcutaneous or intraperitoneal injections. Furthermore, in the case of exposure to PAHs through ingestion, the application of TEFs underestimates the risks induced by mixture of PAHs (Culp *et al*., 1998; Schneider *et al*., 2002). Indeed, the oral carcinogenic risk is 3 to 5 times higher with PAH mixtures than with BaP alone for equivalent exposures expressed in TEQ (Culp *et al*., 1998). Tumour localization is also different for oral exposure to mixed PAHs or BaP alone at equivalent doses.

For the oral route, EFSA (2008) concluded that BaP is not a suitable indicator for the occurrence of PAHs in, and thus the exposure to PAHs *via*, food. The relative concentrations of the PAHs in food were found to be variable, and BaP was not detected in some samples when other PAHs were measurable. By expanding the marker method to two PAHs (BaP and CHR), four PAHs (BaP, CHR, BaA and BbFA) and 8 PAHs (BaP, CHR, BaA, BbFA, BkFA, BghiP, DBAhA and IP), i.e. the PAHs that were measured in the carcinogenicity study of Culp et al. (1998), EFSA found the PAH4 and PAH8 markers to be more suitable indicators of PAHs in food, with PAH8 not providing much added value compared to PAH4. The EFSA PAH4 and PAH8 approach aims to assess risks of PAH in food, where PAHs will derive from a number of sources. The main PAH contamination of food can be attributed to heating, drying and smoking processes where combustion products come in direct contact with food or may be formed in situ (SCF, 2002; EFSA, 2008).

BaP has in general mostly been used as a marker of occurrence and effect of the carcinogenic PAHs. Indeed, the toxicity of only a limited number of PAHs is currently known. Some PAHs, primarily those with a low molecular weight, induce systemic non-carcinogenic threshold effects (mainly kidney, liver and blood disorders) for which HRVs have been established. Other PAHs, in particular those with a high molecular weight, appear to be carcinogenic and genotoxic.

Recently, ECHAs Risk Assessment Committee (RAC) established a dose-response relationship for the carcinogenicity of coal tar pitch - high temperature (ECHA, 2018). For the oral route, this was done based on the data of Culp *et al*. (1998) using BaP as marker. Another option suggested by RAC was to apply a PAH4 or PAH8 approach.

Table 38 : Comparaison between EFSA PAH8 approach, PAHs searched and detected in single-use baby diapers

Migration tests in whole diapers		**8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications**	**EFSA**		**Culp *et al.* (1988)**
Searched PAHs	**Detected PAHs at least once in single-use baby diapers**		**HAP8**	**HAP4**	
Benzo[c]fluorene					
Benz[a]anthracene	X	X	X	X	X
Cylclopenta[c,d]pyrene					
Chrysene	X	X	X	X	X
5-methyl chrysene					
Benzo[b]fluoranthene	X	X	X	X	X
Benzo[k]fluoranthene	X	X	X		X
Benzo[j]fluoranthene	X	X			
Benzo[e]pyrene	X	X			
Benzo[d,e,f]chrysene	X	X	X	X	X
Dibenz[a,h]anthracene		X	X		X
Indeno[1,2,3-c,d]pyrene			X		X
Benzo[g,h,i]perylene	X		X		X
Dibenzo[def,p]chrysene					
Naphtho[1,2,3,4-def]chrysene					
Benzo[r,s,t]pentaphene					
Dibenzo[b,def]chrysene					

In the Annex XV restriction reports for 8 PAHs in consumer products prepared by BAuA (BAuA 2010) and for 8 PAHs in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications (ECHA, 2019), ECHA followed EFSAs approach for several reasons. *"As the relative concentrations of PAHs in rubber granules varies with BaP being not detectable in all samples, it may be considered that BaP is also not a suitable indicator for the occurrence in, and exposure to PAHs via, rubber granules. As the EFSA PAH8 group largely corresponds with the eight PAHs under current evaluation and thus are largely included in the study of Culp et al. (1998) which was used by EFSA for BMDL-derivation for the PAH8 marker group (EFSAs approach is followed for current* *evaluation of the risks for consumer upon oral exposure). In this marker approach, the total carcinogenicity of the PAH mixtures tested in the Culp et al. (1998) study is assumed to correspond with the PAH8 marker group. So, it is possible to sum the exposures to the eight specified PAHs, and relate the summed exposure to the $BMDL_{10}$ for this marker group."*

In this restriction, the EFSA approach (HAP8) was not used in this restriction for several reasons:

- The EFSA approach is applicable for oral exposure whereas the current risk assessment assesses dermal exposure to baby diapers;
- Furthermore, Even if the concentrations of PAHs in single-use baby diapers vary with BaP being not detectable in all samples (BaP detectable in 3 out of 51 tested single-use baby diapers), the EFSA PAH8 differs from the 8 PAHs detected in baby diapers and the 17 PAHs under current evaluation Two out of the 8 PAHs detected in baby diapers are not reported to be present in the mixtures tested in the Culp *et al*. (1998) study (unclear if measured and not detectable, or not measured at all).

So, the Dossier Submitter chose to use the Toxicity Equivalence Factor (TEF) approach with BaP as marker in this restriction proposal to follow the same approach for all the substances in the scope and assumes this approach is better for monitorability.

For PAHs, BaP was considered as a marker of PAH exposure and carcinogenic effects (WHO-IPCS, 1998). So the toxicity of other PAH was estimated based on toxic equivalency factors (TEFs) contrarily to EFSA's approach retained in the ECHA's restriction for PAHs in granules and mulches (see section B.5.1.8.4.). The Dossier Submitter selected TEFs for 17 PAHs from the various existing TEFs listed in the table below.

Table 39: TEFs proposed by various organisations for PAHs

	OEHHA, 1993 revised in 2015	**INERIS, 2003**	**AFSSA, 2003**	**DFG, 2008 cited in BfR, 2009b**	**US EPA, 2010 (draft)****	**TEFs considered by the Dossier Submitter**
5-methylchrysene	1	0,01	/	/	/	0,01
Benzo[d,e,f]chrysene (BaP)	**1**	**1**	**1**	**1**	**1**	**1**
Benz[a]anthracene	0,1	0,1	0,1	0,1	0,2	0,1
Cyclopenta[c,d]pyrene	/	0,1	/	0,1	0,4	0,1
Chrysene	0,01	0,01	0,01	0,01	0,1	0,01
Benzo[b]fluoranthene	0,1	0,1	0,1	0,1	0,8	0,1
Benzo[j]fluoranthene	0,1	/	0,1	0,1	0,3	0,1
Benzo[k]fluoranthene	0,1	0,1	0,1	0,1	0,03	0,1
Benzo[e]pyrene	/	/	/	/	/	0,01*
Dibenz[a,h]anthracene	/	1	1	1	10	1
Indeno[1,2,3-c,d]pyrene	0,1	0,1	0,1	0,1	0,07	0,1
Benzo[g,h,i]perylene	/	0,01	0,01	/	0,009	0,01
Benzo[c]fluorine	/	/	/	/	20	20
Dibenzo[def,p]chrysene	10	/	/	10	30	10
Naphtho[1,2,3,4-def]chrysene	1	/	/	1	0,4	1

Benzo[r,s,t]pentaphene	10	/	/	10	0,6	10
Dibenzo[b,def]chrysene	10	/	/	10	0,9	10

* INERIS (2003) conducted a review of the various TEF tables. The following TEFs for benzo[e]pyrene were proposed in four studies: 0.004 (Krewski *et al.,* 1989), 0.01 (Malcom and Dobson, 1994), 0 (Muller *et al*., 1995a, b) and 0.002 (Larsen and Larsen, 1992). The Dossier submitter selected the TEF from the study by Malcom and Dobson (1994). ** Arithmetic average

B 5.2 PCDD/Fs and PCBs

Hazards and risks of PCDDs, furans and PCBs were reviewed within various risk assessment frameworks and by various international committees (ATSDR, 1998; ATSDR, 2000 ; ATSDR, 2004 cited in Danish EPA, 2014; Danish EPA, 2014 ; DGS, 1998 ; EFSA, 2018 ; IARC, 1997, 2016 ; INERIS, 2006; INRS, 2007, 2016 ; INSERM, 2000 ; OSAV, 2016 ; US EPA, 1992). These reports have assessed the animal and human toxicological data on PCDDs, furans and PCBs in detail and it's not the goal of this dossier to redo those assessments.

Toxicokinetic (section B.5.2.1), irritation (section B.5.2.3), sensitization (section B.5.2.5), repeated doses toxicity (section B.5.2.6), mutagenicity (section B.5.2.7), carcinogenicity (section B.5.2.8), toxicity for reproduction (section B.5.2.9), and other effects (section B.5.2.10) are discussed below.

Dioxins (polychlorinated dibenzodioxins or PCDDs) and furans (polychlorinated dibenzofurans or PCDFs) will be grouped under the term PCDD/Fs and total PCBs i.e. PCB-DL and PCB-NDL under the term PCBs.

B.5.2.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

B.5.2.1.1 Absorption

B.5.2.1.1.1 PCDD/Fs

- Oral

According to EFSA (2018), "*In mice, the fraction absorbed after a single p.o. dose of 0.1, 1 or 10 µg/kg bw TCDD ranged from 0.70 to 0.88 (Diliberto et al., 1995). In the rat, this fraction ranged from 0.64 to 0.78 (doses of 0.05, 0.20, 0.80 or 1 µg/kg bw: Hurst et al., 2000b). In rats, approximately 90% of a single oral dose of TCDF was absorbed (matrix: 1:1 ethanol:vegetable oil mixture; Birnbaum et al., 1980). Similarly, 70–85% absorption was reported for a single dose of 2,3,4,7,8-PeCDF (Yoshimura et al., 1986; Brewster and Birnbaum, 1987; Kanimura et al., 1998). In contrast, OCDD is poorly absorbed, 2–15% of a single dose being absorbed after administration by gavage in a 1:1 ortho-dichlorobenzene: corn oil mixture (Birnbaum and Couture, 1988; Couture et al., 1988). In mice, the fraction absorbed after subchronic p.o. dosing of TCDD (13 weeks/5 days per week; 0.15, 0.45, 1.5, 4.5, 15, 45, 150 and 450 ng/kg bw per day), was found to depend on the administered dose, with highest absorption found at the two lowest doses (0.69 and 0.88, respectively) and lowest absorption at the two highest doses (0.26 at both doses, Diliberto et al., 1995)*."

EFSA (2019) evaluated the available data on oral absorption on human. Several studies are described:

- *" Poiger and Schlatter (1986) administered an oral dose of 105 ng radiolabelled [1,6-^{3}H]-2,3,7,8-TCDD to one male volunteer and concluded that more than 87% was absorbed. Moser and McLachlan (2001) compared intake and levels in faeces from 5 volunteers with background exposure and estimated absorption to be more than 95% for most PCDD/Fs and DL-PCBs. Lower absorption was observed for the hepta- and especially octachlorinated PCDD/F congeners. Using a toxicokinetic model, Aylward et al. (2005) evaluated data from four of these individuals and concluded that 95–99% of the TCDD was absorbed. These calculations took into account the excretion of TCDD from the body, 'due to simple lipid partitioning from the circulation across the intestinal lumen into fecal contents.*

- *McLachlan (1993) determined the 12-day mass balance, i.e. the difference between the total intake with breast milk and the excretion in the faeces, in a 19-week-old boy for 12 PCDD/Fs and 4 DL-PCBs. TCDD, and penta- (2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD) and hexa-substituted congeners (1,2,3,4,7,8- HxCDF, 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD) showed an absorption of 90% or higher. The absorption of the two hepta congeners (HpCDD and 1,2,3,4,6,7,8-HpCDF) and OCDD was found to be lower, i.e. 61% and 58%, and 23%, respectively.*

- *Dahl et al. (1995) determined the 48-h mass-balance for seven PCDDs (TCDD, PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, HpCDD, OCDD), six PCDFs (TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF) and three DL-PCBs (PCB-77, -126 and -169) in four breast fed children at 1, 2, 3 and 6 months post-partum. For all tetra-, penta- and hexa-substituted PCDD/Fs and PCB congeners the absorption was found to be over 95%.*

- *The absorption of HpCDD, 1,2,3,4,6,7,8-HpCDF and OCDD was found to be somewhat lower (80%, 93% and 87%, respectively). Abraham et al. (1996) determined the 5-day mass balance in two breastfed children at 1 and 5 months of age for TCDD, PeCDD, 2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDD, HpCDD, OCDD, and the sum of these PCDD/Fs in I-TEQ. At the age of 1 month, exposure of the infants was estimated to be 82 and 106 pg I-TEQ/kg bw per day. For TCDD and the sum in I-TEQ, the absorption was found to be ≥ 94% and ≥ 91%, respectively. The absorption of HpCDD and OCDD was found to be lower (78% and 51%, respectively). The absorption of dietary fat was found to be ≥ 95%. The results indicate that the absorption of dioxin-like compounds occurs together with absorption of fat from the food*."

Based on this, the Dossier Submitter selected an oral absorption fraction based on McLachlan (1993) study rounded to 100% for PCDD/Fs which will be used for current evaluation.

- Dermal

No *in vivo* studies on dermal absorption have been identified in humans but a few studies are available in animals.

- Dermal absorption was investigated for 2,3,7,8-TCDD and 3 furans in male F344 rats 3 days after a single application under occlusion (vehicle: acetone) (Brewster *et al*., 1989). Relative absorption (% administered dose) was 38.27% at 0.05 µg/kg to 17.3% at 321 µg/kg. For each compound, a decrease in relative absorption was observed with increasing doses, while absolute absorption (µg/kg) was non-linearly increased. At 0.1 µmol/kg (= 32 µg/kg), 49% of the administered dose of 2,3,7,8-TCDF was absorbed through the skin and was greater than that of 2,3,4,7,8-PeCDF (34%), 1,2,3,7,8-PeCDF (25%) and 2,3,7,8-TCDD (18%). This study suggests that the majority of these compounds remaining at the exposure site are found in the epidermis and do not penetrate the dermis.

- Banks and Birnbaum (1991) studied the dermal absorption rate of 2,3,7,8-TCDD for 120 hours after an application, under occlusion, of 200 pmol (111 pmol/cm² = 1 nmol/kg) to the skin of 10-week-old male F344 rats (vehicle: acetone). During the 120 hours after exposure, approximately 26 ng of 2,3,7,8-TCDD was absorbed (#40% of the applied dose). Absorption followed first-order kinetics with a constant absorption rate constant of 0.005 h^{-1}. At each observation interval (1, 4, 8, 12, 24, 48, 72, and 120 hours after application), approximately 70% of the radioactivity detected on the skin could be removed by buffering with acetone. The authors concluded that very slow dermal absorption at low dose levels was observed.

- The presence of sol or lipophilic agents (e.g. petroleum jelly) significantly decreases dermal absorption of 2,3,7,8-TCDD compared with absorption of the pure substance dissolved in solvents (Poiger and Schlatter, 1980; Shu *et al*., 1988). Approximately 15% of the dose was detected in the liver of rats 24 hours after dermal application of 26 ng of 2,3,7,8-TCDD in 50% methanol, 1.4% following the same dose of TCDD in petroleum jelly and <0.05% in soil or activated charcoal (Poiger and Schlatter, 1980).

- Shu *et al*. showed that dermal absorption of labelled 2,3,7,8-TCDD from soil accounted for only 1.3% of the administered dose after 24 hours of application in male Sprague Dawley rats (Shu *et al*., 1988). Dermal absorption of 2,3,7,8-TCDD after 4 hours of contact was approximately 60% of that after 24 hours of contact.

- Roy *et al*. (2008) applied 2,3,7,8-TCDD neat or in soil to rat skin *in vivo* and *in vitro* and to human skin *in vitro*. Approximately 78% of a 70 ng dose of pure TCDD applied to rat skin was absorbed after 96 hours (#33% after 8 hours). The fraction absorbed was similar between the *in vivo* and *in vitro* rat study (#76%). For an application of 1 ppm 2,3,7,8-TCDD to soil with low organic carbon content (10 ng TCDD/10 mg soil/cm²), the percentage of absorbed dose applied was 16.3% (rat *in vivo*), 7.7% (rat *in vitro*) and 2.4% (human *in vitro*) after 96h exposure. Finally, the mean percentage of the 1 ppm dose of TCDD in soil with high applied organic carbon content absorbed *in vitro* in rats was 1% after 96h. Thus, application of 2,3,7,8-TCDD in soil reduced the percentage of TCDD absorbed by a factor of 5 *in vivo* and 10 *in vitro* compared to pure 2,3,7,8-TCDD. Based on *in vitro* tests conducted on human and rat skin, an absorption flux of 120 ng/cm² in rats and 43 ng/cm² in humans was established.

Three *in vitro* studies are available: two on human skin (Weber *et al*., 1991; Roy *et al*., 2008), one on pig skin (Weber, 1993) and one on rat skin (Roy *et al*., 2008 - described above).

- Weber *et al*. (1991) studied the penetration of 2,3,7,8-TCDD (6.5 and 65 ng/cm²) through intact or stratum corneum-free human cadaver skin for 30, 100, 300 and 1000 min, using acetone as the vehicle, to simulate exposure of 2,3,7,8-TCDD as a dust or from volatile solvent, or mineral oil to simulate industrial accident situations. *In vitro*, 2,3,7,8-TCDD does not easily penetrate human skin. The vehicle plays an important role in skin penetration. Acetone allows 2,3,7,8-TCDD to penetrate strongly into the free surface lamellae of the stratum corneum but little into the lower layers, whereas mineral oil slows skin penetration by competing with the lipophilic constituents of the stratum corneum. With skin without stratum corneum, the amount of 2,3,7,8-TCCD absorbed is increased. The stratum corneum acts as a protective barrier and its removal increases the absorption of 2,3,7,8-TCDD by other layers. For intact skin and acetone as a vehicle, the rate of penetration into the dermis and epidermis was between 6 and 170 pg/h/cm² while the rate of penetration into the dermis was between 100 and 800 pg/h/cm². With mineral oil as a vehicle, the penetration rate was 5 to 10 times lower (in the dermis: 20 to 220 pg/h/cm²; in the dermis and epidermis: 1.4 to 18 pg/h/cm²). They also studied *in vitro* the dermal penetration of 2,3,7,8-TCDD on viable and non-viable pig skin, with and without stratum corneum mimicking injured skin, by testing 2 concentrations (6.5 or 65 ng/cm²) and with different vehicles (acetone, mineral oil) (Weber, 1993). Dermal penetration rates ranged from 14 to 985 pg/cm²/h (0.2-1.5% of the dose/h) depending on the exposure conditions. The percentage of absorbed dose was independent of the concentration applied to pig skin. The dermal penetration rate was 3 times higher for skin without stratum corneum. The use of acetone as a vehicle resulted in higher dermal penetration rates than with mineral oil.

- Dermal absorption in rats is age-related and appears to be higher in young rats than in adults. Indeed, Banks *et al*. (1990) found that 72 hours after application of a 40 nmol dose (approximately 12.9 µg) of labelled 2,3,7,8-TCDD, percutaneous absorption was reduced in middle-aged (36 weeks) and older (120 weeks) F344 rats compared with young adults (10 weeks). The authors suggested a decrease in skin blood flow between 3 and 4 months as a possible explanation for their findings. Banks *et al*. studied the dermal absorption of 2,3,7,8-TCDD in Fischer 344 rats aged 3, 5, 8, 10 and 36 weeks 72 hours after application of 200 pmol 2,3,7,8-TCDD in acetone (Banks *et al*., 1991). Dermal absorption was highest in 3-week-old rats (approximately 64% of the applied dose), decreased to approximately 40% of the applied dose in 5-, 8- and 10-week-old rats and decreased to approximately 22% in 36-week-old rats. In each age group, 70-80% of the radioactivity remaining at the application site 72 hours after dosing was eliminated using acetone buffers. Similarly, Anderson *et al*. (1993) evaluated the dermal age-dependent absorption of 2,3,7,8-TCDD in 3-, 5-, 8-, 10- and 36-week-old male F344 rats. 72 hours after application, under occlusion, of a low dose of labelled 2,3,7,8-TCDD (200 pmol = 111 pmol/cm²) (vehicle: acetone), absorption was greatest in 3-week-old rats (#123 pmol, #64% of the administered dose, decreased to #80 pmol (#40%) in 5-, 87- and 10-week-old rats and #45 pmol (#22%) in 36-week-old rats. For each group, 70-80% of the radioactivity remaining at the application site after 72 hours could be removed with acetone buffers.

Other studies and reports have investigated the dermal absorption of these substances, in particular to estimate the percutaneous absorption of 2,3,7,8-TCDD in soil but also to study the transfer of PCDDs present in textiles and absorbent hygiene products such as tampons, sanitary napkins and baby diapers (Table 40).

Table 40 : Dermal absorption of PCDDs/furans

Studies	Study models	Dermal absorption in human
US EPA, 1992	Percutaneous absorption of TCDD in soil: - *in vivo* in rats (Poiger and Schlatter, 1980; Shu *et al*., 1988) - *in vitro* with human and rat skin Roy *et al*., 1990; US EPA, 1992)	0.1-3%
Klasmeier *et al*., 1999	Transfer of PCDDs from contaminated textiles to stratum corneum in volunteers	< 0.1 and 3%
De Vito and Schecter, 2002 ; Ishii *et al*., 2014 ; OSAV, 2016	Evaluated dermal exposure to PCDDs in absorbent hygiene products: tampons, sanitary napkins and diapers	3%

For single-use baby diapers, since the wood pulp used in the absorbent core is a mixture of large organic fibres, it is likely that PCDDs are strongly bound to these fibres and therefore not readily absorbed. De Vito and Schecter (2002) used a dermal absorption rate of 3%, considered conservative, based on an estimate of dermal absorption from soil with low organic content (US EPA, 1992) and a study on the transfer of substances from cotton textiles to the skin (Klassmeier *et al*., 1999).

B.5.2.1.1.2. PCBs

In 2016, IARC published data on the toxicokinetics of PCBs, including the following syntesis for absorption: « *In humans, gastrointestinal absorption of PCBs was estimated to vary from 50% of the ingested amount to close to 100% (varying according to the number of chlorine atoms) and a similar situation was observed in experimental animals. Although no quantitative data were available regarding absorption of PCBs in humans exposed by inhalation, the levels of residues detected in individuals exposed to high concentrations of PCBs in air suggested that inhaled PCBs are absorbed to a substantial extent. Data from experimental animals indicated that inhalation of PCBs gives a higher uptake of PCBs than ingestion. Studies assessing dermal exposure to commercial PCB mixtures in humans and animals showed that this route of exposure generally results in absorption levels of between 20% and 40%, with dermal penetration varying inversely with the degree of chlorination of the mixture administered. First-pass metabolism at the site of dermal exposure appears to be responsible for differences in metabolism and disposition between routes of administration. The rate of absorption and the disposition of PCBs after dermal administration may be mediated by transdermal metabolism.* »

Here are more details about oral and dermal absorption.

- Oral
    - Laboratory animals

IARC in 2016 studied the oral intake of PCBs and they selected the following studies as relevant. "*PCBs in food are absorbed from the gastrointestinal tract by simple passive diffusion (ATSDR 2000). Studies in rats have shown that all PCB congeners are well absorbed from the* *gastrointestinal tract, with > 90 % absorption of lower chlorinated congeners (Albro and Fishbein 1972, Safe 1980, Bergman et al. 1982, Tanabe et al. 1981), and possibly lower absorption of higher chlorinated congeners, such as octachlorobiphenyls (75 %) (Tanabe et al. 1981). The reduced absorption of highly chlorinated PCBs is consistent with the data on PCDDs, and probably arises from the inability of these compounds to form a molecular solution in the contents of the gut lumen. Factors such as dietary lipids and bile salts might enhance the extent of absorption, which probably involves incorporation into chylomicrons and uptake via the lymphatic system. The positive influence of bile has been shown by comparing normal and bile canulated rats treated with PCB (Bergman et al. 1982)."*

- Human

The Danish EPA (2014) studied the oral intake of PCBs and they selected the following study as relevant.*"Absorption of NDL-PCBs in a nursing infant was estimated to be 96-98 % for the main congeners present in human milk based on the difference between the amount ingested and the unabsorbed PCBs excreted in the faeces (McLachlan, 1993). Any variable that influences mobilisation of the PCB body burden, such as fasting, would alter the extent of faecal elimination of the pre-existing body burden.Precise estimates of the oral bioavailability of PCB residues in soil are not available (ATSDR, 2004)."*

In 2016, IARC identified two oral absorption studies, presented below.

"*The absorption of polychlorinated biphenyls (PCBs) was studied in four breastfed infants in Sweden by Dahl et al. (1995). Absorption was measured by comparing the estimated total intake and the excretion in faeces for 48 hours, at 1, 2, and 3 months postpartum. The concentrations of 56 congeners in maternal milk were determined. For tetrachlorosubstituted to octachlorosubstituted congeners, absorption was found to be close to 100%, while absorption of trichlorinated congeners was 60–98%, probably due to the low levels at which they were present and ensuing analytical difficulties in detection. Another possible explanation could be metabolism of the trichlorinated congener.*

The gastrointestinal absorption of 10 congeners from food was investigated using a mass balance approach in seven individuals aged 24–81 years with different contaminant body burdens (Schlummer et al., 1998). The difference between ingested and excreted amounts of the chlorinated compounds was defined as net absorption. Nearly complete net absorption was observed for PCB-28, PCB-52, PCB-77, PCB-101, and PCB-126. Absorption of PCB-105, PCB-138, PCB-153, and PCB-180 was > 60% in most volunteers, but limited absorption was observed in the three older subjects. In all cases, absorption of PCB-202 was < 52%".

Based on this, the Dossier Submitter selected an oral absorption fraction based on McLachlan (1993) study rounded to 100% for total PCBs which will be used for current evaluation.

- Dermal
  - Laboratory animals

Several studies investigating dermal absorption are summarized in ATSDR (2000):

"In a related study, Wester et al. (1990, 1993) assessed the in vivo percutaneous absorption of PCBs in adult female Rhesus monkeys. 14C-Labeled Aroclor 1242 and 1254 were separately administered iv and topically to Rhesus monkeys and urinary and fecal excretion of

radioactivity was measured for the next 30 days. Following iv administration, the 30-day cumulative excretion was 55% of the administered dose (39% urine, 16% feces) for Aroclor 1242 and 27% (7% urine, 20% feces) for Aroclor 1254. The percentage of the dose absorbed following topical administration to abdominal skin (after light clipping of hair) was estimated from the ratio of the total urinary and fecal excretion following topical and iv administration. Topical administration of Aroclor 1242 in soil, mineral oil, trichlorobenzene, or acetone resulted in 14, 20, 18, and 21% absorption of the administered dose, respectively. In contrast to the above in vitro results with human skin, the vehicle had little effect on the systemic absorption of the PCBs applied to the skin of monkeys. This may be due to the uncertain viability of the human skin used in the in vitro studies and the fact that the in vitro study primarily assessed retention of PCBs in human skin and could not estimate systemic absorption.

The effectiveness of methods for decontaminating or removing Aroclor 1242 from Rhesus monkey skin was also investigated by Wester et al. (1990). Use of soap and water was similar in effectiveness to washing with trichlorobenzene, mineral oil, or ethanol. At 15 minutes following dermal exposure, 93% of the applied dose was removed from skin by washing with soap and water. At 24 hours following dermal exposure, only 26% of the dose was removed from skin by washing with soap and water, suggesting that with time, most of the PCB dose undergoes systemic absorption and/or retention in the skin. Thus, washing with soap and water is an effective method for removing PCBs from skin, particularly when washing immediately following a known dermal exposure.

Dermal absorption of PCBs has been measured in monkeys and guinea pigs by comparing excretion following topical administration to excretion following parenteral administration. Single doses of 14C-labeled PCBs (42% chlorine content) in benzene/hexane were applied to the abdominal skin of four Rhesus monkeys and to the lightly clipped skin behind the ear of three guinea pigs (Wester et al. 1983). To an additional group of three guinea pigs, PCB with 54% chlorine content was applied. The application amount ranged between 4.1 and 19.3 µg/cm2 skin. The application sites were washed with water and acetone after 24 hours, and radioactivity was monitored in the urine for several weeks postdosing. Absorption efficiency ranged from .15 to 34% of the applied radioactivity in the monkeys and averaged .33% (42% chlorine) and 56% (54% chlorine) of the applied radioactivity in the guinea pigs. Washing the skin immediately after PCB application removed 59% of the applied dose. However, only 1% of the applied label from the PCB containing 42% chlorine and 20% of the label from the PCB containing 54% chlorine could be recovered from the application site when the skin was washed 24 hours after dosing. Dermal absorption of PCBs (48% chlorine) has also been demonstrated in rats (Nishizumi 1976); however, quantitative data were not provided.

Dermal penetration rate constants have been measured in male Fischer 344 rats after single 0.4 mg/kg dermal doses of 14C mono-, di-, tetra-, and hexachlorobiphenyls applied for 48 hours to shaved back skin (Garner and Matthews 1998). Congeners used were 4-chlorobiphenyl (PCB 3), 4,4′-dichlorobiphenyl (PCB 15), 2,2′,4,4′-tetraCB (PCB 47), and 2,2′,4,4′,6,6′-hexaCB (PCB 155). Penetration rate and degree of penetration (defined as penetration through the stratum corneum into the viable epidermis) were inversely related to degree of chlorination. Rate constants for penetration were 0.14, 0.074, 0.028, and 0.0058 hour-1 for the mono-, di-, tetra-, and hexachlorinated forms, respectively. Rate constants correlated strongly with the logarithm of the octanol-water partition coefficient. Jackson et al. (1993) also reported a strong inverse correlation between octanol-water partition coefficient estimates and the dermal absorption of several halogenated aromatic hydrocarbons, including

3,3',4,4'-tetraCB (PCB 77). Cumulative penetration at 48 hours was near 100% for the mono-, 95% for the di-, 75% for the tetra-, and 30% for the hexachlorinated forms. Absorption of the tetra- and hexachlorinated forms continued after washing the site with acetone at 48 hours, indicating that the viable epidermis served as a reservoir for these higher chlorinated forms. The rate of systemic absorption of radioactivity was kinetically complex and not a first-order process like penetration into the skin. This may be due to metabolism and partitioning within the skin.

The dermal absorption of 14C-3,3',4,4'-tetraCB (PCB 77) and 2,2',4,4',5,5'-tetraCB (PCB 153) in female F344 rats was assessed under conditions where the PCB was applied as either a solid, aqueous paste, aqueous suspension, or dissolved in ethanol (Hughes et al., 1992). The chemicals were applied to the clipped mid-dorsal region of the rat. The treatment area was then occluded, and urine and feces were collected and analyzed for radioactivity. At 24-hours postexposure, the treatment area was washed with soap and water, recovering 61–91% of PCB 77 and 81–92% of PCB 153. The percentage of the dose absorbed ranged from 6 to 8% for PCB 77 and from 5 to 8% for PCB 153, while the treated skin retained from 3 to 31% of the PCB 77 and from 3 to 12% of the PCB 153. Although significantly greater absorption of PCB 153 was observed when administered as a solid, compared to using the ethanol vehicle, the remainder of the results indicate that the dermal absorption of PCBs 77 and 153 was similar even when the PCBs were applied in four different physical forms."

- Human

According to ATSDR (2000), *« experimental data on the percutaneous absorption of PCBs in humans is limited to in vitro studies thatused human cadaver skin (Wester et al., 1990; 1993). These studies utilized 14C-labeled Aroclor 1242 and 1254 (mixtures containing 42 or 54% chlorine by mass) in soil, mineral oil, and water. Over a 24-hour period, 2.6, 10, and 43% of the dose was retained in human skin when the Aroclor 1242 was formulated in soil, mineral oil, or water, respectively. Similar results were observed with Aroclor 1254, with 1.6, 6.4, and 44.3% of the dose retained in human skin, following PCB exposure in a soil, mineral oil, or water vehicle, respectively. The in vitro data indicate that PCBs readily enter human skin and are available for systemic absorption, and that the dosing vehicle has a major role in regulating the relative retention of PCBs in human skin. »*

B.5.2.1.2 Distribution

B.5.2.1.2.1 PCDD/Fs

In organs and blood, a large of PCDD/Fs are linked to lipoproteins. Data observed in humans and animals show that PCDD/Fs pass easily through the gastrointestinal wall and are transported by proteins to organs and tissues. Because of their lipophilic nature, these molecules accumulate preferentially in the liver and fatty tissue. Thus, the distribution depend on the fat content of the different tissues and but depend also on their concentration of cytochromes P450. The more chlorinated the PCDDs are, the more they bind to CYP450. Mechanisms of sequestration and excretion can induce considerable variation in the concentration of cellular targets, partly explaining the variation in sensitivity between species (Afssa, 2005).

In humans, the metabolism of 2,3,7,8-TCDD by CYPs may not be significant at the concentrations usually encountered, and it's the lipid content of the tissues which determines its distribution (INSERM, 2000).

Placental passage is easy: the concentrations measured in the mother and child at birth are very similar (INRS, 2016).

B.5.2.1.2.2 PCBs

In 2016, IARC published data on the toxicokinetics of PCBs, including the following syntesis for distribution: « *PCBs are lipophilic compounds that are preferentially retained and may accumulate in adipose tissue and lipid-rich tissues.* » In decreasing order, we observe a distribution in the adipose tissues, then in the skin, the liver and the gall bladder, the muscles, and finally the blood where they are transported by lipoproteins (Cornu, 2012). « *A few studies mentioned substantial retention of certain congeners in the lung and spleen in mice and rats, respectively. The pattern of congeners observed in tissues of humans or experimental animals does not correspond to the congener profiles of PCB formulations. The major PCB components in the plasma and adipose tissue of occupationally exposed individuals are the hexa- and heptachlorobiphenyls. PCB congeners with chlorine atoms in the para positions are generally found at relatively high concentrations, while PCBs with unsubstituted meta, para positions on at least one ring are present at lower concentrations. The most abundant congeners found in adipose tissue, plasma, and liver are 2,2′,3,4,4′,5′-hexachlorobiphenyl (PCB-138), 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) and 2,2′,3,4,4′,5,5′-heptachlorobiphenyl (PCB-180). PCBs have been found to cross the blood–brain barrier, and data from humans and experimental animals provided clear evidence for the transplacental passage of these chemicals. Metabolites of PCBs, including hydroxylated PCBs and methylsulfone PCBs, are also known to distribute to various tissues.* » In addition, because of its high fat content, breast milk also concentrates PCBs: the average total PCB content is 0.5 to 1.5 mg/kg of breast milk lipid (Cornu, 2012).

B.5.2.1.3 Metabolism

B.5.2.1.3.1. PCDD/Fs

PCDDs are poorly metabolized (dechlorination, oxidation, glutathione conjugation, then sulpho and glucuroconjugations) (INRS, 2016). PCDDs behave similarly in animal and human organisms. Toxicokinetic differences between PCDDs and between species seem to arise mainly from variability in fat affinity, metabolism rate, solubility in the vehicle of administration or adsorption to environmental matrices (INERIS, 2006). The metabolism of 2,3,7,8-TCDD occurs *via* oxidation and dechlorination reactions. The main metabolite obtained is 2-hydroxy-3,7,8-trichlorodibenzo-p-dioxin (2-hydroxy-3,7,8-TrCDD) (INSERM, 2000).

The biotransformation of PCDD/Fs dépends on the chlorine substitution pattern in the molecule. Metabolic reactions include oxidation and reductive dechlorination, involving arene oxide intermediates and NIH-shifts as well as breakage of the oxygen bounds. Substitution of the 2,3,7 and 8 positions by chlorines strongly reduces the metabolic conversion rate. In the 2,3,7,8-substituted PCDF molecule, the 4 and 6 positions are more susceptible toward metabolic attack than the 1 and 9 positions. As a result, PCDFs with chlorines on the 4 and 6 positions are highly persistent in organism (Van den berg *et al*., 1994).

These congeners tend to be very resistant to metabolism, as these positions are also preferentially oxidized by the cytochrome P450 system, most likely by the CYP1A enzymes. Because of the stress on the furan ring, PCDFs are more susceptible to biochemical degradation than PCDDs. In addition, the positions adjacent to the oxygen bridge in the PCDF molecule (position 4 and 6) are more sensitive to metabolic attack than those in the PCDD molecule (Van den berg *et al*., 1998). PCDFs, which are more readily metabolized, are more easily degraded and therefore probably less accumulated than PCDDs.

B.5.2.1.3.2. PCBs

In 2016, IARC published data on the toxicokinetics of PCBs, including the following syntesis for metabolism. *« Individual PCB congeners differ greatly in the ease with which they are metabolized in humans and animals. Congeners with four or fewer chlorines and those with adjacent unsubstituted meta,para positions are metabolized more readily than those with more than four chlorines and with substituents at meta,para ring positions. The initial step in the biotransformation of all PCB congeners is cytochrome P450 (CYP)dependent mono-oxygenation. Readily metabolized congeners can be converted to potentially electrophilic and genotoxic metabolites of PCBs, arene oxides, and quinones. Quinones arise from dihydroxylated PCB metabolites through the action of peroxidases or prostaglandin endoperoxide synthase. The other major pathway of metabolism of PCBs is conversion of an arene oxide metabolite to a glutathione conjugate. The glutathione conjugate is then converted either to the excreted non-toxic mercapturic acid, or to the generally poorly excreted methyl sulfone metabolite. »*

B.5.2.1.4 Elimination

B.5.2.1.4.1. PCDD/Fs

PCDD/Fs elimination is mostly biliary. The elimination half-life for PCDD/Fs averages 7-8 years in adults (range 2-12 years). Toxicokinetic analysis of human data indicates that the elimination half-life is approximately 8.5 years for occupational cohorts and 15.5 years for the general population (Van der Molen, 1996 and 2000). This half-life varies widely among individuals, with elimination half-lives for 2,3,7,8-TCDD ranging from 2 years (in children) to at least 30 years (in older adults). The half-life is therefore highly dependent on age, but also on other individual factors, probably related to diet (independent of PCDD intake), adiposity and variability in metabolism from one individual to another (INSERM, 2000).

Milk excretion is important the concentration of PCDD/Fs is approximately constant in the lipid fraction of all tissues and body fluids in a single individual and milk is rich in lipids (INRS 2016). During lactation, the mothers' stock of 2,3,7,8-TCDD decreases but this is transferred to the child (INSERM, 2000).

B.5.2.1.4.2. PCBs

In 2016 IARC published data on the toxicokinetics of PCBs, including the following syntesis for elimination. *« Highly chlorinated congeners persist in the body, with half-lives averaging about 8–15 years ; the half-lives of less chlorinated PCBs are distinctly shorter. In addition, PCB halflives vary according to species, being longer in humans than in experimental animals, including monkeys. PCBs are mainly excreted via the faeces, while urine usually represents a minor route of excretion. Faecal excretion concerns not only unabsorbed PCBs, but also the* *excretion of biliary metabolites in the intestine. The proportion as well as the rate of elimination in the excreta depends on the type of mixture or congener and the route of exposure. Excretion profiles, and metabolite profiles in excreta, were different after administration of a dermal dose of PCBs when compared with an equivalent intravenous dose. In addition to hydroxylated and dihydroxylated PCBs, the corresponding glucuronide and sulfate conjugates, as well as mercapturic acids, have also been characterized in the urine. Lactation is also a major route of excretion of PCBs in animals and humans. Minor routes of excretion such as elimination through the intestinal wall in the gastrointestinal tract or via the skin may also occur. »*

B.5.2.2. Acute toxicity

Not relevant for this dossier.

B.5.2.3. Irritation

- PCDD/Fs

There is no European harmonised classification for PCDDs, only a self-classification (2,3,7,8-TCDD as Eye Irrit. 2 - H319). However, a Japanese classification exists. The Chemical Management Center (CMC) of Japan National Institute of Technology and Evaluation (NITE) had classified 2,3,7,8-TCDD with Serious eye damage/eye irritation - Category 2A-2B but also Skin corrosion/irritation - Category 2.

1,2,3,6,7,8 HxCDD, 1,2,3,4,6,7,8 HpCDD, 2,3,4,6,7,8 HxCDF, 1,2,3,4,6,7,8 HpCDF are self-classified as Eye irrit 2 – H319.

- PCBs

PCBs cause several types of irritation. Brief skin contact causes local irritation; repeated or prolonged contact may result in skin damage. In case of occupational exposure to PCBs, brief skin contact does not cause any abnormalities other than possible local irritation. In the case of repeated or prolonged contact, the following disorders may be observed: skin disorders (chloracne, pigmentation, skin thickening and nail discoloration, "eczematous rashes"). There may also be signs of eye irritation and conjunctivitis but also and respiratory if inhaled (INRS 2007). However, no classification has been established.

B.5.2.4. Corrosivity

Not relevant for this restriction proposal.

B.5.2.5. Sensitisation

No harmonised classification has been established.

B.5.2.6. Repeated dosed toxicity

Critical effects are mainly based on impaired fertility, hormonal changes or hepatic effects. The Dossier submitter will therefore review in the chronic toxicity only studies on hepatic effects, the other critical effects impacting rather mostly the reprotoxicity.

- In terms of hazard, the properties of PCDDs and PCDFs are qualitatively similar, and quantitatively PCDFs are slightly less toxic than PCDDs for the same number of chlorine atoms as shown by their TEF (a factor of 10 below) (WHO, 2005). PCDD/Fs

The toxic effects of PCDD/Fs are relatively similar. Indeed, comparative data on PCDDs and PCDFs show common effects (ATSDR 1994 for PCDFs; ATSDR, 1998 for PCDDs ; EFSA, 2018; OEHHA, 1999; INERIS, 2006 for both of them). Their toxic effects are detailed below.

Data is available for comparing the link capacities at the AhR and thus the activities of PCDDs and PCDFs (PCDFs would have a lower binding capacity than PCDDs).

« Convincing data for the importance of the receptor in TCDD-induced toxicity could be based on structure activity relationships, i.e., that the binding affinities of TCDD and other PCDDs or PCDFs to the receptor correlate with their biological potencies. The binding affinities of PCDDs and PCDFs have been demonstrated to correlate with their biological potencies, particularly the induction of enzyme activities as well as the production of acute toxic effects (Poland & Kende,1976; Poland et al., 1976; Knutson & Poland, 1982). Furthermore, the structure-activity relationships observed for enzyme induction, thymic atrophy, body weight loss, and LD_{50} values were comparable to the structure-activity relationships observed for receptor binding (Bandiera et al., 1984a,b; Mason et al., 1985, 1986; Sawyer & Safe, 1985; Safe et al., 1986). Interactive studies, i.e., studies where PCDD and PCDF congeners have been given both separately and as mixtures, have also been used to investigate the role of the Ah receptor in the mechanism of action of TCDD" (WHO, 1989).

- Laboratory animals

In 2006, INERIS published a toxicological and environmental data sheet on dioxins. The following chronic toxicology studies are included. A chronic toxicity study (Kociba *et al*., 1978), is cited and was used for the selection of HRVs based on the critical liver effects. This study was conducted in rats, groups of 50 males and 50 females were exposed to 2,3,7,8-TCDD *via* the diet at doses of 1, 10 or 100 ng/kg/day for 2 years. A group of 86 males and 86 females served as controls. At 100 ng/kg/day, various effects were noted (excluding carcinogenic effects), including increased mortality, weight loss, increased excretion of urinary porphyrins and delta aminolevulinic acid, increased serum activity of liver enzymes (γ-GT, alkaline phosphatase, etc.). Histopathological changes were found in the liver, lymphoid, lung and vascular tissues. Proliferation of granular endoplasmic reticulum was detected in the liver. At 10 ng/kg/d, the effects were less, with liver and lung damage still present. The dose of 1 ng/kg/d produced no detectable toxic effects.

EFSA (2018) and OEHHA (1999) published information on the chronic toxicity of the family dioxin, furan, PCB-DL which confirms the study selected by INERIS (2006). Here's the information we could extract from it:

- Hepatic disorders "*with induction of hyperplasia and hypertrophy of liver parenchymal cells. Morphological and biochemical changes in the liver include increased SGOT and SGPT, induction of microsomal monooxygenases and proliferation of the smooth endoplasmic reticulum, porphyria, increased regenerative DNA synthesis, hyperlipidemia, hyperbilirubinemia, hyperchloesterolemia, hyperproteinemia, degenerative and necrotic changes, mononuclear cell infiltration, multinucleated giant* *hepatocytes, increased numbers of mitotic figures, and parenchymal cell necrosis*" (US EPA, 1994d; WHO/IPCS, 1989 cited in OEHHA, 1999).

- Epithelial effects "*seen include chloracne (rabbit ear and the hairless mouse) (Jones and Krizek, 1962; Schwetz et al., 1973) and hyperplasia and/or metaplasia of gastric mucosa, intestinal mucosa, the urinary tract, the bile duct and the gall bladder*" (US EPA 1994 cited in OEHHA, 1999).

- « *TCDD and other dioxin like PCDDs and PCDFs are potent suppressors of both cellular and humoral immune system function, characteristically producing thymic involution at low doses and involution of other lymphoid tissues at higher doses (US EPA, 1994* cited in OEHHA, 1999). »

In 2001, Jamsa *et al*. reported bone effects found in the study of Viluksela *et al*. (2000). A significant reduction of bone growth was seen at 10 ng/kg bw per day ($p < 0.01$) in the Long-Evans rats, while in Han Wistar rats the effect of TCDD was seen only at the high dose of 1,000 ng/kg bw per day ($p < 0.05$).

- Humans

The toxicity of PCDD/Fs has been the subject of numerous studies. The toxicity of these compounds has been extensively demonstrated at high doses in many animal species. In humans, numerous epidemiological studies have been conducted in industrial environments, particularly following contamination accidents, including Seveso. However, the uncertainties in the assessment of the health risk associated with dioxins remain significant, in particular with regard to the effects of prolonged exposure to low levels.

The effects presented below are drawn from the conclusions held by EFSA in 2018, OEHHA in 1999 and INERIS in 2006.

- Dermatological effects: Chloracne is often observed in accidental situations, but cases of chloracne have also been reported among workers involved in the daily production of products contaminated with 2,3,7,8-TCDD (Suskind and Hertzberg, 1984). Chloracne caused by PCDD/Fs is now considered to be the most reliable and specific indicator of toxicity in humans but epidemiological data available for 2,3,7,8-TCDD have not allowed a determination of the threshold dose required for production of chloracne (US EPA, 1994b) and thus is not appropriate in risk assessment. According to OEHHA (1999), "*Chloracne is a persistent condition, which is characterized by comedones, keratin cysts and inflamed papules and is seen after acute and chronic exposure to various chlorinated aromatic compounds (Moses and Prioleau, 1985). Other dermal effects include hyperpigmentation and hirsutism or hypertrichosis (Jirasek et al., 1974; Goldman, 1972; Suskind et al., 1953; Ashe and Suskind, 1950).*"

- Hepatic effects: Five studies were found comparing blood PCDD/F levels of occupational or accidental exposed cohorts and potential non-cancer hepatic and digestive disorders or abnormal function in the EFSA report. Based on these studies it was concluded that there is no evidence for an association of hepatic or digestive diseases with prolonged accidental or occupational exposure to PCDD/Fs.

- Neuropsychic effects: There are numerous reports associating acute or chronic exposure to 2,3,7,8-TCDD with headache, insomnia, nervousness, irritability, depression, anxiety, loss of libido, encephalopathy. There are reports of persistent symptoms. No association was found between exposure to 2,3,7,8-TCDD and depression in the NIOSH study (Roegner *et al*., 1991; Alderfer *et al*., 1992).

- Thyroid function: EFSA (2018) concluded that from studies reporting high exposure (resulting from accidental exposure or incidents) to TCDD or PCDD/F and DL-PCB-TEQs there is insufficient evidence for an association with thyroid function/disease in adults. The study by Baccarelli *et al*. (2008) in highly exposed children from Seveso provides relatively strong support for a causal association between prenatal exposure to TCDD and increased neonatal blood TSH concentration, indicating possible subclinical hypothyroidism. However, EFSA indicates that the association has only been demonstrated at high exposure since most studies of low-moderate exposure to PCDD/Fs and DL-PCBs (resulting from background exposure) in newborns or children do not suggest any adverse effects on thyroid function in children.

- Metabolic effects (Type 2 diabetes and obesity): the currently available studies on diabetes and obesity are inconclusive and cannot be used as a basis for a risk assessment according to EFSA (2018).

- Immunological effects: Some studies analyze the effects on the immune system when exposed to PCDD/Fs and DL-PCBs in adolescence or adulthood. However, the results differ between studies and a consistent link seems difficult to make. Therefore, no association has been established at this time.

- Cardiovascular effects and blood lipid levels: The increased cardiovascular risk from exposure to TCDD has only been demonstrated at very high exposure, much higher than blood concentrations resulting from exposure at the present TWI of 14 pg TEQ/kg bw per week. Studies at lower doses are inconsistent and do not support an association between exposure to these substances and increased cardiovascular risk.

- Effects on teeth and bone: The effect of this family of substances has been studied in three different population groups (Seveso, Helsinki, Yucheng). Childhood exposure to TCDD and/or other PCDD/Fs was dose-relatedly associated with tooth enamel hypomineralisation or enamel defects. Hypomineralisation has mainly been shown in permanent teeth and is likely to be a postnatal effect. Hypomineralisation weakens the enamel and is adverse as it increases the risk of caries and impaired tooth health later in life. One cohort in EFSA report indicated limited evidence for some changes in bone parameters and noted that observations at a later age might be more sensitive for assessing possible associations between early life TCDD exposure and measures such as bone strength.

The different forms of toxicity of TCDD are well known, in contrast to its mechanisms of toxicity. The toxicity of 2,3,7,8-TCDD in humans is currently established for the dermatological effects and many other suspicious links are increasingly being studied, particularly for: hepatic, neuropsychic, metabolic, immunological and teeth and bone effects but also for cardiovascular effects and blood lipid levels and modification of thyroid function.

- PCBs

There are few data on responsibility for the type of PCB (dioxin-like or non-dioxin-like) in the toxic effects reported. The toxicity of PCBs is mainly linked to the long-term accumulation in the body of these compounds (INVS, 2009).

- According ATSDR (2000), *"hepatotoxic effects commonly induced in laboratory animals exposed to commercial PCB mixtures include increased serum levels of liver enzymes indicative of hepatocellular damage (e.g., AST and ALT), serum and tissue biochemical changes indicative of liver dysfunction (e.g., altered levels of lipids, cholesterol, porphyrins, and vitamin A), and histopathologic changes (particularly fat deposition), fibrosis, and necrosis. Intermediate- and chronic-duration oral studies have shown hepatotoxic effects in monkeys that include fatty degeneration, hepatocellular necrosis, and hypertrophic and hyperplastic changes in the bile duct at oral doses of PCBs as low as 0.1–0.2 mg/kg/day (Aroclor 1254 or 1248)."* According to IARC (2016) pre-neoplastic liver damage may also be induced.

- PCBs could affect the immune system, by reducing the immune response, especially in children exposed in utero and during breastfeeding (ATSDR, 2011; Institut National de Santé Publique du Québec, 2006). According to IARC (2016) *"the limited data available for human exposure suggested that PCBs may cause immunosuppression. PCBs can affect an impressive number of immune parameters that include changes in bone-marrow cellularity; shifts in T-lymphocyte subsets and function; thymus and spleen atrophy, which correlate strongly with humoral and cell-mediated immunosuppression; reduced resistance to microbial infection; and a compromised immune-surveillance mechanism. Alterations in the immune system and immunotoxicity were also reported after PCB exposure during prenatal or early life. The effects on the immune system were shown to persist in children at a later age. The severity of effects correlated with PCB concentrations in the children's blood, or with those in maternal blood during pregnancy and lactation. Similar results were obtained in experimental animals."*

- Effects on bone mineral density : According to ATSDR (2011), "*the sum of the three most abundant non-dioxin-like PCBs (PCB-138, PCB-153, PCB-180) was positively associated with* bone mineral density*, but not with a decreased risk of low* bone mineral density*. In females, PCB-118 was positively associated with* bone mineral density*, but this congener did not influence the risk of low* bone mineral density *in women (Hodgson et al., 2008)".*

- PCBs could increase the frequency of respiratory infections such as chronic bronchitis (ATSDR, 2000).

- PCBs could promote the appearance of type 2 diabetes (ATSDR, 2011) and neurodegenerative diseases (Parkinson's disease, dementia, etc.) (ATSDR, 2011).

- PCBs could also cause chloracne and other dermal alterations. *"Chloracne generally appears in individuals with serum PCB concentrations that are 10–20 times higher than those of the general population, but there is large variability between individuals. At birth, children exposed in utero during food poisoning incidents had increased rates of* *hyperpigmentation, eyelid swelling and discharge, deformed nails, and acne, compared with controls. Long-term oral administration of relatively low doses of PCBs to rhesus monkeys resulted in dermal alterations similar to those observed in humans exposed at high concentrations. Offspring from monkeys exposed during gestation and nursed by exposed mothers also developed dermal alterations after a few weeks of suckling. Rodents also develop skin alterations, but only after high exposures to PCBs. Exposure of normal human melanocytes to TCDD resulted in activation of the aryl hydrocarbon receptor signalling pathway, an aryl hydrocarbon receptor-dependent induction of tyrosinase and – as a consequence – an elevated total melanin content. These effects were due to the induction of expression of tyrosinase and tyrosinase-related protein 2 genes. Thus, the aryl hydrocarbon receptor is able to modulate melanogenesis by controlling the expression of melanogenic genes. This lends biological plausibility to the epidemiological findings of increased risks of melanoma of the skin after exposure to PCBs"* (IARC, 2016).

- According to ATSDR (2000) "*ocular effects including hypersecretion of the Meibomian glands, abnormal pigmentation of the conjunctiva, and swollen eyelids have also been observed in humans occupationally exposed to PCBs. These ocular alterations almost always accompany chloracne. Ocular effects may continue to appear after exposure has ceased, possibly as a result of accumulation of the causative agent in skin adipose. Chronic duration oral exposure studies in monkeys showed that adverse dermal and ocular effects can occur at dose levels as low as 0.005 mg/kg/day."*

- Inflammation mechanisms may also be associated with PCB exposure. *"In in-vivo studies in mice, it has been reported that PCB-77, PCB-104, and PCB-153 are associated with inflammation in target organs since they induced the production of specific inflammatory mediators, including intercellular adhesion molecules (e.g. ICAM, VCAM-1, MCP-1) in the liver, lungs, and brain. In vitro, PCB-153 may induce expression of several pro-inflammatory cytokines through NF-κB pathway inhibitor. Several PCB congeners and mixtures, including Aroclor 1242 and PCB-47, interfere with O2– elimination by suppressing the activity of superoxide dismutase which converts O2– to H2O2. Non-dioxin-like PCBs are capable of stimulating neutrophil O2– production, while dioxin- like congeners with a high affinity for the aryl hydrocarbon receptor do not activate neutrophils to produce O2– and may inhibit this response. Certain congeners (PCB-77, PCB-114, PCB-126, and PCB-169) disrupted the normal functions of the vascular endothelium, thus allowing increased transfer of albumin across endothelial monolayers. The same congeners enhanced oxidative stress, increased production of interleukin-6 by endothelial cells, increased the levels of intracellular calcium, increased the activity of cytochrome P450 1A, enhanced expression of the adhesion molecule VCAM-1, and decreased levels of vitamin E in the culture medium. In contrast, PCB-153 did not have an effect on cellular oxidation or on endothelial barrier function"* (IARC, 2016).

B.5.2.7. Mutagenicity

Dioxins and PCBs haven't harmonised classification for mutagenicity.

- PCDD/Fs

Genotoxicity was studied in the EFSA (2018) report on the dioxin and furans. Here is the information it contains. "*The genotoxicity of TCDD has been studied intensively over the last five decades. The evidence for the direct genotoxicity of TCDD is negative or equivocal for a large array of in vitro and in vivo endpoints (Giri, 1986; IARC, 1997; ATSDR, 1998; NTP, 2006a; Budins ky et al., 2014). These include aneuploidy, chromosomal aberrations, DNA damage, dominant lethal mutation, gene mutation, micronuclei, mitotic recombination and gene conversion, sister chromatid exchange (SCE) and cell transformation. Studies have shown induction of oxidative stress-related DNA damage by high-dose acute exposure to TCDD. It is hypothesised that TCDD-mediated persistent activation of AhR may be responsible for inducing oxidative stress and associated indirect genotoxicity (NTP, 2006a). Few studies have recently addressed the potential genotoxicity of PCDD/Fs. In an interlaboratory comparison of TCDD among five laboratories, no significant increase in the induction of micronuclei formation was detected in human peripheral blood cells exposed in vitro (Katic et al., 2010). In vivo, no increase in mutation frequency or change in mutational spectra was observed after 6 weeks of exposure to 2 µg TCDD/kg bw twice a week for 6 weeks, in both male and female Big Blue® lacI transgenic rats (Thornton et al., 2001).*"

- PCBs

*"The results of in vitro and in vivo genotoxicity studies are generally negative and indicate that commercial PCB mixtures are not potent genotoxicants. Although PCBs have been found to be generally inactive as mutagens in S. typhimurium strains and in several other tests of genotoxicity that may be predictive of tumor initiation activity, in vitro studies with rat microsomes have indicated that metabolism of lower chlorinated congeners can lead to covalently modified macromolecules including proteins and DNA (Hayes 1987; Robertson and Gupta 2000; Silberhorn et al. 1990). Therefore, although the available dataindicate that PCBs are not potent genotoxicants, there is some experimental support for the possible involvement of genotoxic mechanisms in the development of PCB-induced cancer" (*ATSDR, 2000*).* There is a lack of data about levels or even occurrence of individual PCB congeners in publications on the genotoxic effects of PCBs in humans. Only a few recent studies had analysed a very small number of congeners - some DL-PCBs and two NDL-PCBs (PCB-153 and PCB-209, respectively hexa and decachlorinated) and calculated correlations with biological effects.

- PCB-77 caused DNA damage to human peripheral lymphocytes at the highest dose tested as assessed by the Comet assay but was significantly less potent than the non-dioxin-like congener PCB-52 (Sandal *et al*., 2008 cited in EFSA, 2018).

- PCB-126 (125,250 or 500 lg/kg) during pregnancy doesn't increase the frequency of mutations *in vivo* transgenic transgenerational mutagenicity assay using Muta (M) in mice (single doses: 125,250 or 500 lg/kg) (Inomata *et al*., 2009 cited in EFSA, 2018). However, according to IARC (2016), *"a dose-dependent increase in DNA-adduct formation – resulting from lipid peroxidation or oxidative damage of the DNA backbone – has been reported in rats exposed to PCB-126 in the long-term. Thus, a genotoxic mechanism, probably via generation of reactive oxygen species, seems to contribute to the mode of action of PCB-126."*

- *"Statistically positive correlations were found between serum concentration of PCB-118 and formation of micronuclei and DNA strand breaks (comet assay) in peripheral lymphocyte"* (IARC, 2016).

- *"PCB-3 causes mutation in vitro and in vivo. However, metabolic activation to electrophilic species, i.e. quinones, is required, as shown by direct testing of PCB-3 metabolites for gene mutagenicity in vitro. The experimental evidence overall suggested that both DNA-adduct formation and generation of reactive oxygen species must be considered equally plausible modes of action"* (IARC, 2016).

- PCB-153 induced structural chromosomal aberrations in human lymphocytes and a statistically significant dose-dependent increase in the frequency of micronucleus formation in human breast epithelial MCF-10A cells and in human hepatocarcinoma Hep-G2 cells (IARC, 2016).

- PCB-209 (heavily chlorinated) did not induce mutations at the thymidine kinase locus in mouse lymphoma cells ; it did not increase micronucleus formation in bone marrow cells of male and female mice given a single oral and high dose (2000 mg/kg bw) (IARC, 2016) .

B.5.2.8. Carcinogenicity

- PCDD/Fs

2,3,7,8-TCDD is classified since 1997 group 1 by the IARC and other dioxins belong to group 3 mainly based on studies in workers who have been exposed to industrial accidents and on evidence of carcinogenicity in animals. According to IARC many epidemiological studies have been carried out on the health effects of emissions from older generation household waste incinerators. The effects of chronic exposures observed in occupationally exposed workers or the effects of accidental poisoning would suggest that exposure to TCDD is associated with an increased risk of all types of cancer in humans. The three human cancer sites for which an association was most often found in the studies are: lung cancer, non-Hodgkin's lymphoma (NHL) and soft tissue sarcoma (STS) (Baan, 2009). The liver is also a particular target for dioxin carcinogenicity.

The WHO concluded in 2001 that the carcinogenicity of 2,3,7,8-TCDD was not related to mutagenic effects or DNA binding and that carcinogenic effects were observed at doses higher than those for other toxic effects. The Commission considered that the mechanisms of carcinogenesis involving the AhR (arylhydrocarbon receptor) suggest an effect threshold for carcinogenicity. The main mechanism is the promotion of tumor development via the activation of cellular replication and the alteration of cellular senescence and apoptosis. IARC also considers a secondary mechanism related to the increase of oxidative stress resulting in DNA damage. Therefore, the WHO concluded that the establishment of a threshold HRV based on non-carcinogenic effects also protects the population from the effects of carcinogens (WHO, 2001). In the circular of 11 June 1998, the Directorate General for Health also considered that dioxins were not genotoxic and that the mechanism of carcinogenesis had an effect threshold (DGS, 1998).

In 2012, IARC concludes that the carcinogenic mechanism of TCDD is valid for all dioxins, furans and DL-PCBs and detailed this mechanism of action. *"There is strong evidence to* *support a receptor mediated mechanism of action for TCDD associated carcinogenesis in humans where the primary mechanism is the promotion of tumour development through the activation of cellular replication and the alteration in cellular senescence and apoptosis. Dioxin, through activation of an array of metabolic enzymes also increases the risk for oxidative stress, which serves as an indirect initiator of carcinogenesis. These events make dioxin a complete carcinogen. The conservation of the AhR and the related signalling pathways across species strongly support this mechanism in humans. The receptor-mediated mechanism of action for TCDD-associated carcinogenesis in humans is strongly suggested as the mechanism of action that would result in 2,3,4,7,8-PeCDF and PCB 126 causing cancer in humans. The primary mechanism is the promotion of carcinogenesis through the activation of cellular replication and the alteration in cellular senescence and apoptosis through the aryl-hydrocarbon receptor (AhR). These congeners, through activation of an array of metabolic enzymes, increase the risk for oxidative stress as an indirect initiator of carcinogenesis, which makes these congeners complete carcinogens. The conservation of the AhR and the related signalling pathways across species strongly support this mechanism of action in humans. There is compelling evidence that the mechanism of action for TCDD-associated carcinogenesis in humans operates as the mechanism of action for carcinogenesis in humans for 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8HpCDD, OCDD, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, OCDF and PCBs 77, 81, 105, 114, 118, 123, 156, 157, 167, 169, and 189. These compounds all bind to the AhR in human cells and demonstrate changes in gene expression consistent with those seen for TCDD and 2,3,4,7,8-PeCDF. The secondary mechanism relate to activation of cell replication, alterations in cellular senescence and apoptosis, and increases in oxidative stress causing DNA damage."*

2,3,4,7,8-Pentachlorodibenzofuran is classified since 2012 group 1 by the IARC. The other furans in the family are classified as group 3.

- PCBs
  - Laboratory animals

According to IARC (2016), « *There is sufficient evidence in experimental animals for the carcinogenicity of PCB-126, PCB-118, Aroclor 1260, Aroclor 1254, and Kanechlor 500. There is limited evidence in experimental animals for the carcinogenicity of PCB-153, 4′-OH-PCB-30, 4′OH-PCB-61, Aroclor 1242, Aroclor 1016, Clophen A30, and Clophen A60. There is inadequate evidence in experimental animals for the carcinogenicity of PCB-138, Kanechlor 300, and Kanechlor 400. Congeners for which there is sufficient evidence in experimental animals for carcinogenicity (PCB-126 and PCB-118) are agonists of the aryl hydrocarbon receptor and exhibit dioxin-like properties. Commercial mixtures for which there is sufficient evidence in experimental animals for carcinogenicity are highly chlorinated and are known to include aryl-hydrocarbon receptor agonists that exhibit dioxin-like properties, as well as agonists of the constitutive androstane receptor. The commercial mixtures for which there is limited evidence in experimental animals generally have a low degree of chlorination, but are also known to contain congeners that are agonists of the aryl hydrocarbon and/or constitutive androstane receptors. The relative contributions of the different congeners (dioxin-like and non-dioxin-like) to the carcinogenicity of the commercial mixtures is not known.* »

- Humans

On the basis of sufficient evidence of carcinogenicity in humans and experimental animals, the IARC Working Group classified PCBs as carcinogenic to humans (Group 1) in 2013. DL-PCBs were classified in Group 1 on the basis of extensive evidence of an AhR-mediated mechanism of carcinogenesis that is identical to that of 2,3,7,8-TCDD, and sufficient evidence of carcinogenicity in experimental animals. These informations are reinforced by the IARC in 2016: « There is sufficient evidence in humans for the carcinogenicity of polychlorinated biphenyls (PCBs). PCBs cause malignant melanoma. Positive associations have been observed for non-Hodgkin lymphoma and cancer of the breast. Others locations of cancers have been investigated in some studies. There were positive findings for cancer of the prostate and brain in several studies, but null findings in others. Other cancers with sporadic positive findings were those of the liver and biliary tract, extrahepatic biliary tract, lung and respiratory tract, thyroid, stomach, pancreas, colon and rectum, urothelial organs, uterus and ovary combined, as well as childhood acute lymphatic leukaemia, and multiple myeloma. There is strong evidence to support a receptor-mediated mechanism for carcinogenesis associated with dioxin-like PCBs in humans, based upon demonstration of carcinogenicity in experimental animals and upon extensive proof of activity identical to 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) for every step of the mechanism described for TCDD-associated carcinogenesis in humans, including receptor binding, gene expression, protein-activity changes, cellular replication, oxidative stress, promotion in initiation– promotion studies and complete carcinogenesis in experimental animals. According to the WHO, (2016), DL-PCBs with Toxicity Equivalent Factor (TEF) (PCB-77, PCB-81, PCB-105, PCB-114, PCB-118, PCB-123, PCB-126, PCB-169, PCB-156, PCB-157, PCB-167, PCB-189) are considered to be carcinogenic to humans (Group 1) in 2016. However, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs. »
Indeed, *« non-dioxin-like PCBs induce many of their effects via multiple aryl hydrocarbon receptor-independent mechanisms, including activation of the constitutive androstane or pregnane X receptors, and perturbations in cell–cell communication and cell adhesion. Non-dioxin-like PCBs induce production of reactive oxygen species, activation of NF-κB transcription factors, and suppression of plasma membrane proteins, constituents of gap, adherens, and tight junctions, all of which may play a significant role in tumour promotion and progression. A series of non-dioxin-like PCBs, including less chlorinated congeners (e.g. PCB-18, PCB-47, PCB-52, and PCB-74), environmentally abundant congeners (e.g. PCB-138 and PCB-153), and hydroxylated metabolites, such as 3′,4′-di(OH)PCB-5, 4-OH-PCB-109 (4-OH-2,3,3′,4′,5-pentaCB), and 4-OH-PCB-187, inhibited gap junction intercellular communication in rat liver epithelial cells. A mixture of seven non-dioxin-like PCBs (PCB-28, PCB-52, PCB-101, PCB-138, PCB-153, PCB-180, and PCB-209) induced production of reactive oxygen species and cell motility in human breast cancer cells. Both the dioxin-like congener PCB-126, and the non-dioxin-like congeners PCB-118 and PCB-153 disrupted the expression of cytosolic scaffold proteins of tight junctions in brain endothelial cells in mice. Expression of anti-apoptotic Bcl2 gene in a short-term study in female rat liver, to decrease apoptotic index and to suppress the levels of gap junction and adherens junction proteins (connexin 43, β-catenin, E-cadherin) in rat liver epithelial cells. PCB-28, PCB-101, PCB-153, and also PCB-187 (to a lesser extent) suppressed apoptosis in rat hepatocytes and human hepatoma HepG2 cells"* (IARC, 2016).

On this basis, PCDD/Fs and DL-PCBs were considered carcinogens. Caution should be taken because the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of DL-PCBs. Indeed, NDL-PCBs may play a significant role in tumour promotion and progression.

B.5.2.9. Toxicity for reproduction

In 2003, Afsse declared that reproductive and developmental effects of dioxins, furans and PCBs have been the subject of conflicting results and cannot be considered formally demonstrated in the current state of knowledge. Despite increasing evidence of an association between exposure to these substances and reproductive effects, at the present time, there is still no classification by ECHA or US EPA is available. On the other hand, TCDD was classified as Category 1B reprotoxic by the Chemical Management Center of Japan National Institute of Technology and Evaluation. The reprotoxic effects found are detailed below.

- PCDD/Fs

Several studies suggest that PCDD/Fs have reproductive toxicity. EFSA in 2018 and INERIS in 2006 have described a number of these effects. Here, only the impact of these substances on fertility. Other impacts related to reprotoxicity may occur during in utero exposure. We'll just quickly mention them: teratogenic effects and miscarriage have been reported, changes in birth weight, changes in sex ratio and puberty development, behavioural disorders and also immunoteratoly have been reported (INERIS, 2006).

Based on various epidemiological studies available EFSA (2018) and INERIS (2006) tend to conclude that fertility is declining.

- Male: *"Sperm abnormalities have been found upon exposure to these substances. For exemple, a study among boys/men from the Russian Children's Study, reported that high serum TCDD concentrations at age 8–9 years were associated with impaired semen quality later in life (Mınguez-Alarcon et al., 2017). The study also showed significant associations for PCDD-TEQs, but not for PCDF-TEQs, DL-PCB-TEQs or total TEQs (based on WHO2005-TEFs). Strong associations were also found between exposure to TCDD during infancy/prepuberty and altered sperm quality in the Seveso population (Mocarelli et al., 2008, 2011). The evidence from these studies suggests that there may be a postnatal period of sensitivity that might expand into puberty. Significant disturbance of testosterone levels was also found".*

- Female: *"Endometriosis cases have been reported from exposure to dioxin through an increase of Ah receptors and CYP1A2 in endometriosis tissues in vitro" (EFSA, 2018).*

These observations and the fact that AhR activation may induce the estrogen signalling pathways make TCDD a possible endocrine disruptor (Sorg *et al*., 2014).

- PCBs

According to Danish EPA (2014): *"oral studies with animals provide conclusive evidence for reproductive toxicity of commercial PCB mixtures. In females of various species, effects include oestrus changes and reduced implantation rate in adult rats and/or their offspring, decreased conception in mice, and menstrual alterations and decreased fertility in monkeys. There is limited evidence for reproductive effects in male adult animals whereas marked effects on morphology and production of sperm, and on fertility have been noted in male offspring of rats exposed to relatively high doses of Aroclor 1254 during gestation and lactation".*

As for dioxins and furans, impacts related to reprotoxicity may occur during *in utero* exposure. It should be noted that effects such as neurobehaviour alterations, neurological effects (abnormal reflexes and deficits in memory, learning, and IQ) depressed serum levels of T4 and T3, reduced birth weight and postnatal weight gain were found children born to mothers exposed to PCBs (ATSDR, 2000).

According to ATSDR (2000) *"limited data indicate that menstrual disturbances in women and effects on sperm morphology and production, which are effects that can result in difficulty in a couple conceiving, may be associated with exposure to PCBs. Overall, the studies of reproductive end points in humans are limited; however, the weight of the existing human and animal data suggests that PCBs present a potential reproductive hazard to humans. In a small number of occupationally exposed women, there was no apparent effect of Aroclors 1254, 1242, and/or 1016 on mean number of pregnancies. A study of the general population found that blood PCB levels were higher in women who had repeated miscarriages, but levels of other organochlorine compounds were also elevated. Studies that examined reproductive end points in women whose diets contained Great Lakes fish found suggestive evidence that consumption of the fish may be associated with a slightly shorter length of menstrual cycle and reduced fecundability among couples attempting pregnancy, but not with increased risk of conception delay. The slight decreases in menstrual length seen in this population were considered of unknown clinical relevance. Menstrual cycle changes (altered intervals, duration, and flow) have also been observed in women exposed to higher doses of PCBs during the Yusho poisoning incident. However, another general population study did not find an association between endometriosis or increased risk for spontaneous fetal death and concentrations of PCBs in the blood.*

The ability of PCBs to cause reproductive effects in males is less clear-cut than in females. Sperm counts, fertility history, and testicular examinations were normal in workers who were exposed to Aroclor PCBs for several years. However, analysis of semen showed that increasing concentrations of some individual congeners, but not total PCBs, were associated with decreasing sperm motility in infertile men."

B.5.2.10. Other effects

Endocrine disruptive effects

As for PAH, an overview of endocrine-related disrupting effects for PCDD/Fs and PCBs was done based on DHI Water and Environment for European Commission (2007) and the presence of dioxins/furans and PCBs on the following lists: The Endocrine Disruption Exchange Inc (TEDX), and the Sin List (Substitute It Now) (Table 40 and Table 41).

- PCDD/Fs

According to OEHHA (2008) « *TCDD exposure results in endocrine like effects including epidermal growth factor like effects such as early eye opening and incisor eruption in the mouse neonate (Madhukar et al., 1984), glucocorticoid like effects such as involution of lymphoid tissues (U.S. EPA, 1994g; Sunahara et al., 1989), alteration in thyroid hormone levels and in some cases thyroid hormone like effects (WHO/IPCS, 1989; Rozman et al., 1984), decreases in serum testosterone and dihydrotestosterone (Mittler et al., 1984; Keys et al., 1985; Moore and Peterson, 1985), and changes in arachidonic acid metabolism and prostaglandin synthesis (Quilley and Rifkind, 1986; Rifkind et al., 1990). TCDD is known to decrease hepatic vitamin A storage (Thunberg et al., 1979)".*

Table 41: Endocrine disrupting effect of dioxins/furans: overview of evaluations

Chemical	CAS number	CE (2007)	TEDX List	SIN List	
Dibenzo-p-dioxines	262-12-4	-	No	No	
2,3,7,8 TCDD	1746-01-6	1 (human health)	Yes	No	
1,2,3,6,7,8 HxCDD	57653-85-7	-	No	No	
1,2,3,4,7,8-HpCDD	35822-46-9	-	No	No	
OCDD	3268-87-9	-	No	No	
2,3,7,8 TCDF	51207-31-9	**-**	Yes	No	
1,2,3,7,8 PeCDF	57117-41-6	**-**	Yes	No	
2,3,4,7,8 PeCDF	57117-31-4	1 (human health)	Yes	No	
1,2,3,4,7,8 HxCDF	70648-26-9	**-**	Yes	No	
1,2,3,6,7,8 HxCDF	57117-44-9	**-**	Yes	No	
2,3,4,6,7,8 HxCDF	60851-34-5	**-**	Yes	No	
1,2,3,4,6,7,8 HpCDF	67562-39-4	**-**	No	No	
1,2,3,4,7,8,9 HpCDF	55673-89-7	**-**	No	No	
OCDF	39001-02-0	**-**	No	No	

- : Not studied

- PCBs

According to IARC (2016) "*population-based studies in men and women have shown an inverse correlation between serum concentrations of PCBs and circulating testosterone, including testosterone bound to sex-hormone-binding globulin. Studies on mother–infant pairs showed an inverse relationship between indicator PCBs and testosterone in female infants, which was statistically significant with the mono-ortho congeners PCB-105 and PCB-118, while male infants showed a stronger reduction in estradiol with higher serum concentrations of PCBs. In studies on extracts of PCBs from human serum, higher serum PCB concentrations correlated with lower activities of the estrogen, androgen, and aryl hydrocarbon receptors. The observed inverse trend between dioxin- like PCBs and activities of the aryl hydrocarbon and estrogen receptors suggests that these compounds have anti-estrogenic activity. In cultured cells, highly chlorinated congeners generally act as anti-estrogens and their hydroxylated metabolites are more active than the parent compound. In contrast, less chlorinated PCBs and their hydroxylated metabolites are generally estrogenic, and their potency is dependent upon ortho chlorination and para hydroxylation; estrogenic activities of the hydroxylated metabolites of less chlorinated PCBs were reported to be additive. Studies with cultured cells demonstrated that some PCBs are androgen-receptor antagonists, the anti-androgenic effects of dioxin-like PCBs being more pronounced than those of ortho- substituted PCBs. This antagonism has been associated in humans with several factors related to an increased risk of cancer of the testis. In population-based studies, an inverse correlation was also reported between total serum PCBs and triiodothyronine,* *thyroxine, and thyroid-stimulating hormone. For hydroxylated PCBs, a positive correlation was found with free thyroxin in umbilical cord tissue of fetuses after in-utero exposure. Studies in rats demonstrated that hydroxylated PCBs that bind to the thyroid receptor act as agonists to the thyroid hormone; one metabolite even displayed a higher binding affinity than does thyroxine, the natural ligand. PCBs with chlorines in the ortho position only have significant binding affinity for the transport protein transthyretin. Hydroxylated PCBs may cross the placental barrier, probably through binding to transthyretin, thus causing a reduction of total and free thyroxine concentrations in fetal plasma and brain. Moreover, pre- and postnatal exposure to PCBs and their hydroxylated metabolites can interfere with the thyroid-hormone system, which may lead to a decrease in levels of thyroid hormone. Disturbance of thyroxine-binding to transthyretin by PCB metabolites and increased glucuronidation causes a reduction in serum thyroxine concentrations in Aroclor 1254-exposed rats. The interference of PCBs with the thyroid system in vitro as well as in animals corroborates the effects observed in human population studies. The effects of PCBs on thyroid-hormone function, metabolism and transport may increase the risk for toxicity and pre-cancerous processes. In a study that considered 10 different mechanisms to establish in-vitro toxicity profiles for 24 PCB congeners, hierarchical cluster analysis showed that 7 indicator PCBs contributed most to the anti-androgenic, (anti)estrogenic, and anti-thyroidal effects of PCBs reported to be present in human samples.”*

Table 42: Endocrine disrupting effect of PCBs: overview of evaluations

Chemicals	CAS number	CE (2007)	TEDX List	SIN List
PCB	1336-36-3	-	No	No
PCB 81	70362-50-4	-	Yes	No
PCB 77	32598-13-3	1 (human health)	Yes	No
PCB 123	65510-44-3	-	Yes	No
PCB 118	31508-00-6	1 (human health and wildlife)	Yes	No
PCB 114	74472-37-0	-	Yes	No
PCB 105	32598-14-4	-	Yes	No
PCB 126	57465-28-8	-	Yes	No
PCB 167	52663-72-6	-	No	No
PCB 156	38380-08-4	2 (human health)	Yes	No
PCB 157	69782-90-7	-	No	No
PCB 169	32774-16-6	1 (human health)	Yes	No
PCB 189	39635-31-9	-	No	No

- : Not studied

<u>Toxicity Mediated by Epigenetic Mechanisms</u>

Patrizi *et al*. review (2018) is focus on the recent literature dealing with epigenetic mechanisms induced by 2,3,7,8-TCDD, considering three main epigenetic mechanisms: DNA methylation, histone modifications and non-coding RNAs (ncRNAs) (Table 43, Table 44,Table 45). Here is a summary of the effects they found.

Table 43: Summary of the recent papers dealing with new insights in TCDD-induced epigenetic Methylation/Demethylation of target genes (from Patrizi et al., 2018)

Model	Target Genes	Epigenetic Mechanism: DNA Methylation/Demethylation	Refs.

Activated T cells from C57BL/6 mice	Foxp3 and IL-17	Dymethylation of CpGs of Foxp3 promoter; Hypermethylation of IL-17 promoter.	Singh *et al*. (2011)
Jcl:ICR mice embryos	H19 and IGF2	Hypermethylation of CpGs of H19 and IGF2 promoters; Over-expression of DNMT.	Wu *et al*. (2004)
Palate tissue of fetal C57BL/6J mice	DNMT3a	Dymethylation of CpGs in DNMT3a promoter; Over-expression of DNMT3a.	Wang *et al*. (2017)
Zebrafish embryos	cfos and ahrra	Hypermethylation of CG dinucleotides of cfos and ahrra promoters; Up-regulation of dnmt1 and dnmt3b2; Down-regulation of dnmt3a1, dnmt3b1, dnmt3b2.	Aluru *et al*. (2015)
Adult C57BL/6 mice Liver	Cyp1a	Demethylation of CpGs of Cyp1a1 promoter; Cyp1a1 transcriptional activation.	Amenya *et al*. (2016)

Table 44: Summary of the recent papers dealing with new insights in TCDD-induced epigenetic histone(from Patrizi et al., 2018)

Model	Target Genes	Epigenetic Mechanism: Histone Modification	Refs.
Human breast cancer MCF-7 and human hepatic cancer HepG2 cell lines	CYP1A1 and CYP1B1	Promoters of CYP1A1 and CYP1B1 of MCF-7 and HepG2 cell lines: Acetylation of Histone H3 (Lys 9 and Lys 14); Trimethylation of Histone H3; Acetylation of Histone H4 (Lys 4)	Beedanagari *et al*. (2010)
Human prostate cell line RWPE-1	CYP1A1	Acetylation of histone H3 and H4 in CYP1A1 promoter; Histone acetylation upstream the regulatory elements of CYP1A1 gene	Okino *et al*. (2006)
Fetal mice C57BL/6J	TGF-β3	Increased TGF-β3 gene expression; Hyperacetylation of Histone H3; Up-regulation of HAT activity	Yuan *et al* (2016)
Hepatocytes isolated from AhR-wild type and AhR-null mice	RB1	Over-expression of HDAC8; Decreased expression of Rb1 tumor suppressor.	Wang *et al*. (2017)
Cultured C57BL6 mouse primary hepatocytes	PADI2 and CPS1	Homocitrullination by CPS1 of Lys 34 of histone H1; Enhanced expression of PADI protein with consequent histone H3 citrullination.	Joshi *et al*. (2015)

Table 45 : Summary of the recent papers dealing with new insights in the role of ncRNAs in mediating TCDD toxicity (from Patrizi et al., 2018)

Model	Target Genes	Epigenetic Mechanism: Non-Coding RNAs	Refs.
Kunming mice embryos	IGF2	Lower expression levels of lncRNA H19 in TCDD-treated mice between gestation days 13.5 and 15.5, associated with augmented expression	Gao *et al*. (2016)

		of IGF2 (on days 13.5 and 15.5); Higher expression levels of lncRNA H19 on gestation day 14.5 associated with a strong reduction of IGF2 expression.	
MCF-7 and Jurkat cells	CYP1B1	The expression of miRNA-27b strongly regulates the expression of CYP1B1 protein in cancerous cells and tissues.	Tsuchiya *et al*. (2006)
WT, L-E, H/W, AhR-null mices and mouse Hep	CYP17a1, CYP7a1, Thrsp, Scd1, Tgfbp1i4	Very little effects in lowering levels of few miRNA (101a, 138, 203, 361, 498, 542-5p), but especially miRNA 122a.	Moffat *et al.* (2007)
Fetuses Thymic cells (C57BL/6 mice)	CYP1A1	Down-regulation of miRNAs 27a, 28, 29, 182, 203, 290, 31, 101b, and 335.	Singh *et al*. (2012)

B.5.12.11. Mode of action

According to EFSA (2019) and IARC (2016), the current consensus states that the molecular initiating event of toxicity in vertebrates of the most dangerous dioxin, TCDD, is the binding to AhR and its consequent activation.

AhR is a cytosolic, ligand-activated transcription factor and is a highly conserved, over 600 million-year-old protein (Hahn *et al*., 2017 cited by EFSA, 2019). AhR mediates many toxic and carcinogenic effects in vertebrates. AhR "*has proven to have important physiological functions throughout life, including early development of organs such as the immune, hepatic, cardiovascular and reproductive systems. At the cellular level, AhR is involved in the control of cell proliferation and differentiation, while at the molecular level AhR regulates transcription of a large number of physiologically important genes and may have effects on processes involving epigenetic mechanisms (Mulero-Navarro and Fernandez-Salguero, 2016*)" (EFSA, 2019). AhR-mediated toxic responses are consequences of deregulated physiological functions, and sustained (chronic) AhR activation by persistent "dioxin-like" compounds is the key process in dioxin-like toxicity (Bock & Köhle, 2006 cited by IARC, 2012).

According to EFSA (2019), "*TCDD has extremely high affinity to the AhR and is the reference AhR agonist and toxicant. Ensuing TCDD toxicity results from inappropriate (in terms of timing, location and/or degree) and sustained activation of AhR (Bock and Kohle, 2006; Denison et al., 2011; Mulero-Navarro and Fernandez-Salguero, 2016). Compared to most other PCDD/F and DL-PCB congeners, TCDD has a higher binding affinity to the AhR and exhibits a greater AhR activation potency*". *The major advantages of this concept are that most (if not all) effects of dioxin-like compounds are mediated via AhR activation"* (IARC 2016).

B.5.12.12. Derivation of DNEL(s)/DMEL(s)

B.5.12.12.1 Oral

Taking into account the close contact of single-use baby diapers with the buttocks, the use of dermal HRVs seemed appropriate. However, since no HRVs were available for this route of exposure, a search for HRVs by the oral route was carried out.

Several organisations propose no-threshold oral HRVs for dioxins, or DL-PCBs (Table 46).

Table 46 : No threshold HRVs for PCDD/Fs and DL-PCBs

Chemicals (CAS Number)	US EPA	OEHHA*
2,3,7,8-TCDD and related compounds (1746-01-6)	/	Oral slope factor: 1,3.10^5 $(mg/kg/day)^{-1}$ Critical effect: Liver cancer Evaluation date: 2011
1,2,3,6,7,8 HxCDD (57653-85-7)	Oral slope factor: 6.2.10^3 $(mg/kg/day)^{-1}$ Critical effect: Liver Evaluation date: 1987	Oral slope factor: 1.3.10^4 $(mg/kg/day)^{-1}$ Critical effect: Liver cancer Evaluation date: 2011
1,2,3,7,8,9 HxCDD (19408-74-3)		Oral slope factor: 1,3.10^4 $(mg/kg/day)^{-1}$ Critical effect: Liver cancer Evaluation date: 2011
PCBs	Oral slope factor: 2 $(mg/kg/day)^{-1}$ Critical effect: Liver tumors Evaluation date: 1996	Oral slope factor: 2 $(mg/kg/day)^{-1}$ Choice of the US EPA oral slope factor (US EPA, 1996)

* OEHHA propose oral slope factor for congeners of PCDDs, PCDFs and PCBs by applying the WHO 2005 TEF.

However, JECFA considered in 2001, that dioxins, furans and DL-PCBs carcinogenic effects are not linked to mutagenic effect or to ADN bindings and are observed for higher doses than for other toxic effects. So JECFA concluded that a threshold exists for all the effects including the carcinogenic ones. Indeed, TCDD was not directly genotoxic and its carcinogenic activity is probably due to a long half-life (7.2 years), in particular in humans, causing an important activation of the Ah receptor (arylhydrocarbon receptor) (IARC, 2012).

So IARC concluded in a carcinogenic mechanism in humans mediated by a receptor. The main mechanism is the promotion of tumor development *via* the activation of cellular replication and the alteration of cellular senescence and apoptosis. IARC also considers a secondary mechanism related to the increase of oxidative stress resulting in DNA damage. In 2012, IARC also evaluated 1,3,4,7,8-PeCDF and PCB126 and also considered a receptor-mediated carcinogenesis mechanism based on carcinogenic effects observed in animals and extensive evidence identical activity with TCDD. IARC also concludes that the carcinogenic mechanism of TCDD is valid for all dioxins, furans and DL-PCBs.

On this basis, dioxins, furans and DL-PCBs were considered as threshold carcinogens. Therefore, only chronic threshold HRVs were selected.

Ten organisations and one publication propose chronic threshold HRVs for dioxins, furans and/or DL-PCBs, or only for the leader for this class, 2,3,7,8-TCDD. The construction of these HRVs is described in the above table. All of the HRVs, except that of the US EPA and EFSA values, were based on animal studies. According to R8 guidance (ECHA, 2012), epidemiological data should be favoured over animal data.

US EPA and EFSA values are based on different epidemiological studies. All these studies have explored the association between organochlorine compounds during childhood exposures and semen parameters in young men. These studies indicate that exposure to organochlorine compounds during childhood is associated with decreased sperm concentration in adulthood. US EPA used studies from the Seveso cohort (Mocarelli, 2008; Bacarelli, 2008) to derive the HRV, while the recent EFSA HRV value has been derived from an ongoing prospective study on Russian children (Mínguez-Alarcón *et al*., 2017). This study has several advantages compared to the first one. Even the studies were comparable in the methods or in size; the study used by EFSA group had a narrow age range (8 – 9 years followed for up to ten years) compared to the studies used by US EPA were adjustments for age were done. The Russian children's study use measurement of not only TCDD concentration but also PCDD/Fs and DL-PCBs. The collection and analysis of semen seems to be technically more reliable. The main disadvantage, according to EFSA, of the Seveso study is the reference group which is less comparable with men from Seveso.

The Dossier Submitter adopted the EFSA's HRV for dioxins/furans/DL-PCB since it was recent, described clearly and transparently, and established based on epidemiological studies.

The EFSA's HRV covers long-term effects on spermatogenesis linked to exposure from childhood. This HRV is considered applicable to children between the ages of zero and three years, on the basis of the suggestion that exposures of immature testes to organochloride compounds interfere with their maturations and in the spermatogenesis.

Table 47 : Chronic oral threshold chronic HRVs for PCDD/Fs and DL-PCBs

Organism	Health Canada	ATSDR	OMS	SCF*		JECFA		OEHHA	Simon *et al.* reviewed by ITER	RIVM	US EPA		EFSA
Year	1990	1998	2000	2001		2002		2008	2009	2009	2012		2018
Chemicals	TCDD	TCDD	Dioxins and DL compounds	Dioxins, furans and DL-PCBs				TCDD	TCDD	TCDD	TCDD		Dioxins, furans and DL-PCBs
HRV name	ADI	MRL	TDI	THD		DMTP		REL	HRV	provisionnal TDI	RfC		DHT
HRV value	10 pg/kg/d	1 pg/kg/d	1 to 4 pg/kg/d	14 pg/kg/ week (2 pg/kg/d)		70 pg/kg/months 2,33 pg $_{TEQ}$/kg/d		10 pg/kg/d	10^{-7} mg/kg/d	2.10^{-9} mg $_{TEQ}$/kg/d	0.7 pg/kg/d		2 pg $_{TEQ}$/kg/week 0,3 pg/kg/d
critical effect	Reproduction (fertility, litter size, fetal resorption, organs function)	Altered social behaviour in young	Rats, in the offsprings : ↓ sperm count, immunosuppression, ↑ genital malformations. Monkeys: endométriosis or neurobiologic effects (learning of the object) in the offspring	Reprotoxicity (↓ anogenital distance in males pups)	Reprotoxicity (↓ sperm production and altered sexual behaviour in males pups)	Effects on the male reproductive system		↑ plasma levels of alkaline phosphatase, γGT and ALAT, histopathological changes in the liver	Hepatocellular aAdenomas and cholangiocarcinomas	= SCF and JECFA TRVs	↓ concentration and sperm mobility in human	↑ TSH in newborns exposed *in utero*	Fertilty (association between serum levels of TCDD, PCDD $_{TEQ}$ and PCDD/F $_{TEQ}$ and decreased sperm concentration)
Species	SD Rats	Rhesus monkeys	Rats and monkeys	Holzman rats	Wistar rats	Wistar rats	Holtzman rats	SD Rats	Females SD rats		Human		Human

Exposure time	3 generations	During mating, gestation and lactation	In utero Perinatal or 4 years	Single exposure at GD15	Before and during mating, gestation and lactation	Before and during mating, gestation and lactation	Single exposure at GD15		Chronic (2 years)		Chronic (Seveso industrial accident)		
Exposure route	Oral	Oral	Oral	Oral (gavage)	SC	SC	Oral	Oral	Oral (gavage)		Oral		Oral
Dose descriptor	NOAEL = 1 ng/kg/d	LOAEL = 2.10^{-4} µg/kg pc/d	LOAEL = 28–73 ng/kg pc/d	NOAEL = 25 ng/kg NOAEL (equilibrium body burden in mothers at GD16) = 20 ng/kg	LOAEL = 12.5 ng/kg LOAEL (equilibrium body burden in mothers at GD15) = 40 ng/kg	LOEL = 25 ng/kg pc/d	NOEL = 13 ng/kg pc/d	NOAEL = 1 ng/kg pc/d LOAEL = 10 ng/kg pc/d	PBPK modeling to express the dose in average hepatic concentration over the entire lifetime (LALC**) BMD_{01} = $2.1.10^{-3}$ mg/kg LALC		LOAEL = 68 ppt (median serum TCDD concentration adjusted on lipids, at initial exposure)	LOAEL = 235 ppt (maternal serum TCDD concentration adjusted on lipids)	Serum NOAEL = 7 pg $_{TEQ}$/g fat at age 9 years (toxicocinetic mode)
Allometric adjustment	Not specified	No adjustment	$LOAEL_{HED}$ = 14-37 pg/kg pc/d	NOAEL $_{HED}$ = 10 pg/kg/d	LOAEL $_{HED}$ = 20 pg/kg/d	$LOEL_{HED}$ = 630 pg/kg pc/d	$NOEL_{HED}$ = 330 pg/kg pc/d	No adjustment	$BMD_{01\ HED}$ = $1,3.10^{-6}$ mg/kg/d		LOAEL $_{ADJ}$ (PBPK) = 0,02 ng/kg pc/j		/
AF	100 AF_A = 1 AF_H = 10 AF_D = 10	100 AF_A = 3 AF_H = 10 AF_H = 3	10	3,2 AF_A = 1 AF_{H-TK} = 3,2 AF_{H-TD} = 1	9,6 AF_A = 1 AF_{H-TK} = 3,2 AF_{H-TD} = 1 AF_L = 3	9,6 AF_H = 3,2 AH_L = 3	3,2 AF_H = 3,2	100 AF_A = 10 AF_H = 10	100 AF_{A-TD} = 0,1 AF_H = 10		30 AF_H = 3 AF_L = 10		1 AF_H = 1

Key study	Murray *et al.* (1979)	Schantz *et al.* (1992)	Leeuwen *et al.* (2000)	Ohsako *et al.* (2001)	Faqi *et al.* (1998)	Faqi *et al.* (1998)	Ohsako *et al.* (2001)	Kociba *et al.* (1978)	NTP (2006)		Mocarelli *et al.* (2008)	Baccarelli *et al.* (2008)	Minguez-Alarcon *et al.* (2017)

* Scientific Committee on Food; ** Lifetime average liver concentration

To bring more precision with PCBs, several organizations have proposed TRVs (

Table 48). Three organisations propose chronic threshold TRVs for PCB-NDL: RIVM (2001) and Health Canada (2010). Two organisations propose chronic threshold TRVs for PCB based on the same critical effect and the same key study: ATSDR (2000), RIVM (2001) and OMS (2003). Only the choice of assessment factors differs between these three organisations. These three organisations choose an assement factor of 3 for extrapolation from monkeys to humans and 10 for human variability. For extrapolation from a LOAEL to a NOAEL, ATSDR and WHO choose an assement factor of 10 but RIVM choose an AF_L of 3 without explanation. RIVM applied also an additional AFs for extrapolation to chronic exposure considering that the key study is a semichronic study. "*After an exposure period of 23 months a steady state condition of uptake and elimination can be assumed, and thus a UF [AF] is considered sufficient for extrapolation to chronic exposure"* (RIVM, 2001).

The Dossier Submitter adopted the HRV of 0.02 µg/kg/day for PCBs since it was established in accordance with high quality standards and took into account a set of consistent studies. This HRV is considered applicable to children between the ages of zero and three years.

Table 48 : HRVs for PCBs

	NDL-PCB		**PCB**			**Aroclor 1254**
Organism	Health Canada	RIVM		WHO	ATSDR	US EPA
Year	2010	2001		2003	2000	1994
HRV name	DJT	TDI	TDI	TDI	MRL	RfD
HRV value	0.13 µg/kg/d	0.01 µg/kg/d	0.02 µg/kg/d			
Critical Effect	Not specified	Immunological and neurobehavioural effects				Ocular exudate, inflamed and prominent Meibomius glands, distorted growth of finger and toe nails; decreased response of antibodies (IgG and IgM) to sheep erythrocytes
Species	Macaques Rhesus	Macaques Rhesus				
Exposure	65-102 weeks	23 months				23-55 months
Route of exposure	Oral (diet)	Oral (capsules) to Aroclor 1254				
Critical Dose	NOAEL = 13 µg/kg/d	LOAEL = 5 µg/kg/d				
Adjustment	/	TDI Aroclor 1254 = 0.02 µg/kg/d PCBs present in Aroclor 1016, 1242 and 1248 for about 20-30% of the total concentration and in Aroclor 1254 and 1260 for 40-50%. Historical Contaminations of PCB mixtures in soils assessed by Aroclor 1254. Since 7 indicator PCBs* make up 40-50% of the total concentration in Aroclor 1254, TDI = 0.02 µg/kg/d x 50% = 0.01 µg/kg/d	/			/
AF	100 $AF_A = 10$, $AF_H = 10$	300 $AF_A = 3$, $AF_H = 10$, AFs = 3 ; $AF_L = 3$		300 $AF_A = 3$, $AF_H = 10$, $AF_L = 10$		
Key study	Bowman *et al.* (1981)	Tryphonas *et al.* (1989 et 1991)				Tryphonas *et al.* (1989 et 1991) ; Arnold *et al.* (1994)

* indicators PCBs 28, 52, 101, 118, 138, 153 and 180

B.5.12.12.2 Internal

After the selection of chronic oral HRVs for threshold effects, corrections of HRVs will be made using the estimation of the relative bioavailability of each substance *via* oral route in order to establish the potential internal dose linked to the selected HRV. Internal DNEL is a better indicator to take into account the bioaccumulation of chemical (WHO, 2015, see section B.5.1.11.3). Afterward for risk characterisation, the internal DNEL will be compared with the estimation of the daily exposure dose (DED). This approach corresponds to a route-to-route extrapolation according to the REACH or IGHRC Guidances (ECHA, 2012b; IGHRC, 2006). Nevertheless, an oral route to dermal route extrapolation needs to consider the following statements: the route should not modify the metabolic profile of the substance and only systemic adverse effects should be considered. For dioxins, furans and DL-PCBs, data on oral bioavailability are available and will be used to establish an internal DNEL (see section B.5.2.1.1 Absorption). The previously determined absorption fraction (100%) will be used for this evaluation.This value will only be applied to obtain internal DNELs (see section B.5.2.11.), and the risk assessment will be based on this internal dose metric. For the general population, the resulting (Dossier Submitter) chronic internal DNELs is 0.3 pg/kg/day for PCDD/Fs and DL-PCBs and 0.02 µg/kg/day for total PCBs.

B.5.12.12.3 TEF approach

For PCDD/Fs and DL-PCBs, the concept of TEQ based on different toxic equivalency factors (TEFs) was chosen in order to compare the toxicity of all congeners. According to EFSA (2018), "t*he concept assumes that the relevant PCDD/Fs and DL-PCBs bind to the intracellular aryl hydrocarbon receptor (AhR) and cause the same type of AhR-mediated biochemical and adverse effects"* (see section B.5.12.11*). Another important requirement of the TEQ concept is the persistence and accumulation of the compounds in the body. Moreover, it is assumed that the effects are purely additive. By definition, "Seveso" dioxin (2,3,7,8-TCDD), as the most toxic congener, was assigned a value of 1, and the TEFs for the other toxic PCDD/Fs with 2,3,7,8-chlorine substitution and DL-PCBs are between 0.00003 and 1 (see figure below). Thus, a TEF indicates an order of magnitude estimate of the potency of a dioxin-like compound relative to TCDD. TEF values have been (re-)evaluated several times taking into account the multiple endpoints with priority on in vivo responses (e.g.immunosuppression, hepatotoxicity and fetotoxicity) known to be affected by PCDD/Fs and DL-PCBs;* They were defined in 1998 and revised in 2005 by the WHO for PCDD/Fs and PCB-DL (Van den Berg *et al.,* 2006). **The Dossier Submitter retained the values of TEF from WHO 2005.**

	Isomer or homologue series (IUPAC number for PCB isomers)		TEF (WHO, 1998)		TEF (WHO, 2005)
PCDDs	2,3,7,8-tetraCDD		1		1
	1,2,3,7,8-pentaCDD				1
	1,2,3,4,7,8-hexaCDD		0.1		0.1
	1,2,3,6,7,8-hexaCDD		0.1		0.1
	1,2,3,7,8,9-hexaCDD		0.1		0.1
	1,2,3,4,6,7,8-heptaCDD		0.01		0.001
	OCDD		0.0001		**0.0003**
PCDFs	2,3,7,8-TCDF		0.1		0.1
	1,2,3,7,8-pentaCDF		0.05		0.03
	2,3,4,7,8-pentaCDF		0.5		0.3
	1,2,3,4,7,8-hexaCDF		0.1		0.1
	1,2,3,6,7,8-hexaCDF		0.1		0.1
	1,2,3,7,8,9-hexaCDF		0.1		0.1
	2,3,4,6,7,8-hexaCDF		0.1		0.1
	1,2,3,4,6,7,8-heptaCDF		0.01		0.01
	1,2,3,4,7,8,9-heptaCDF		0.01		0.01
	OCDF		0.0001		**0.0003**
Non-ortho PCBs	3,3',4,4'-TCB(77)		0.0001		0.0001
	3,3',4',5-TCB(81)		0.0001		**0.0003**
	3,3',4,4',5-PeCB(126)		0.1		0.1
	3,3',4,4',5,5'-HxCB(169)		0.01		**0.03**
Mono-ortho PCBs	2,3,3',4,44-PeCB(105)		0.0001		**0.00003**
	2,3,4,4',5-PeCB(114)		0.0005		**0.00003**
	2,3',4,44,5-PeCB(118)		0.0001		**0.00003**
	2',3,4,4',5-PeCB(123)		0.0001		**0.00003**
	2,3,3',4,4',5-HxCB(156)		0.0005		**0.00003**
	2,3,3',4,4',5-HxCB(157)		0.0005		**0.00003**
	2,3',4,4',5,5'-HxCB(167)		0.00001		**0.00003**
	2,3,3',4,4',5,5'-HpCB(189)		0.0001		**0.00003**
The values in bold indicate a change in the TEF value.					

Figure 16: Toxic equivalency factors proposed by the WHO (1998 and 2005) for PCDD/Fs and DL-PCBs

B.5.3. Formaldehyde

Hazards and risks of formaldehyde were reviewed by various international committees (WHO, 1989, 2002, 2005; Bfr, 2006; NICNAS, 2006; OECD SIDS, 2002; ATSDR, 1999). A CLH report for formaldehyde was realised by ANSES in 2011. Furthermore, ECHA published a RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a), an Annex XV restriction report for formaldehyde and formaldehyde releasers (ECHA, 2019c) and the substance evaluation conclusion as required by REACH Article 48 and evaluation report for formaldehyde (ECHA, 2019b).

Given the targeting, primarily mutagenicity (section B.5.3.7.) and carcinogenicity (section B.5.3.8.) will be addressed, as well as irritation (section B.5.3.3), sensitisation (section B.5.3.5) endocrine disruting effects (section B.5.3.10) and toxicokinetics (section B.5.3.1.).

B.5.3.1. Toxicokinetics (absorption, metabolism, distribution and elimination)

Information as presented below is taken primarily from the WHO (1989), Bfr (2006), and NICNAS (2006) evaluations, the SIDS Initial Assessment Report (OECD, 2002), the CLH report for formaldehyde (ANSES, 2011), the substance evaluation conclusion as required by REACH Article 48 and evaluation report for formaldehyde (ECHA, 2019b), the Annex XV restriction report for formaldehyde and formaldehyde releasers (ECHA, 2019c).

B.5.3.1.1 Absorption

B.5.3.1.1.1 Oral route

Formaldehyde and reaction products with nucleophilic substances, like proteins, are readily absorbed in the gastrointestinal tract. No human data on oral bioavailability of formaldehyde is available. In rodents, formaldehyde is absorbed rapidly from the gastro-intestinal tract. In rats, gastrointestinal absorption of ^{14}C-formaldehyde (7 mg/kg) lead to the elimination of 40 % of the radioactivity by exhalation as $^{14}CO_2$ within 12 hours, 10 % in the urine and 1 % in the faeces (Buss *et al*., 1964; Mashford and Jones, 1982 cited by BfR, 2006). Moreover, four days after oral application, radioactivity was determined in numerous organs. Following oral exposure (gavage) of 5 anaesthetized dogs to formaldehyde (70 mg/kg), formate levels in the blood increased rapidly. However, 15 minutes after treatment, all the dogs vomited making quantitative determinations impossible (Malorny *et al*., 1965 cited by WHO, 1989). These data suggest that formaldehyde and reaction products are easily absorbed and well distributed. Thereby, it can be estimated in rodents, that the oral bioavailability of formaldehyde is around 51 %. If information suggests good bioavailability of the substance following oral administration, it is assumed that its availability will not be superior to 50%.

B.5.3.1.1.2 Dermal route

Formaldehyde is poorly absorbed following dermal application. According to ECHA (2019b), "*dermal absorption should differentiate between penetration through the skin possibly leading to systemic effects and penetration into the skin possibly leading to local effects. For monkeys penetration through the skin was 4% and through + into skin 15%. In rats and guinea pigs, ca. 40% of the applied formaldehyde is absorbed via the skin. In in vitro experiments using guinea pig skin the percutaneous absorption rate was ca. 30% after 1 h of exposure. The following values are further considered for dermal absorption: 4% for penetration through the skin possibly leading to systemic effects; 15% for penetration through and into the skin possibly leading to local effects*."

Formaldehyde is rapidly metabolised at the initial site of contact. Due to rapid metabolism, distribution of formaldehyde molecules to other more distant organs is not likely, y ECHA, except from exposure to high concentrations (Lyapina *et al*., 2012 cited in ECHA, 2019c). However evidence that topically applied formaldehyde will not be – at least partly – systemically available is given by the fact, that formaldehyde elicits positive responses in different methods for investigation of contact sensitising properties in mice and guinea pigs

(Hilton *et al.,* 1996 cited by BfR, 2006). Formaldehyde can induce contact dermatitis in humans (Maibach, 1983 cited by BfR, 2006) and is a significant hand allergen in women (Cronin, 1991 cited by BfR, 2006*).*

B.5.3.1.2 Distribution

According to ECHA (2019c), *"in biological systems, formaldehyde first reacts reversibly with water to form an acetal (methanediol). At physiological temperature and pH, > 99.9% of formaldehyde is present as methanediol, with < 0.1% as free formaldehyde (Andersen et al., 2010; Golden, 2011).*

Formaldehyde reacts at the site of first contact instantaneously with primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Due to its electrophilic properties, formaldehyde also reacts with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links (WHO, 2010)."

B.5.3.1.3 Metabolism

A summary is provided by ECHA (2019c):
"The simplified metabolism of formaldehyde (acetal) involves (Andersen et al., 2010; Golden, 2011; Tulpule and Dringen, 2013; WHO, 2010):

1. *reduction to methanol by alcohol dehydrogenase 1;*
2. *oxidation to formate by aldehyde dehydrogenase 2;*
3. *spontaneous reaction with glutathione (GSH) to form S-hydroxymethyl GSH, which is subsequently oxidised by alcohol dehydrogenase 3 (also known as formaldehyde dehydrogenase) to the intermediate S-formyl GSH, which is metabolised by S-formylglutathione hydrolase to formate and reduced glutathione.*

Due to high circulating concentrations of glutathione in human blood, the S-hydroxymethyl GSH is the major form of formaldehyde seen in vivo (Sanghani et al., 2000).

Formate is oxidised to 10-formyl tetrahydrofolate (THF) by methylene tetrahydrofolate dehydrogenase 1; 10-formyl THF is either metabolised to CO_2 by 10-formyl THF dehydrogenase or further metabolised within the one-carbon metabolism pathway that is centred around folate (Tulpule and Dringen, 2013)."

B.5.3.1.4 Elimination

A summary is provided by WHO (2002):
"In animal species, the half-life of formaldehyde (administered intravenously) in the circulation ranges from approximately 1 to 1.5 min (Rietbrock, 1969; McMartin et al., 1979). Formaldehyde and formate are incorporated into the one-carbon pathways involved in the biosynthesis of proteins and nucleic acids. Owing to the rapid metabolism of formaldehyde, much of this material is eliminated in the expired air (as carbon dioxide) shortly after exposure. Excretion of formate in the urine is the other major route of elimination of formaldehyde (Johansson & Tjälve, 1978; Heck et al., 1983; Billings et al., 1984; Keefer et al., 1987; Upreti et al., 1987; Bhatt et al., 1988)."

B.5.3.2. Acute toxicity

Not relevant for this restriction proposal.

B.5.3.3. Irritation

B.5.3.3.1 Skin irritation

According to ECHA (2019b), "*There is one key study on skin irritation in rabbit, supporting studies with rat and additional information from the skin sensitization in animals and humans. According to the registrants, irritant effects are expected at concentrations > 3%. This conclusion was confirmed by a recent study on microvascular leakage of rat skin, where skin damage was demonstrated at concentrations ≥ 2.5% formaldehyde.*"

B.5.3.3.1 Eye irritation

Not relevant for this restriction proposal.

B.5.3.4. Corrosivity

Formaldehyde has an harmonised classification for skin corrosion (category 1B).

B.5.3.5. Sensitisation

B.5.3.5.1 Skin sensitisation

Formaldehyde has an harmonised classification for skin sensitization (category 1).

A short summary is provided in the Annex XV restriction report for formaldehyde and formaldehyde relasers (ECHA, 2019b):

"Related to skin sensitisation, the registration dossier (BASF, 2017) clearly sets out that formaldehyde is a strong skin sensitiser with positive results in several studies including Local Lymph Node Assay (LLNA). Formaldehyde solution is a primary skin sensitiser inducing allergic contact dermatitis Type IV and may induce contact urticaria Type I (WHO, 1989). The EC3 value (3-fold stimulation of proliferation as an index of the relative potency of a contact allergen) was 0.93% formalin[25] or 0.35% formaldehyde. No induction was detected at 0.04% formaldehyde and first sensitising effects were seen at 0.2% (BASF, 2017). This is consistent with the special concentration limit in CLP for substances in mixtures. Concentrations leading to elicitation of effects are lower than the concentrations leading to induction.

The biocidal assessment for formaldehyde (ECHA, 2017) concluded: "However, the currently available methodology is not considered suitable for derivation of an acceptable exposure level protecting from sensitisation by formaldehyde which is relevant to human health. Nevertheless, the available data is in support of the current legal classification limit for formaldehyde formulations of ≥ 0.2% (w/w) with regard to its sensitising properties and the resulting labelling provisions with EUH208 at ≥ 0.02% (w/w)."

B.5.3.5.2 Respiratory sensitisation

Not relevant for this restriction proposal.

[25] Aqueous solutions of formaldehyde(40% by volume).

B.5.3.6. Repeated dosed toxicity

Information as presented below is taken primarily from OECD SIDS (2002), WHO (2005) and the NICNAS (2006) evaluations and from the substance evaluation conclusion as required by REACH Article 48 and evaluation report for formaldehyde (ECHA, 2019b).

In experimental studies, formaldehyde induces toxic effects only at the site of first contact after oral or dermal exposure. General signs of toxicity occur secondary to these local lesions.

Repeated exposure studies in mice were performed using dermal application, mostly in the context of skin initiation / promotion (Krivanek *et al*., 1983; Iversen, 1986 cited by OECD, 2002 and NICNAS, 2006). None of these studies showed evidence of substance-specific systemic toxicity. In the study of Krivanek *et al*. (1983 cited by OECD, 2002 and NICNAS, 2006) a formaldehyde solution in acetone/water 50:50 was tested on 30 mice. Initially 50 µl of a 10% solution (5 mg/animal = 125 mg/kg b.w.) was applied and then 100 µl of a solution containing 0.1, 0.5, or 1% (2.5, 12.5, or 25 mg/kg b.w., respectively) was applied 3 times a week for 26 weeks. After termination of exposure, the mice were post-observed for additional 26 weeks. Local irritation to mouse skin was minimal at formaldehyde concentrations of 0.5 to 1% (Krivanek *et al*., 1983 cited by OECD, 2002 and NICNAS, 2006). Systemic toxicity was not seen at any dose level. However, the limited details provided prevent identification of a reliable NOAEL or LOAEL from this study.

WHO (2005) provided a summary of short- and long-term exposure studies for oral route:

"<u>Short-term exposure</u>

In a 4-week study, Wistar rats (10 per sex per dose) received formaldehyde in drinking-water at doses of 0, 5, 25, or 125 mg/kg of body weight per day. Rats receiving the highest dose showed lowered food and liquid intake, histopathological changes in the stomach (i.e., focal hyperkeratosis of the forestomach, moderate papillomatous hyperplasia), and, in males only, lowered total protein and albumin levels in plasma. The NOAEL was 25 mg/kg of body weight per day (Til et al., 1988; IPCS, 1989).

Oral doses of 0, 50, 100, or 150 mg/kg of body weight per day in rats and 0, 50, 75, or 100 mg/kg of body weight per day in dogs for 91 days had no effect on haematology, clinical chemistry, urinalysis, or gross microscopic pathology. Depression in body weight gain was observed in both species at the highest dose levels and in male rats given 100 mg/kg of body weight per day (Johannsen et al., 1986).

<u>Long-term exposure</u>
In a 2-year study, Wistar rats were exposed to formaldehyde in drinking-water at mean doses of 0, 1.2, 15, or 82 mg/kg of body weight per day for males and 0, 1.8, 21, or 109 mg/kg of body weight per day for females. The average concentrations of formaldehyde in the drinking-water were 0, 20, 260, and 1900 mg/litre in the control, low-, mid-, and high-dose groups, respectively. Adverse effects were observed only in animals receiving the highest dose and included lower food and liquid intake, lower body weights, and pathological changes in the stomach, characterized by thickening of the mucosal wall. Relative kidney weights were increased in high-dose females, and an increased incidence of renal papillary necrosis was found in both sexes.

Exposure did not appear to affect survival, haematology, or clinical chemistry. The NOEL was 15 mg/kg of body weight per day, or 260 mg/litre (Til et al., 1989).

In a similar study, Wistar rats were given formaldehyde in drinking-water at 0, 10, 50, or 300 mg/kg of body weight per day. At the end of 12 months, rats of both sexes in the high-dose group were observed to have gastric erosions, ulcers, squamous cell hyperplasia, hyperkeratosis, and basal cell hyperplasia. Only one male and one female from the mid-dose group showed hyperkeratosis (IPCS, 1989; Tobe et al., 1989)."

In conclusion, the principal non-neoplastic effect in animals exposed orally to formaldehyde is the development of histopathological changes within the forestomach and glandular stomach, with effects in rats at 82 mg/kg body weight per day and above (Til *et al*., 1989; Tobe *et al*., 1989).

B.5.3.7 Mutagenicity

Formaldehyde has an harmonised classification for mutagenicity (category 2). This classification is based on genotoxic effects observed in vivo in somatic cells at the site of contact. Positive evidence in mutagenicity tests are available from induction of chromosomal aberrations in rats by inhalation at high dose (Dallas, 1992) and of micronuclei in rats in the GI tract by oral route (Migliore, 1989). These positive data are further supported by in vitro positive results in numerous genotoxicity and mutagenicity tests, in vivo induction of DNA adducts and DNA protein cross links at the site of contact and indications of consistent increases in micronuclei frequency in humans at the site of contact after formaldehyde inhalation.

In vivo at distant sites in somatic cells, indications of consistent increases in micronuclei frequency in humans is available. However, it is not supported by experimental data that report an absence of induction of either genotoxicity or mutagenicity and by inconsistent results for induction of SCE and chromosomal aberrations in humans. No evidence of an effect on germ cells by a relevant route of exposure is available (ECHA, 2012a; 2019b).

Experimental data

<u>In vitro</u>

According to the RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a):

"Formaldehyde, which induced mutagenic and genotoxic effects in proliferating cells of directly exposed cell lines, should be regarded as an in vitro mutagen with a predominantly clastogenic mode of action. Gene mutation tests gave insufficient evidence for induction of gene mutations.

The substance induced clastogenic effects (such as chromosomal aberrations, increased micronucleus formation and sister chromatid exchanges) as well as genotoxic effects (DPX and DNA adducts) in cultured mammalian cells as well as in cultured human cells.

Results of gene mutation tests (HPRT test in V79: Grafstrom, 1990; Merck, 1989) were contradictory. The positive result in a mouse lymphoma assay (MLA) (Speit and Merk, 2002) *was based on an increase in the frequency of small colonies, suggestive of chromosomal aberrations. Only a marginal increase in the frequency of large colonies, suggestive of gene mutations, was observed in the study. The positive results of MLA's conducted by Blackburn et al. (1991) and Mackerer et al. (1996) were not evaluated in detail, because no differentiation into small and large colonies was carried out."*

<u>In vivo, on somatic cells at site of contact</u>

The majority of studies has been conducted on nasal, bronchial or pulmonary cells who are not relevant for this restriction proposal.

Only one study was described by oral route, in the RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a) : " *Migliore et al. (1989) reported the induction of micronuclei in epithelial cells along the gastro-intestinal tract of rats after oral administration (gavage) of formaldehyde. The result could not be clearly evaluated, because the positive effect was observed only in conjunction with signs of severe local irritation. In addition the positive control was of questionable relevance."*

<u>In vivo, on somatic cells at distant site of exposure</u>

Several studies show that formaldehyde does not induce chromosomal aberrations or micronuclei in mice by IP (Natarajan, 1983 cited by ANSES, 2011) or oral and i.v. routes (Morita, 1997 cited by ANSES, 2011).

<u>In vivo, on germ cells</u>

According to the RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a):

"Few studies are available regarding the induction of germ cell mutagenicity after intraperitoneal (i.p.) injection. The results of these studies are inconsistent and inconclusive. No information on toxic effects was given. Inadequate test descriptions or methodological limitations (e.g. Odeigah et al., 1997: due to the lack of a positive control, the result of a dominant lethal test is not fully reliable) made it difficult to assess the results. Altogether, no clear conclusion could be drawn that formaldehyde induces mutagenic effects in germ cells after i.p. injection. Therefore the positive results from certain germ cell mutation studies were not taken into account for supporting justification of a formaldehyde classification."

Human data

<u>In humans, at site of contact and at distant site of exposure</u>

The available studies has been conducted in people exposed to formaldehyde by inhalation route only. This route of exposure is considered as not relevant for this restriction proposal. In studies on localised mutagenicity in humans, formaldehyde exposure was by inhalation and induction of micronuclei was used as the endpoint for genotoxicity. The reported results on induction of micronuclei in buccal and nasal mucosa cells were contradictory. Furthermore, contradictory results were obtained for genotoxic effects as well as for mutagenic effects in peripheral blood of humans after inhalation exposure to formaldehyde. There is not sufficient evidence to conclude that formaldehyde induces systemic genotoxicity in man (ECHA, 2012a; ANSES, 2011).

In humans, on germ cells

According to the RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a): *"No studies investigated the effect of formaldehyde on human germ cells. Due to the extremely low systemic bioavailability, it can be assumed that formaldehyde does not reach the germ cells after inhalation."*

B.5.3.8. Carcinogenicity

Formaldehyde has harmonised classification for carcinogenicity (category 1B), based on nasal tumours (site of contact) observed in rats of both sexes exposed to formaldehyde at concentrations of 2 ppm and higher for ≥ 24 months and limited evidence by inhalation route in humans.

In 2012, RAC concluded that "*there is no convincing evidence of a carcinogenic effect at distant sites or via routes of exposure other than inhalation*. »

B.5.3.8.1 Dermal route

Information as presented below is taken primarily from WHO (1989), ATSDR (1999), and the IARC (2012) evaluations and from the substance evaluation conclusion as required by REACH Article 48 and evaluation report for formaldehyde (ECHA, 2019b).

Only three initiation/promotion studies were carried out on mice to test whether formaldehyde solution applied to the skin induced papilloma or malignant tumours as an initiator, or promoter of cancer, or as a complete carcinogen (Krivanek *et al*., 1983a; Spangler & Ward, 1982; Iversen, 1986 cited by ANSES, 2011). Formaldehyde proved to be neither a complete carcinogen, nor an initiator (with phorbolmyristateacetate as a promoter). With respect to promoting activity (with benzo(a)pyrene or dimethylbenyanthracene as an initiator) the results were either negative or inconclusive. Theses studies did not report skin tumours after treatment with formaldehyde alone and do not provide evidence of tumours at sites other than the skin. They did not report an increase of tumours but their limited duration of exposure (26-60 weeks with once or three times per week dosing) and number of animals exposed and their focus on skin tumours raise doubts on the validity of the studies in the assessment of the carcinogenic potential of formaldehyde by dermal route.

In 2012, ECHA concluded that "*no valid information is available to conclude on formaldehyde's potential to cause skin tumours and no conclusion on its carcinogenic potential via the dermal route can be drawn" and that* "*no valid information is available to conclude on formaldehyde's potential to cause tumours at distant sites".*

B.5.3.8.2 Oral route

Information as presented below is taken primarily from OECD SIDS (2002), WHO (2002, 2005) and the IARC (2012) evaluations, from the RAC opinion proposing harmonised classification and labelling at EU level of formaldehyde (ECHA, 2012a) and from the substance evaluation conclusion as required by REACH Article 48 and evaluation report for formaldehyde (ECHA, 2019b).

Only animal data are available.

Systemic carcinogenicity

In the most comprehensive study in Wistar rats administered drinking-water containing formaldehyde in amounts estimated to achieve target intakes ranging up to 125 mg/kg body weight per day for up to 2 years, there was no significant increase in tumour incidence compared with unexposed controls (Til *et al*., 1989). Tobe *et al*. (1989) also reported, although data were not presented, that, compared with unexposed controls, tumour incidence was not increased in small groups of male and female Wistar rats administered drinking-water containing up to 5000 mg formaldehyde/ litre (i.e., providing intakes up to 300 mg/kg body weight per day).

In contrast, in a 2-year study in which Sprague-Dawley rats were exposed to formaldehyde in drinking-water at dose levels of 0, 1, 5, 10, 50, 100, or 150 mg/kg of body weight per day, a dose-dependent increase in the incidence of leukaemia (mainly lymphoblastic) and lymphosarcoma was reported at dose levels of 5 mg/kg of body weight per day or greater Soffritti *et al*. (1989 cited by ANSES, 2011 and ECHA, 2012a). The proportion of males and females with leukaemias (all "haemolymphoreticular neoplasias," e.g., lymphoblastic leukaemias and lymphosarcomas, immunoblastic lymphosarcomas, and "other" leukaemias) increased from 4% and 3% in the controls, respectively to 22% and 14% in the animals receiving drinking-water containing 150 mg/kg bw/day, respectively. Compared with unexposed controls, the increase in the incidence of gastrointestinal neoplasms was not dose-related. Limitations of this study include the "pooling" of tumour types, the lack of statistical analysis, and limited examination of non-neoplastic end-points. This study was considered as non-valid, since the re-evaluation in 2002 resulted in markedly higher incidences of lymphohaematopoietic tumours (about two-fold in all dose groups) (ECHA, 2012). Parenthetically, it should be noted that the incidence of haematopoietic tumours (e.g., myeloid leukaemia, generalized histiocytic sarcoma) was not increased in Wistar rats receiving up to 109 mg formaldehyde/kg body weight per day in drinking-water for up to 2 years (Til *et al*., 1989).

In another study, formaldehyde induced ornithine decarboxylase activity (an indication of tumour-promoting activity) in rats given a single oral formaldehyde dose of up to 100 mg/kg bw (Overman, 1985 cited by NICNAS, 2016). There is no evidence that formaldehyde acts as a carcinogen or promoter when applied to mouse skin (Krivanek *et al.,* 1983 cited by ANSES, 2011 and ECHA, 2012).

A number of other long-term studies by the oral route have been conducted, and these are reviewed in detail by Restani & Galli (1991) and WHO/IPCS (2002). The conclusion of these reviews was that formaldehyde is a normal mammalian metabolite and is not carcinogenic at very low levels of exposure.

No evidence on lymphohaematopoietic tumours was provided by the study of Til (1989), and evidence from Soffritti (1989 cited by ECHA, 2012) and Soffritti *et al.* (2002 cited in ANSES, 2011) studies was considered equivocal. However, RAC (2012) concluded that "*no firm conclusion can be drawn for carcinogenicity by the oral route*".

Carcinogenicity at the site of contact

Three oral studies with a 2-year treatment period and one 32-week study are available with rats. In a carcinogenicity study, a group of 10 male Wistar rats was given drinking-water containing 0.5% formalin (0.2% formaldehyde) for 32 weeks. Histopathological changes were observed in the stomach, as well as neoplastic changes in the forestomach and papillomas. In addition, the authors reported evidence that formaldehyde had tumour promoting activity. However, because of the presence of high levels of methanol in formalin, the usefulness of this information is limited (Takahashi *et al*., 1986 cited by WHO, 2005 and RAC, 2012a). Increased incidences of squamous cell papillomas in the forestomach observed in the study of Takahashi (1986 cited by WHO, 2005 and RAC, 2012a) was not consistent with two other carcinogenicity studies at similar high doses (Til, 1989 and Tobe *et al*., 1989). The most valid carcinogenicity study of Til (1989) applied a comparable concentration of 1900 mg formaldehyde/L of drinking water and observed focal ulcerations of the forestomach, papillary hyperplasia of the limiting ridge (frequently located at the borderline between forestomach/stomach), chronic atrophic gastritis, ulceration and glandular hyperplasia of the stomach, but no papillomas at doses up to 82 mg/kg/d in males and 109 mg/kg/d in females. Erosive-ulcerative lesions and hyperplasia in the limiting ridge area and absence of papillomas was consistently found in the studies of Tobe *et al*. (1989) and Takahashi *et al*. (1986 cited by WHO, 2005 and RAC, 2012a).

In conclusion, oral exposure to concentrations of 0.19% formaldehyde in drinking water consistently caused erosive-ulcerative lesions and (regenerative) hyperplasia in the limiting ridge area in three studies. The induction of benign tumours in the forestomach in Takahashi (1986 cited by RAC, 2012a) is considered equivocal by the RAC (2012a).

B.5.3.9. Toxicity for reproduction

Formaldehyde is not classified for toxicity to reproduction.

In conclusion, there is no convincing evidence that formaldehyde would lead to reproductive effects in human or in experimental animals after oral or dermal exposure. Indeed, experimental or epidemiological studies do not highlight systemic effects of formaldehyde, especially reprotoxic ones, even at high doses.

B.5.3.10. Other effects

Endocrine disruptor

As for PAH, an overview of endocrine-related disrupting effects for formaldehyde was done based on DHI Water and Environment for European Commission (2007) and the presence of formaldehyde on the following lists: The Endocrine Disruption Exchange Inc (TEDX) and the Sin List (Substitute It Now).

Table 49 : endocrine disrupting effect of formaldehyde: overview of evaluations (website consulted : 28/08/2020)

CE (2007) [a]	TEDX list	SIN list
-	Yes	No

- : Not studied

B.5.3.11. Derivation of DNEL(s)/DMEL(s)

Taking into account the close contact of single-use baby diapers with the buttocks, the use of dermal HRVs seemed appropriate. However, since no HRVs were available for this route of exposure, a search for HRVs by the oral route was carried out.

B.5.3.11.1. Oral

Only OEHHA has proposed a no-threshold HRV of $2.1.10^{-2}$ $(mg/kg/d)^{-1}$ based on squamous cell carcinomas of the nasal cavity (OEHHA, 2011). This HRV was not selected because the available oral data do not provide clear evidence of carcinogenic effects of formaldehyde by the oral route (Anses, 2011).

Four organisations propose chronic threshold TRVs based on the same critical effect, the same key study and the same uncertainty factors: the US EPA (1990), Health Canada (2001), WHO/IPCS (2005) and ATSDR (1999).

Table 50 : Chronic oral-route threshold HRVs for formaldehyde

<table>
<tr><th>Organism</th><th>US EPA*</th><th>ATSDR</th><th>WHO/IPCS</th><th>ECHA[26]</th><th>Health Canada</th></tr>
<tr><td>year</td><td>1990</td><td>1999</td><td>2005</td><td>2019</td><td>2001</td></tr>
<tr><td>TRV name</td><td>RfD</td><td>MRL</td><td>TDI</td><td>ADI</td><td>TC</td></tr>
<tr><td>TRV value</td><td>0.2 mg/kg/d</td><td>0.2 mg/kg/d</td><td>0.15 mg/kg/d (2,6 mg/L drinking water)</td><td>0.15 mg/kg/d</td><td>2.6 mg/L**</td></tr>
<tr><td>critical effect</td><td colspan="2">Histological changes of the pre-stomach, hyperkeratosis</td><td>Stomach irritations and nephrotoxicity</td><td colspan="2">Stomach lesions, renal papillary necrosis and reduced body weight gain</td></tr>
<tr><td>Species</td><td colspan="5">Rats</td></tr>
<tr><td>Exposure time</td><td colspan="5">2 years</td></tr>
<tr><td>Exposure route</td><td colspan="5">Oral (drinking wtaer)</td></tr>
<tr><td>Dose descriptor</td><td colspan="4">NOAEL = 15 mg/kg/d
LOAEL = 82 mg/kg/d</td><td>NOAEL = 260 mg/L = 0.15 mg/kg/d</td></tr>
<tr><td>Adjustment</td><td></td><td colspan="4">/</td></tr>
<tr><td>AF</td><td></td><td colspan="4">100
AF_A = 10, AF_H = 10</td></tr>
<tr><td>Key study</td><td></td><td colspan="4">Til et al. (1989)</td></tr>
</table>

* the RfD proposed by US EPA-IRIS has been under review since 2014.

[26] https://echa.europa.eu/documents/10162/08239b9d-5380-70ba-ed40-4ec972b7cec3

** the value was not expressed in mg/kg/day since the authors considered that the observed effects are related to the concentration of formaldehyde consumed *via* drinking water and not to a cumulative effect.

In the study by Til *et al*., rats were exposed to formaldehyde for two years *via* drinking water. The males were exposed to 0, 1.2, 15 or 82 mg/kg/day and the females to 0, 1.8, 21 or 109 mg/kg/day. At 82 mg/kg/day for the males, histological changes in the forestomach (hyperplasia, hyperkeratosis, ulceration, chronic gastritis) and renal necrosis were observed. The NOAEL was therefore identified at 15 mg/kg/day. A factor of 10 for inter-species variability and a factor of 10 for interindividual variability were applied**.**

The four available HRVs are equivalent. The Dossier submitter adopted TRV of 0.15 mg/kg/day derived by WHO-IPCS (2002) and ECHA (2019) since it was the most disadvantageous (not rounded).

The selected HRV is applicable to children between the ages of zero and three years. Indeed, studies during gestation were taken into account by WHO/IPCS in 2005 for the establishment of the TRV (Saillenfait *et al*., 1989; Martin, 1990 cited in WHO/IPCS, 2005).

B.5.3.11.1. Internal

After the selection of chronic oral HRVs, corrections of HRVs will be made using the estimation of the relative bioavailability of each substance *via* oral route in order to establish the potential internal dose linked to the selected HRV. Internal DNEL is a better indicator to take into account the bioaccumulation of chemical (WHO, 2015, see section B.5.1.11.3). Afterward for risk characterisation, the internal DNEL will be compared with the estimation of the daily exposure dose (DED). This approach corresponds to a route-to-route extrapolation according to the REACH or IGHRC Guidances (ECHA, 2012; IGHRC, 2006). Nevertheless, an oral route to dermal route extrapolation needs to consider the following statements: the route should not modify the metabolic profile of the substance and only systemic adverse effects should be considered. For formaldehyde, information suggests good bioavailability following oral administration, it is assumed that its availability will not be superior to 50%. If no data is available on oral bioavailability, as a protective approach, it will be considered the same and no extrapolation will be made.

The HRV chosen is based on local effect (histological changes in the forestomach) and also systemic effect (renal papillary necrosis). According to ECHA (2019), it is unclear if the systemic effects *"are primary, i.e. directly resulting from formaldehyde or its metabolites, or secondary to local lesions and inflammatory reactions. This uncertainty is reflected by derivation of a systemic reference dose to protect from potential internal effects following prolonged exposure to low concentrations of the active substance."* Whereas renal effects are systemic effect which may not be solely a consequence of local effects, the Dossier Submitter choose to derive an internal DNEL as conservative approach.

For the general population, the resulting chronic internal DNEL is 0.075 mg/kg/day.

B.6. Human health hazard assessment of physicochemical properties

B.6.1. Explosivity

Not relevant

B.6.2. Flammability

Not relevant

B.6.3. Oxidising potential

Not relevant

B.7. Environmental hazard assessment

Not relevant

B.8. PBT and vPvB assessment

Not relevant

B.9. Exposure assessment

B.9.1. General information on releases and exposure

B.9.1.1. Summary of the existing legal requirements

The existing legal requirements are presented in Annex E.1.

B.9.1.2. Summary of the effectiveness of the implemented operational conditions and risk management measures

Please refer to the Annex E.1

B.9.2. Use: Traditional single-use baby diapers

B.9.2.1. General information

The frequent everyday use of single-use baby diapers may lead to exposure of children and infants. Most of the articles covered by the restriction proposal are also used for prolonged periods of time and exposure occurs under occlusion, which increases the likelihood for substances to cross the skin and trigger diseases.

Hazardous chemical substances can intentionally or unintentionally remain in the final product following the manufacture and single-use baby diapers. They can be released through several mechanisms: from direct release of the substance from the articles, or released by urine absorbed by diapers during normal wear resulting in exposures of the babies.

Prolonged skin contact with single-use baby diapers is expected over the day. Migration of hazardous substances from inner layers to outer parts of such articles cannot be formally excluded. In addition, a tearing of the outer parts of the diapers may occur, leading to skin contact with the inner parts of the article.

Hence, the assessment of the exposure to chemical substances released by urine from the material would ideally be based on presence in single-use baby diapers and information on migration of the substance to skin during use. The parameters needed to perform the assessment of exposure to chemicals were, for most of them, available to the Dossier Submitter (concentration in a urine simulant, frequency of use, body weight, diapers weight, absorption) that's why the Dossier Submitter has performed a quantitative exposure assessment based on available data and justified assumptions when needed.

B.9.2.2. Exposure estimation

In order to be exposed to the chemicals of concern, they have to be released from the diaper upon contact with the skin or the genital mucosa. To monitor and account for the release from the diaper, the French laboratory SCL (Service Commun des Laboratoires) performed migration studies to assess the availability for exposure through dermal contact.

The analyses were carried out with entire diapers soaked with urine simulant and then placed in an oven at 37°C for 16 hours. 200 mL of simulant were added to the diaper three times, with a 30-minute rest period between each addition. The tested simulant was extracted by pressing (recovery of 130 to 250 mL). The majority of the 600 mL of urine simulant remained trapped in the SAP[27]. Direct release and migration of chemical substances from diapers are dependent on a number of factors:

- the inherent chemical/physical properties of the substance,
- how the substance is incorporated into the diaper,
- the quality of the manufacturing process,
- sweat and urine that can enhance the migration of chemicals out of the diapers to be in contact with the skin of the children and infants.

In 2018 and 2019, SCL carried out analysis onto 51 single-use baby diapers according to the migration analysis described above. Formaldehyde, PCDD/Fs, DL-PCBs and PAHs were detected or quantified.These studies were performed by the same laboratory, with the same methodology between 2018 and 2019(further details available in Annex E.8)
For the first set of analysis, in 2018, 19 of the best-selling brand-name and own-brand diapers in France were collected . Samples were only taken from single-use diapers.
For the second set of analysis, in 2019, 32 single-use references were tested and analysed according to the same methodology followed for the first set of analysis performed in 2018

In summary out of the 51 samples analysed in 2018 and 2019 :
- 26% were best selling brand samples,
- 29% were "eco friendly" brand samples,
- 31% were own-brand samples,

[27] https://www.chimie-experts.org/Annales/Articles-a-paraitre-dans-les-Annales-des-Falsifications-et-de-l-Expertise-Chimique-et-Toxicologique

- 14% were local diapers not sold on the metropolitan French market (meaning sold on the French islands)

At least quite 60% of the references tested are sold all over the EU market (by taking into account only the best selling brand and the own-brand references). The Dossier Submitter also considers that some of the "eco-friendly" brand samples may also be available on the EU market due to the fact that the EU single-use baby diapers manufacturing market is oligopolistic.

Between 2018 and 2019, 12 references of diapers tested have been the same (same reference, same brand).

The Dossier Submitter is of the view that most of the samples tested in the 2018 and 2019 studies are representative of the EU diaper market. Indeed the best selling brands samples and the own-brand samples should be the same all over the EU market (which represents 57% of the diapers tested). Moreover, the industry, claimed, during the hearings performed, that the diapers sold on the EU market for their brand are the same whatever is the country. Nevertheless the Dossier Submitter can not state that the "eco friendly" samples are the same sold on the EU market.

In light of the results described in Table 51, it can be noted that:

- No analysed fragrances were detected in the extracted urine simulant,
- No analysed VOCs were detected in the extracted urine simulant,
- Dioxins, furans and DL-PCBs were **quantified** in the extracted urine simulant **with all the diapers,**
- Formaldehyde was quantified or detected in the urine simulant extracted from **39 diapers**,
- PAHs were detected but not quantified in the urine simulant extracted from **20 diapers** (benzo[e]pyrene; benzo[a]pyrene; benzo[b]fluoranthene; dibenzo[a,h]anthracene; 5-methylchrysene; chrysene; benzo[g,h,i]perylene; benzo[k]fluoranthene; benzo[j]fluoranthene, Benzo[a]anthracene).The LOD and LOQ vary from one reference to another for the same chemical analysed for the diferent references tested, due to the test sample. (see annex E.8 for more details on LOD and LOQ).

Table 51 : Aggregated results from the 2018 and 2019 SCL studies (extraction through an urine simulant)

Chemicals	Number of times where the substance was detected	For the susbstances detected		Number of times where the substance was quantified	For the susbstances quantified		
		Lowest LQ	Highest LQ		Lowest C°	Highest C°	Mean C°
Formaldehyde (mg/kg of diaper)	**17**	**0.269**	**0.742**	**22**	**0.403**	**2.75**	**0.958**
PAHs(mg/kg of diaper)							
Benzo[e]pyrene	**10**	**0.499**	**0.836**	**0**			
Benzo[a]pyrène	**4**	**0.649**	**0.81**	**0**			
Benzo[b]fluoranthene	**6**	**0.627**	**0.763**	**0**			
Dibenzo[a,h]Anthracene	**2**	**0.198**		**0**			
5-methyl chrysene	**1**	**0.623**		**0**			
Chrysene	**1**	**0.499**		**0**			
Benzo[g,h,i]perylene	**5**	**0.499**	**0.836**	**0**			
Benzo[k]fluoranthene	**1**	**0.737**		**0**			
Benzo[j]fluoranthene	**1**	**0.737**		**0**			
Benzo[a]anthracene	**4**	**0.0004**	**0.001**	**0**			
PCDDs(ng/kg of diaper)							
1,2,3,4,6,7,8 HpCDD	**0**			**48**	**0.0017**	**0.455**	**0.032**
OCDD	**0**			**48**	**0.0032**	**0.372**	**0.048**
1,2,3,6,7,8 HxCDD	**0**			**5**	**0.0004**	**0.015**	**0.0072**
1,2,3,4,7,8 HxCDD	**0**			**2**	**0.0039**	**0.0047**	**0.0043**
1,2,3,7,8,9 HxCDD	**0**			**2**	**0.0051**	**0.0097**	**0.0074**
PCDFs(ng/kg of diaper)							
1,2,3,6,7,8 HxCDF	**0**			**7**	**0.0004**	**0.015**	**0.0069**
2,3,4,6,7,8 HxCDF	**0**			**13**	**0.0007**	**0.031**	**0.010**

1,2,3,4,6,7,8 HpCDF	**0**		**43**	**0.0008**	**0.059**	**0.010**
OCDF	**0**		**43**	**0.0008**	**0.078**	**0.014**
2,3,7,8 TCDF	**0**		**2**	**0.00066**		
1,2,3,7,8 PeCDF	**0**		**1**	**0.0039**		
2,3,4,7,8 PeCDF	**0**		**9**	**0.0007**	**0.015**	**0.0065**
1,2,3,4,7,8 HxCDF	**0**		**4**	**0.0027**	**0.013**	**0.0077**
1,2,3,7,8,9 HxCDF	**0**		**2**	**0.0056**	**0.0067**	**0.0062**
1,2,3,4,7,8,9 HpCDF	**0**		**4**	**0.0067**	**0.014**	**0.010**
DL PCBs (ng/kg of diaper)						
PCB 77	**0**		**40**	**0.038**	**2.72**	**0.283**
PCB 81	**0**		**2**	**0.048**	**0.072**	**0.06**
PCB 123	**0**		**40**	**0.022**	**0.051**	**0.131**
PCB 118	**0**		**51**	**0.749**	**9.119**	**3.939**
PCB 114	**0**		**31**	**0.0309**	**0.291**	**0.1333**
PCB 105	**0**		**51**	**0.3063**	**5.232**	**2.224**
PCB 126	**0**		**3**	**0.011**	**0.069**	**0.04**
PCB 167	**0**		**32**	**0.0073**	**0.919**	**0.198**
PCB 156	**0**		**47**	**0.0449**	**1.857**	**0.4103**
PCB 157	**0**		**17**	**0.0114**	**0.412**	**0.125**
PCB 169	**0**		**3**	**0.0068**	**0.06**	**0.029**
PCB 189	**0**		**23**	**0.0051**	**0.353**	**0.093**

The concentrations indicated in the table above have been transformed from the concentration measured in ng of substance per mL of urine simulant into the concentration of mg of substance/kg of diaper according to the volume of urine simulant added in the diaper and the volume of urine simulant extracted which is different according to each diaper (please refer to the equation 7). All the concentrations for each sample and each chemical is available in the excel sheet provided as an annex to the restriction proposal. It can be noted that the values for the PAHs are much lower in the 2019 analysis compared to the 2018. The Dossier Submitter would like to underline that the SCL indicated that no changes in the methodology during 2018 or 2019 was made. The assumption for the differences of concentrations values for PAHs, according to the SCL, may be linked to an improvement of the diapers or the raw materials used by the manufacturers between 2018 and 2019.

B.9.2.3. Exposure assessment

The assessment of exposure relies on the calculation of a Daily exposure Dose (DED), which is the quantity of a substance to which a population (children between zero and three years of age here) is exposed on a daily basis. The DED is expressed in mg/kg bw/day. The calculation of this DED requires the development of exposure scenarios reflecting the population's habits and the selection of exposure variables from the available data or from hypotheses when the necessary data are not available. The Dossier Submitter decided to use a **deterministic approach.**

The **dermal route of exposure was the one taken into account in this assessment, and more specifically exposure in the diaper area.** Until a child is toilet trained, this area is a warm, occlusive and moist environment with ideal kinetic conditions facilitating the percutaneous absorption of substances (ANSM, 2010; SCCS, 2018).

The **establishment of exposure scenario** aimed to characterise the exposure of children, from birth to the completion of toilet training, to chemicals previously identified in baby diapers.

One scenario was considered based on the available data set: synthetic urine was added to the diapers before being pressed out. The urine thus released from the diapers was then analysed. The Dossier Submitter considered that this scenario was a test providing realistic estimates of the capacity of urine to extract a number of chemicals from diapers (that are in direct contact of the skin or that can migrate from the outer part of the diapers to the parts of the diaper in direct contact with the skin). The doses contained in the urine recovered after pressing enabled quantities of chemicals in contact with a child's skin to be estimated. Taking into account the capacity of these chemicals to penetrate the skin, the Dossier Submitter was able to estimate more realistic internal exposure doses.

The Dossier Submitter considered that averaging lifetime exposure was not conservative enough. For certain effects, such as reprotoxicity and certain forms of endocrine disruption, there can be short exposure windows during which the risk of inducing harmful effects is high. It is therefore necessary to ensure that the HRV is complied with every day and not just on average, to avoid exposure peaks that may occur during these susceptibility windows. Therefore, the calculated DED corresponds to the daily exposure of a baby using single-use baby diapers.

A DED was calculated for each chemical individually, using the following equation:

$$\mathbf{DED = (C_{diaper} \times W \times F \times Abs_{skin}) / BW} \qquad \textbf{equation 1}$$

where

- DED: daily exposure dose (mg/kg bw/day)
- C_{diaper}: concentration of the chemical extracted with a urine simulant from an entire diaper, in relation to the weight of the diaper taking into account the extracted simulant volume (mg/kg of diaper)
- W: average weight of a diaper (kg)
- F: frequency of use (number/day)
- Abs_{skin}: fraction absorbed by the skin (%)
- BW: body weight of a child (kg)

It should be noted that this DED seems the most realistic since:

- the capacity to extract substances from diapers to urine was not modelled but was observed during the experiments.
- quantities of substances were only measured in urine actually coming out of the diapers after pressing, which avoided the need to use the modelled reflux ratio parameter.

For PCDD/Fs, DL-PCBs and PAHs, exposure and risks were assessed for each congener taken individually. Cumulative exposure was taken into account for each class of substances.

For PCDD/Fs and DL-PCBs, exposure was assessed using the Toxicity Equivalence Factor (TEFs) indicating the toxicity of all congeners having the same mechanism of toxicological action as the "Seveso" dioxin (2,3,7,8-TCDD), considered the most toxic. Exposure was therefore expressed in toxic equivalent quantities (TEQs). The TEFs were defined in 1998 and revised in 2005 by the WHO (Van den Berg *et al.,* 2006). The Dossier Submitter retained the values of TEF from WHO 2005 (see Figure 16).

For PAHs, exposure was also assessed using TEFs, considering BaP as the reference compound. TEF values chosen by the Dossier Submitter are available in the Table 39.

Consequently, the calculation of the DED, for each PCDD/Fs, DL-PCBs and PAHs is then:

$$DED_{TEQ} = (C_{diaper} \times W \times F \times Abs\ skin \times TEF) / BW \qquad \text{equation 2}$$

B.9.2.3.1 Levels of substances of concern in single-use baby diapers

The Dossier Submitter found some published data on measured levels of substances of concern in single-use baby diapers by solvent extraction.

Valuable information has been received through the Call for evidence, the RMOA comments and the ANSES opinion collective expert appraisal report (ANSES, 2019). The available information on approximate levels of the targeted substances in single use baby diapers is summarised in the table below.

Table 52 : Measured levels of targeted substances in single use baby diapers

Substance	Approximate levels in single use baby diapers	Composition (solvent extraction) or migration (urine extraction)	Reference
Formaldehyde	Detection	Composition	Danish EPA (2009)
	1.51-37.4 mg/kg	Composition	ANSES (2019) *via* SCL
	1.1-7.18 mg/kg (entire diaper)	Migration	
PCDD/Fs	Sum (TEQ) = 0.1-0.3 ng/kg	Composition	ANSES (2019) *via* SCL
	Sum (TEQ) = $7.62.10^{-4}$ - $4.29.10^{-2}$ ng/kg (shredded diaper)	Migration	

	Sum (TEQ) = 0.06-1.36 ng/kg (entire diaper)		
	Sum (TEQ) : 0.16-0.61 ng/kg	Composition	VITO (2018)
	Quantified (levels not specified)	Composition	OSAV (2018)
	2,3,7,8-TCDF = 2.7 pg/g 2,3,7,8-TCDD = 0.54 pg/g 2,3,4,7,8-PeCDF = <0.2 pg/g 1,2,3,7,8-PeCDD = <0.3 pg/g		Wiberg *et al* (1989)
	PCDD = 1.8-3.9 ppt PCDF = 0.2-1.8 ppt	Composition	Schecter *et al* (1998)
	Sum (TEQ) PCDD/F = 0.023 pg/g	Composition	De Vito et Schecter (2002)
DL-PCB	PCB 106 = 1.17 pg/g PCB 105 =2,733 pg/g PCB 118 = 6,27 pg/g PCB 123 = 0,203 pg/g PCB 77 = 0.981 pg/g Sum (TEQ max) = 0.020 pg/g	Not specified	Company in the call for evidence
	Sum (TEQ) = 0.032-0.186 ng/kg	Composition	ANSES (2019) *via* SCL
	Sum (TEQ) = $8.65.10^{-4}$ – $7.55.10^{-3}$ ng/kg (for shredded diaper)	Migration	
	Sum (TEQ) = 7.39-43.4 ng/kg (entire diaper)		
HAP	Detection of Benzo[b]fluoranthene, Benz[a]anthracene, Indeno[1,2,3-c,d]pyrene, Benzo[g,h,i]perylene	Composition	ANSES (2019) *via* SCL
	Detection of Benzo[e]pyrene, BaP, Benzo[b]fluoranthene, Dibenz[a,h]Anthracene, 5-methychrysene, chrysene, Benzo[g,h,i]perylene, Benzo[k]fluoranthene, Benzo[j]fluoranthene	Migration	
	Nothing < 100 ng/g	Not specified	Company in the call for evidence
	Quantified (levels not specified)	Composition	OSAV (2018)
	Chrysene = 0.0182-0.104 mg/kg Benz[a]anthracene = 0.11-0.194 mg/kg		Confidential industrial study (2016)

In 2009, the Danish Environmental Protection Agency **(Danish EPA)** published a report on the assessment of exposure of two-year-olds to chemical substances in consumer products (Danish EPA, 2009). The agency selected several consumer products including baby diapers. Five single-use diapers from various sources were analysed (range of prices, popular brands, organic/non-organic brands). Several diaper parts were studied (a screening then a quantitative analysis and finally a migration analysis). Aliphatic hydrocarbons and polymers were found but not identified. Very low levels of formaldehyde were detected but not quantified in three diapers and more specifically in the printed backsheet and the acquisition layer. For all of the diapers, the table below summarises the chemicals detected, semi-quantified or quantified and the part of the diaper in which each chemical was found.In their Tier 1 risk assessment, the Danish EPA chose to retain the maximum concentration of the chemicals, a frequency of use of 5/day and 100% absorption of the measured values from the diapers were absorbed. The concentration of the chemicals retained for the risk assessment comes from the resultats of the quantitative content analyses.

Table 53 : Detected, semi-quantified or quantified chemicals in tested baby by Danish EPA (2009)

Baby diaper description	Information stated on the packaging or product	Filling material	Elastic rim	Strech closures	VoInner waist lining	Frontal print	All parts of the diaper (not in the filling material)
Diaper with strech closure. Print on the front side of diaper. Junior/5 11-25 kg	Latex free. Contains no lotion or fragrance -Contains: Cellulose, bleached without chlorine, polypropylene, polyethylene, polyurethane, synthetic rubber.		2,4-di-tert-butylphénol = 14 µg/g BHT = 100 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 480 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 180 µg/g Irgafos 168 oxydized = 200µg/g	2,4-di-tert-butylphénol = 19µg/g BHT = 29 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 1000 µg/g Irgafos 168 oxydized = 180 µg/g	BHT = 18 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 430 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 92 µg/g Irgafos 168 oxyized = 98 µg/g	BHT = 25 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 130 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 100 µg/g Irgafos 168 oxydized = 81µg/g	2.4-bis (1,1-dimethylethyl)-phenol BHT Tris(2,4-ditert-butylphenyl) phosphite Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate
Trouser diaper, print on the front side of diaper. 13.20 kg	-Anti leak technology - All-round soft fit	Irganox 245 = 160 µg/g	2,4-di-tertbutylphenol = 14 µg/g BHT = 9 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 1200 µg/g Irgafos 168 oxydized = 180µg/g	No sterch closure	BHT = 7 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 890 µg/g Irgafos 168 oxydized = 61 µg/g	2,4-di-tert-butylphenol = 8 µg/g BHT = 7 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 960 µg/g	2.4-bis (1,1-dimethylethyl)-phénol BHT Tris(2,4-ditert-butylphenyl) phosphite Octadecyl 3-(3,5-di-tert-butyl-4-

Baby diaper description	Information stated on the packaging or product	Filling material	Elastic rim	Strech closures	VoInner waist lining	Frontal print	All parts of the diaper (not in the filling material)
						Irgafos 168 oxydized = 160µg/g	hydroxyphenyl) propionate
Diaper with strech closure. Print on the front and back sides of the diapers. Junior 11-25 kg	- Non-stop fit - Stretch & Hold - Contains: Petrolatum, stearyl alcohol, paraffinum liquidum, aloe barbadensis extract.		2,4-di-tert-butylphenol = 8 µg/g BHT = 11 µg/g 1-Octadecanol = 4800µg/g Tris(2,4-ditert-butylphenyl) phosphite = 550 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 280 µg/g Irgafos 168 oxydized = 240 µg/g	Limonene = 42 µg/g 2,4-di-tert-butylphénol = 11 µg/g BHT = 9 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 300 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 500 µg/g	BHT = 8 µg/g Naugard Tris(2,4-ditert-butylphenyl) phosphite = 550 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 55 µg/g Irgafos 168 oxydé = 67 µg/g	2,4-di-tert-butylphenol = 8 µg/g BHT = 10 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 430 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 150 µg/g Irgafos 168 oxydized = 140µg/g	Limonene 2.4-bis (1,1- dimethylethyl)-phenol BHT 1-Octadecanol Tris(2,4-ditert-butylphenyl) phosphite Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate

Baby diaper description	Information stated on the packaging or product	Filling material	Elastic rim	Strech closures	VoInner waist lining	Frontal print	All parts of the diaper (not in the filling material)
Diaper with strech closure. Print on the front side of diaper. Junior 12-22. Kg	Fragrance and lotion free		2,4-di-tert-butylphenol = 7 µg/g BHT = 8 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 560 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 76 µg/g Irgafos 168 oxydized = 150µg/g	Limonène = 60 µg/g 2,4-di-tert-butylphenol = 10 µg/g BHT = 10 µg/g 13-Docosenamide = 82 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 210 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 480 µg/g Irgafos 168 oxydizedé = 89µg/g	Tris(2,4-ditert-butylphenyl) phosphite = 380 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 50 µg/g Irgafos 168 oxydized = 180 µg/g	Limonene = 41 µg/g Caprolactame = 610 µg/g 2,4-di-tert-butylphenol = 7 µg/g BHT = 6 µg/g Isobutyle palmitate = 210 µg/g sobutyle stearate = 560 µg/g Octadecyle oleat = 210 µg/g	Limonene Caprolactame 2.4-bis (1,1-diméthyléthyl)-phénol BHT Isobutyle palmitate isobutyle stearate Octadecyle oleate 13-Docosenamide Tris(2,4-ditert-butylphenyl) phosphite Irganox 1076 Formaldehyde

Baby diaper description	Information stated on the packaging or product	Filling material	Elastic rim	Strech closures	VoInner waist lining	Frontal print	All parts of the diaper (not in the filling material)
Diaper with strech closure. Print on the front side of diaper.	- 100% free of chlorine - Contains over 50% "renewable resources". - Compostable packaging. - Dermatologically and clinically tested - Breathable foil 100% biodegradable		Limonene = 140 µg/g Dilactide = 160 µg/g 2,4-di-tert-butylphénol = 6 µg/g BHT = 8 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 260 µg/g Phthalate containing a long a alkyl chain = 170 µg/g Irgafos 168 oxydized = 130µg/g	Limonene = 210 µg/g 2,4-di-tert-butylphénol = 25 µg/g BHT = 41 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 830 µg/g Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate = 62 µg/g Irgafos 168 oxydized = 100µg/g	Limonene= 33 µg/g Dilactide = 220 µg/g BHT = 10 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 220 µg/g Phthalate containing a long alkyl chain = 100 µg/g Irgafos 168 oxydized = 41 µg/g	Limonene = 92 µg/g Caprolactame = 240 µg/g Palmitate d'isobutyle = 1200 µg/g Tris(2,4-ditert-butylphenyl) phosphite = 390 µg/g	Limonene 3.6-Dimethyl-1.4- dioxan-2.5-dione Caprolactame 2.4-bis (1,1-diméthyléthyl)-phénol BHT Isobutyl stearate Tris(2,4-ditert-butylphenyl) phosphite Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate Phthalates containing a long alkyl chain

Baby diaper description	Information stated on the packaging or product	Filling material	Elastic rim	Strech closures	VoInner waist lining	Frontal print	All parts of the diaper (not in the filling material)
							Ester

The Belgian Federal Public Service (VITO, 2018) screened four baby diapers in order to identify all of the compounds that could be extracted from a diaper. Levels of esters, heavy alcohol, alkanes and siloxanes were observed, but with "no risks to health".

In a second phase, 20 baby diapers of big-name brands, "store" brands and "bio" brands were analysed in order to screen for 17 PAHs, glyphosate and AMPA (aminomethylphosphonic acid), pesticides, phthalates (DEHP, DBP, DMP, DINP), parabens, isothiazolinones, phenolic compounds, PFOA, BTEX and dioxins and furans. Only the inner surface in contact with babies' skin was analysed after shredding. SAP was removed before extraction. The concentrations of most of the detected chemicals were below the limit of quantification. Some chemicals were quantified but at concentrations below 1 mg/kg with the exception of nonylphenol in a few diapers and BIT in one diaper:

- Nonylphenol in 17 products (0.038-4.4 mg/kg),
- Isothiazolinones in three products (MIT: 0.019-0.44 mg/kg; BIT: 1.6 mg/kg),
- Glyphosate (0.072-0.13 mg/kg) and AMPA (0.18 mg/kg) in two products,
- 6-caprolactam (0.029-0.59 mg/kg) in 10 products,
- Phthalates in one product (DEHP: 0.4 mg/kg; DBP: 0.18 mg/kg).

Dioxins and furans (2,3,7,8-TCDF; 1,2,3,7,8-PeCDF; 2,3,4,7,8-PeCDF; 1,2,3,4,7,8-HxCDF; 1,2,3,6,7,8-HxCDF; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 1,2,3,4,6,7,8-HpCDF) were quantified in eight products. Toxic equivalent quantity (TEQ) values for the sum of dioxins and furans ranged from 0.16 to 0.61 ng $_{TEQ}$/kg.

The most frequently quantified chemicals were nonylphenol and caprolactam. Possible sources of caprolactam include nylon threads and poly(ether-amide) elastomers. This chemical causes skin irritation. However, VITO considers it to be safe in baby diapers since the concentrations found are low. Nonylphenol is an endocrine disruptor, whose presence probably originates from the use of nonylphenolethoxylates (surfactants used for cleaning, surface treatment, emulsification, solubilisation, etc.). Another source may be antioxidants (TNPP: tris(4-nonylphenyl) phosphite). The presence of nonylphenol should be further investigated and measures should be taken to reduce levels of this chemical in baby diapers.

In 2018, the Swiss Federal Food Safety and Veterinary Office (FSVO), in collaboration with the Fédération Romande des Consommateurs (FRC), a Swiss consumer association, also carried out tests with 21 single-use diapers available on the Swiss market. One hundred and fourteen chemicals were screened for in shredded diapers: dioxins and furans, PAHs, perfluorinated substances, glyphosate and AMPA, phthalates, volatile organic compounds (VOCs) and solvent residues. Dioxins and furans (1,2,3,4,6,7,8-HpCDD, OCDD and 1,2,3,4,6,7,8-HpCDF) were quantified in one product. PAHs (naphthalene, anthracene and pyrene) were quantified in 17 out of 19 diapers. Lastly, DIBP was quantified in one product. The FSVO concluded that baby diapers do not contain chemicals likely to pose health risks for infants or toddlers (FSVO, 2018; FRC, 2018). It should be noted that these conclusions were drawn without conducting a QHRA.

For the previous studies listed above, the Dossier Submitter would like to underline that either these studies are quite old (and the manufacturing of diaper may have changed in between) or that no QHRA were conducted before concluding that there is no health risk.

As part of tests undertaken by a company, polycyclic aromatic hydrocarbons (**PAHs**) were screened for in several parts of three diapers of two different brands (LQ = 0.1 mg/kg). Benzo[a]anthracene (0.11-0.194 mg/kg) and chrysene (0.0182-0.104 mg/kg) were quantified in two diapers, more particularly in the elastics for the first diaper and in the front and rear parts for the second diaper (industrial study, 2016).

In the **scientific literature**, some studies have screened for the presence of **dioxins and furans** in disposable and re-usable baby diapers (Wiberg *et al.,* 1989; Schecter *et al.,* 1998; DeVito and Schecter, 2002; Shin *et al.*, 2005). TEQs were calculated in these various studies, primarily using the WHO's toxic equivalency factors (TEFs), in order to express the overall toxicity of dioxin mixtures. This is because dioxins are generally found in mixtures containing several types of dioxins and dioxin-like compounds, each with a specific degree of toxicity.

In 1989, Wiberg *et al.* measured levels of polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) in baby diapers on the Swedish market that had or had not been bleached without chlorine (Table 54). These authors also presented results for cloth diapers. The packaging of the diapers included the statement "chlorine-free" or "dioxin-free".

Table 54 : Levels of PCDDs and PCDFs in baby diapers (Wiberg et al., 1989)

	TCDD equivalent*	2,3,7,8-TCDF	2,3,7,8-TCDD	2,3,4,7,8-PeCDF	1,2,3,7,8-PeCDD
Disposable diapers	1.0 pg/g	2.7 pg/g	0.54 pg/g	<0.2 pg/g	<0.3 pg/g
Cloth diapers (unwashed)**	<0.2 pg/g	<0.2 pg/g	<0.1 pg/g	<0.1 pg/g	<0.1 pg/g

* calculated using "Nordic toxic equivalency factors" (1988)

** 1,2,3,7,8-PeCDF, 1,2,3,4,6,7,8-HpCDF, OCDF and OCDD were detected.

In 1998, Schecter *et al.* conducted a preliminary study on sanitary products including baby diapers of four different brands. Three of these were disposable diapers and one was a reusable cotton diaper. The authors quantified PCDDs and PCDFs (Table 55). The lowest concentrations were found in the cotton diaper.

Table 55 : Concentrations of dioxins and furans in baby diapers (Schecter et al., 1998)

Diapers	Measured levels (ppt)			Dioxin TEQ (ppt)		
	PCDDs	PCDFs	Sum	PCDDs	PCDFs	Sum
Disposable - Brand E	3.9	1.8	5.6	0.005	0.064	0.069
Disposable - Brand F	2.2	0.5	2.7	0.005	0.010	0.015
Disposable - Brand G	1.8	0.5	2.3	0.004	0.010	0.014
Reusable diaper	2.6	0.2	2.7	0.005	0.001	0.006

De Vito and Schecter (2002) analysed four baby diapers, including three disposable diapers and one cotton diaper, all purchased in San Francisco. They screened for 17 PCDDs and PCDFs. Only five of the 17 dioxins were detected in the diapers (LD = 0.1 - 0.2 ppt). There were similar concentrations in the disposable and reusable diapers. Total PCDD/F concentrations in the diapers ranged from 1.8 to 3.7 pg/g, i.e. from 0.0042 pg $_{TEQ}$/g (cotton diaper) to 0.023 pg $_{TEQ}$/g (disposable diaper).

Despite all these studies available, the Dossier Submitter chose to not retain the substances detected and/or quantified in these studies in the present restriction proposal for several reasons : either these studies are too old and the diapers composition may have evolved over the years or either because the extraction methods used are not the one recommended in the present restriction proposal.

The French SCL studies performed various analysis on single-use diapers and detected and/or quantified the substances of concern. As already mentionned, the analysis were performed onto 51 different diapers that are available on the French market between 2017 and 2019. The Dossier Submitter chose to report the level according to the ECHA R15 guidance, meaning that the Dossier Submitter calculated the Q95 of the distribution of the 51 samples. To do so:

- **if the substance was not detected, the LOD was retained**
- **if the substance was detected, the LOQ was retained**
- **if the substance was quantified, the concentration was retained.**

B.9.2.4. Selection of exposure parameters

B.9.2.4.1. Population to be included in the scope

The age at which children are toilet trained varies considerably depending on the individual. By two and a half years of age, approximately 90% of girls and 75% of boys have complete bladder control (Stoppard, 1990 cited in UK Environment Agency, 2005a). The average child will stay dry at night at the age of 33 months (normal range from 18 months to eight years) (Green, 1998 cited in UK Environment Agency, 2005a).

In 2004, the UK Environment Agency undertook a study on the use of single-use baby and re-usable diapers. It showed that the average age out of diapers was 26.17 months (1,553 respondents). By the age of two and a half years, 95% of children are out of single-use baby diapers (UK Environment Agency, 2005b). However, some children continue wearing training pants and/or diapers at night for varying lengths of time.

Table 56 : Percentage of children wearing single-use baby diapers (all types) (UK Environment Agency, 2005b)

Age of child	Children wearing nappies (%)	Children not wearing nappies (%)
up to 6 months	100.0%	0.0%
6 to 12 months	95.7%	4.3%
12 to 18 months	82.8%	17.2%
18 to 24 months	45.6%	54.4%
24 to 30 months	17.6%	82.4%
30 to 36 months	4.8%	95.2%
36 to 42 months	1.8%	98.2%
42 to 48 months	0.4%	99.6%
48 to 54 months	0.1%	99.9%
54 to 60 months	0.1%	99.9%
60 to 66 months	0.1%	99.9%

In this restriction proposal, the health risk assessment was undertaken for children aged from birth to 36 months included. The population of interest was divided into six age groups in order to better take into account the weight evolution and psychomotricity developments of children between the ages of zero and 36 months involving the use of different diaper sizes and a daily frequency of use adapted to each age group.

B.9.2.4.2. Contact between single-use baby diapers and skin

The dose per skin surface area is considered to be the most relevant dose metric for risk assessment of the chemicals of concern. Therefore, the area of the exposed skin is typically an important parameter to consider in such calculations. However, in single-use baby diaper exposure scenario the relationship between the diaper surface and surface of the exposed skin is 1:1, i.e. **the exposed skin area is 100% covered by the material**.

B.9.4.3. Exposure duration

It is generally agreed that it is not only the dose per skin area that is the determinant of the adverse effect but also that the duration of the exposure, i.e. the accumulated dose per skin area is important.

24 hours was selected as an **appropriate time frame** for accumulated dose when chemicals have **threshold effects** given that exposure is expected throughout the day until the child or the infant is fully toilet trained.

On the contrary, for chemicals with **non-threshold effect**s (carcinogenic ones), **3 years** corresponding to the time until that a child is fully toilet trained, is considered as the **appropriate time frame**.

B.9.4.4. Babies weight

Body weight depends on the age and sex of the individual and his/her physiological condition. During the diaper wearing period, the weight of a child varies. On average, it is 3.5 to 4 kg for a newborn, 10 kg for a one-year-old child, and 18 to 25 kg for a toddler (Rai *et al.,* 2009).

Companies consider an average body weight of 8 kg (Rai *et al.,* 2009; Dey *et al.*, 2016a; EDANA). As part of a worst-case scenario, they recommend using the smallest body weight for newborns (Rai *et al.,* 2009).

Body-weight data from the 2013 BEBE-SFAE survey, on the eating habits and food consumption of children between the ages of zero and 36 months in metropolitan France, are also available. This study was conducted in the field by TNS-SOFRES for the French Association for Children's Food. Consumption data were collected from 1,188 mothers of children between the ages of 15 days and 36 months, meant to be a representative sample of the French population[28]. Body weights were recorded by the interviewer in the children's homes using a bathroom scale or recent weighing data (cf. Table 9 in section 12.5.5).

The 2014-2015 French Individual and National Food Consumption Survey (INCA 3) documented this parameter (ANSES, 2017b). This was a study that first and foremost aimed to collect individual food consumption data for the population living in France, but the participants' anthropometric data were also recorded. All of the participants were weighed in their homes using electronic bathroom scales. Any participants who refused were invited to report their body weight. As part of the study, body-weight data were thus collected for 5,842 individuals aged from zero to 79 years out of the 5,855 surveyed, i.e. 3,145 adults and 2,697 children) (Table 57).

Table 57 : Distribution of body weight (kg) according to sex and age for children aged zero to 17 years (n = 2697) (ANSES, 2017b)

		Boys (n=1406)					**Girls** (n=1291)					**Total** (n=2697)					**Test**
		Mean	**SD**	p5	Med.	p95	**Mean**	**SD**	p5	Med.	p95	**Mean**	**SD**	p5	Med.	p95	
0-11 months	n=80	**6.6**	**2.2**	3.1	6.0	11.0	**6.5**	**1.7**	3.3	5.5	10.3	**6.6**	**1.9**	3.1	6.0	10.4	ns
1-3 years	n=229	**13.0**	**1.5**	9.8	13.0	16.0	**12.7**	**1.8**	9.6	12.4	17.0	**12.9**	**1.7**	9.6	12.7	16.7	ns
4-6 years	n=454	**18.9**	**3.6**	14.5	18.3	25.2	**19.3**	**4.1**	13.6	18.4	27.0	**19.1**	**3.9**	14.2	18.4	26.0	ns
7-10 years	n=643	**29.5**	**7.6**	20.5	28.0	44.7	**29.0**	**7.6**	19.0	27.8	43.9	**29.3**	**7.6**	19.8	27.9	44.7	ns
11-14 years	n=736	**46.9**	**13.4**	30.2	46.0	67.6	**45.8**	**12.1**	30.0	45.0	65.1	**46.4**	**12.8**	30.0	45.0	67.6	ns
15-17 years	n=555	**66.1**	**17.3**	44.0	63.0	96.6	**57.3**	**12.5**	42.0	55.6	76.8	**61.8**	**15.9**	44.0	60.0	92.8	***
Test of differences by sex: ns (not significant), * (p.0.05), ** (p<0.01), *** (p<0.001)																	
Source: INCA3 study (2014-2015), data processing by ANSES																	

Other studies were available to the Dossier Submitter but did not allow him to gather the weight of children and infants by class of age.

In this restriction proposal, the Dossier Sumitter chose to work with the Q25 of the body weight for each age group described in the BEBE-SFAE study (2013).
The BEBE-SFAE study was retained for this restriction proposal because it is the only european study available that details sufficient data covering all classes between 0 and 36 months old .
The Dossier Submitter chose to retain, as a reasonable worst case, a Q25 of the body weight distribution for each class of age in order to be in line with the RIVM "General Fact Sheet" report about the general default parameters for estimating consumer exposure (RIVM, 2014).

[28] Excluding highly vulnerable populations, based on the following criteria: the baby's age and sex, the mother's occupation, and the family's socio-professional category and region/metropolitan area.

B.9.4.5. Absorbed fraction by the skin

Dermal absorption depends on the specific physico-chemical properties of the chemical, the maturity of the skin tissue, the state of the skin (skin diseases) and the exposure conditions (occlusive or semi-occlusive conditions).

Until a child is toilet trained, the diaper area is a warm, occlusive and moist environment with ideal kinetic conditions facilitating the percutaneous absorption of substances. The available studies have shown that an increase in skin moisture, a high alkaline skin pH, the mixing of urine and faeces and the mechanical action of friction between the skin and diaper can cause irritative dermatitis to develop (Scheinfeld, 2005; Runeman, 2008; Tüzün *et al.*, 2015; Atherton, 2016; Bender and Faergemann, 2017). This prolonged contact impairs skin barrier function. A decline in stratum corneum integrity leaves the skin permeable to chemicals, infectious agents and the enzymes found in urine and faeces. Urine increases the skin's moisture level and supplies urea. Due to faecal urease activity, urea is converted into ammonia, increasing the skin pH and promoting the activity of other faecal enzymes (lipases, proteases) contributing to the deterioration of the stratum corneum (Odio *et al.*, 2014; Lagier *et al.*, 2015; Felter *et al.*, 2017; Bender and Faergemann, 2017).

This environment supports the development of skin diseases that can potentially increase the dermal penetration of substances. Diaper dermatitis is one of the most common skin disorders in neonates and infants, with a prevalence between 7 and 50% (Šikić Pogačar *et al*., 2018). However, the real incidence of diaper dermatitis might be higher because physicians and parents do not report many cases of diaper dermatitis as they usually resolve after a few days without the need for medical treatment (Šikić Pogačar *et al*., 2018; Blume-Peytavi *et al*., 2014). Even though it rarely causes problems for longer periods of time (typically 2-4 days), it causes considerable distress to both infants and parents at the same time. Incidence peaks is reported in infants between 6 and 12 months who are weaning off breast milk and beginning to consume solid foods (Blume-Peytavi *et al.,* 2014; Burdall *et al.,*2019; Carr *et al*., 2020; Cohen, 2017; Odio and Thama, 2014; Ersoy-Evans *et al.,* 2016).

Nonetheless, despite the potential risks associated with the occlusive nature of this environment, a significant decrease in the incidence and severity of diaper dermatitis has been observed over the past few years (ANSM, 2010).

This improvement may result likely from these different factors:

- Improved design and greater use of modern superabsorbent nappies. According to Burdall *et al*. (2019): "The inclusion of super-absorbent gels (reducing skin moisture),
- petrolatum-based lotions (improving skin integrity), and breathable outer layers (reducing local humidity) into thinner diapers with a better fit to the body's contour has seemingly led to a reduction in the presence of erythema and severity of diaper dermatitis."
- Improved design of wipes,
- Improved use of barrier emollients,
- Improved general skin care of infants (Atherton, 2016: Burdall *et a*l., 2019; Odio and Thaman, 2014).

However, the wearing of diapers continues to cause skin diseases in the buttocks area that can affect dermal absorption. Skin conditions such as contact dermatitis and diaper rash can potentially increase the dermal penetration of substances depending on their physicochemical characteristics and the degree of skin damage, in particular for premature infant skin. Indeed *"skin prematurity involves thinner stratum corneum and underdeveloped epidermis/dermis resulting in decreased barrier function, higher TEWL and greater chemical penetration, when compared to healthy full-term neonate/adult skin"* (Dey *et al.*, 2015)

Skin compromised by diaper rash or by mechanical or chemical damage has shown variable penetration properties, with slightly higher dermal penetration compared to normal skin (Gattu and Maibach, 2011 cited in Dey *et al.*, 2016a). Stamatas *et al.* (2011) compared skin barrier function in infants with dermatitis, considering areas of lesional skin, non-lesional skin and control skin (skin on the outer thigh). Barrier function was similar for the non-lesional and control skin (transepidermal water loss (TEWL)[29] 47 ± 29 g/m²/hr vs 48 ± 30 g/m²/hr). The lesional skin showed higher TEWL (104 ± 67 g/m²/hr) than the non-lesional skin and control skin, indicating that skin with erythema can be vulnerable due to loss of stratum corneum, resulting in increased TEWL (Stamatas *et al.,* 2011). Conversely, other studies indicate that compromised skin does not necessarily result in increased dermal penetration (McCormack *et al.,* 1982 cited in Dey *et al.*, 2016a; Dey *et al.*, 2015; Felter *et al*., 2017). Dey *et al*. (2015) developed an *in vitro* skin penetration model using human *ex vivo* skin (n= 12 human skin samples per group from 5 different donors) to estimate penetration for intact (single and repeat dose), moderately (single dose) and highly premature/compromised skin barrier conditions (single and repeat dose)[30]. Baby wipe lotion containing 5 mg/cm^2 [^{14}C]-PEG-7 phosphate was applied 1 or 5 times to human skin samples and once at 25 mg/cm^2 over 24 h (semiocclusive). Penetration of [14C]-PEG-7 phosphate was low (<5%) and only 4 to 6 times higher than that of intact skin, even for highly compromised skin (mean ranging from 3.19 to 4.48%). The absorption rate was higher ($p < 0.001$) for compromised skin versus intact skin and no significant difference was seen between moderately and highly compromised skin by repeated dosing (intact : 0.37 ± 0.22%, moderately: 2.98 ± 3.30%, highly: 2.08 ±2.55%). Under single-dose conditions, penetration through highly compromised skin was significantly higher compared to intact skin ($p = 0.001$; intact: 0.53 ± 0.35%, highly: 1.32 ± 0.88%) (Dey *et al.,* 2015). This study was carried out with PEG-7 phosphate, a surfactant chosen because it is used in the composition of the wipes. However, this substance is not representative of the substances in the scope. According to Felter *et al.* (2017), *"it is appropriate to consider a time-weighted average for exposure in the nappy area that takes into consideration the impact of diaper rash for a safety assessment focused on systemic endpoints. They consider three scenarios to evaluate the potential impact of diaper rash on substances dermal absorption that have a very low, low or moderate degree of absorption through healthy skin. Results confirm that for safety assessments that already assume a degree of dermal absorption of 50% or higher, there is no impact on the overall exposure assessment. For substances that have a low degree of dermal penetration (10%), the impact is less than two-fold and for those with a very low degree of dermal penetration (1%), the impact is less-than four-fold. It is recommended that for compounds that are*

[29] Transepidermal water loss refers to a mixed phenomenon of passive diffusion and water vapour loss as a result of sweating. When the skin is damaged, transepidermal water loss is increased. On the other hand, it returns to normal baseline values when the skin barrier is restored. The value of transepidermal water loss measured with an evaporimeter is expressed as a mass of evaporated water per unit area of skin per unit of time (g/m²/hr).

[30] The degree of skin compromise was evaluated by TEWL, which has been used as an indicator of skin integrity deficiencies, like damage from chemical or physical irritants or changes under occlusive conditions. TEWL was an average of 8.968 g/m²/hr for intact skin, 11.554 g/m²/hr for moderately compromised skin and 27.760 g/m²/hr for highly compromised skin.

assumed to have very low dermal penetration for healthy skin, an explicit consideration of the impact of diaper rash be considered".

Exposure assessment were performed for examples of substances in single-used baby diapers:

- For dioxins and furans, De Vito and Schecter (2002 calculated dermal exposure using several dermal absorption: 3% and 28%. Dioxins are bound to the wood pulp fibres and are not readily available. There are no studies describing dermal absorption of dioxins bound to wood pulp products. The dermal absorption of TCDDs from soil has been estimated at 0.1% to 3% depending on the organic content of the soil. Between <0.1% and 3% of the dioxins contained in polyester or cotton fabrics are transferred to human skin within 72 hours (Klasmeier *et al.*, 1999 cited in De Vito and Schecter, 2002). Since pulp is a mixture of organic fibres, it is likely that dioxins are closely bound to these fibres and are not readily available. However, due to uncertainties, an absorption value of 3%, based on an estimate of dermal absorption from soil with low organic content (US EPA, 1992 cited in De Vito and Schecter, 2002), was used in the first calculation. In the second calculation, an absorption value of 28% was estimated based on *in vivo* and *in vitro* experimental data, considering the dermal absorption of dioxins in aqueous solutions (US EPA, 2000 cited in De Vito and Schecter, 2002).
- For phthalates, Ishii *et al.* (2015) calculated dermal exposure to seven phthalates present in the topsheet of single-use baby diapers using a transdermal absorption of 5% for DEHP, BBP and DNOP (structural similarity with DEHP), 10% for DBP and DIBP (structural similarity with DBP) and 0.5% for DINP and DIDP.
- For acrylic acid, a residual monomer of SAP, a dermal absorption of 100% were used to calculate the DED (Rai *et al.,* 2009; Dey *et al.,* 2016a).

At European level, the Scientific Committee on Consumer Safety (SCCS) recommends using a default absorption rate of 50%. However, the buttocks area has its own particular conditions: wearing of diapers, uncontrolled urination and defecation, and diseases that can damage the skin. Modern diaper technology has shown increasing compatibility with the skin, leading to a reduction in the frequency and severity of diaper dermatitis. That said, diaper dermatitis cannot be completely avoided and may have an impact on the dermal absorption of substances. Thus, the potential impact of irritation on the dermal absorption of chemicals should be taken into account in the final quantitative risk assessments of products intended to be used on the buttocks (SCCS, 2018).

It should be noted that for the assessment of cosmetics intended for children under three years of age, the ANSM recommends applying a worst-case scenario, i.e. 100% topical penetration, when calculating margins of safety for products likely to be applied to the buttocks (ANSM, 2010).

Even though the frequency of diaper dermatitis has decreased due to the use of diapers with increasing skin compatibility, diaper dermatitis cannot be completely avoided and may have an impact on the dermal absorption of chemicals. Moreover diaper area is not only healthy or injured skin, there are also mucous membranes which have an important absorption. In addition, direct contact with damaged skin may increase the skin sensitisation concern.

Even if dermal absorption data are available for substances in the scope (see Annexes B.5.1.1.1, B.5.2.1.1 and B.5.3.1.1), the Dossier Submitter assumed a

mucocutaneous absorption rate of 50% as a realistic conservative choice to calculate exposure for babies including preterm babies.

B.9.4.6. Exposure frequency

The number of diapers used per day is influenced by the age of the child, the size of the diaper, the type of diaper used, the country and cultural habits.

The average number of daytime diaper changes decreases from seven per day at birth to five per day at the age of 2.5 years. When children no longer in diapers are not included, the average number of diapers used per day (daytime and nighttime, considering one diaper per night) by children between the ages of zero and 2.5 years ranges from 4.05 to 4.4.

Some data were gathered through the call for evidence and are summarized in the table below:

Table 58 : Information gathered through the call for evidence on exposure frequency

Company /association	Frequency (diapers per day)	Comments
1	5	-
2	Size 1 : 6 Size 2 : 5-6 Size 3 : 4-5 Size 4 : 4	-
3	Size 1: 6-10 Size 2: 6-10 Size 3: 6-10 Size 4: 4-6 Size 5: 4-6 Size 6: 4-6 Size 7: 4-6	-
4	0-2 months : 6-7 2-24 months : 4-5 24-30 monts : 2	-
5	0-3 monhts: 7.6 (France) – 7.4 (Germany) 4-6months : 6 – 6 7-12 months : 6.1 – 5.8 13-18_ months : 5.4 – 5.4 19 – 24 months : 5.2 – 5.3 25-36 months : 4.1 – 5.2 37 – 48 months : 3.8 – 3.8 Size 0-1-2 : 7.A (France) – 6.3 (Germany) Size 3 : 6.1 – 6.0 Size 4 : 5.1 -5.3 Size 5 : 5.1 – 5.1 Size 6 -7 : 4.7 - 4.9	Figures in 2018

The following table summarises the data on the frequency of use of single-use baby diapers found through a literature search.

Table 59 : Summary of the data on the frequency of use of single-use diapers

Reference	Frequency of use (number/day)	Comment
UK Environment Agency (2005b)	4.16 Average daytime frequency < 6 months: 6.98 6 - 12 months: 5.66 12 - 18 months: 5.75 18 - 24 months: 4.95 24 - 30 months: 4.85 30 - 36 months: 3.70 + one diaper/night	Average
Krause *et al.* (2006) Rai *et al.* (2009)	5 Size 1 (2-5 kg): 6 Size 2 (3-6 kg): 5-6 Size 3 (4-9 kg): 4-5 Size 4 (7-20 kg): 4 Size 5 (11-25 kg): 3	Average
France Nature Environnement (2011)	5	Average
Dey *et al.* (2016a)	Mean: 4.7 Median: 5 P75: 6 P90 and P95 = 7	In France (n = 587) see
	4.7 ± 1.8 Size 2 (5-8 kg): 5.6 ± 2.1 Size 3 (7-13 kg): 4.7 ± 1.5 Size 4 (10-17 kg): 4.4 ± 1.5 Size 5 (14-18 kg): 4.1 ± 1.5	Average USA (collection of data on the frequency of use of size-2 to -5 diapers between 2010 and 2012)
De Vito and Schecter (2002)	0-6 months: 10 6-24 months: 6	Hypothesis
Ishii *et al.* (2015)	12	JHPIA, 2015

As mentionned above, the population of interest was divided into six age groups in order to better take account of rapid developments in terms of weight and psychomotor development in children between the ages of zero and 36 months involving the use of different diaper sizes and a daily frequency of use adapted to each age group.

Based on the available data described above, the daily frequency of use, the Dossier Submitter used the data from the study undertaken in 2002-2003 in the United Kingdom in more than 2,000 households with a child who was in diapers or had worn diapers in the recent past, due to the robustness of this study (Table 59).

Table 60 : Values of the frequency of use retained in the restriction proposal

Parameter	Age groups	Value	Reference
Frequency of use	0-6 months exclusive	7.98	UK Environment Agency, 2005b (average daytime
	6-12 months inclusive	6.66	

	13-18 months inclusive	6.75	frequency + one diaper/night)
	19-24 months inclusive	5.95	
	25-30 months inclusive	5.85	
	31-36 months inclusive	4.70	

B.9.4.7. Baby diaper weights

The average weight of a single-use baby diaper decreased from 64.6 g in the late 1980s to 40 g in 2010 and 33.3 g in 2013, i.e. an almost 50% reduction over a 25-year period (Figure 17) (EDANA, 2005, 2011 and 2015; Group'Hygiène, 2015).

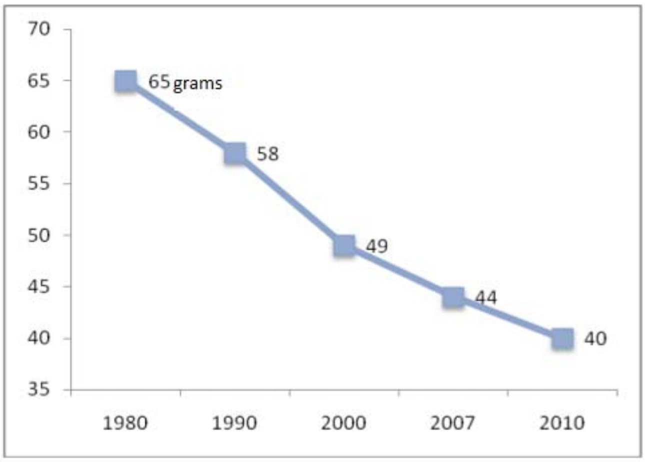


Figure 17: Change in the average weight of a single-use diaper between 1980 and 2010 (Group'Hygiène, 2015)

New data were gathered through the call for evidence published on the ECHA website. Various companies provided baby diaper weights according to their size. This information are gathered in the table below :

Table 61 : Information about baby diapers weight according to the call for evidence

Company	Weight (g)	Comments
1	20-30g for small size 40 for larger size 45-50g for night pants	Size of the diaper not specified
2	24-28g	No more information provided
3	Newborn: 21.0 g Mini: 23.0 g Midi: 29.0 g Maxi: 34.0 g Junior: 36.0 g XL: 38.5 g XXL 39.5 g	-
4	Size 0-1 = 16.4 – 23.1 Size 2 : 16.4- 26.5 Size 3 : 20.6 – 31 Size 4 : 26 – 41	-

	Size 4+ : 26.8 – 42 Size 5 : 29.7 – 34.5 Size 5+ : 29.7 – 34.5 Size 6 : 30.3 – 50 Size 7/8 : 34.1 - 35.7	

The literature data available for this parameter are summarised in the table below.

Table 62 : Average weight of a single-use diaper

Reference	Weight (g)	Comment
De Vito and Schecter, 2002	Average = 40	Hypothesis
Krause *et al.* (2006) Rai *et al.* (2009)	50 Size 1 (2-5 kg): 24 Size 2 (3-6 kg): 25 Size 3 (4-9 kg): 33 Size 4 (7-20 kg): 40 Size 5 (11-25 kg): 45	P&G internal consumer usage data
Gupta *et al.* (2009)	30.1 to 50.7	Test with seven diapers
UK Environment Agency (2005)	42.77	Average UK data, 2001-2002
UK Environment Agency (2008)	38.6	Average
Group'Hygiène (2015)	40	2010
EDANA (2015)	33.3	2013
Group'Hygiene	Size 1 (2-5 kg): 16.4 – 23.1 Size 2 (3-6 kg): 16.4 - 26.5 Size 3 (4-9 kg): 20.6 - 31 Size 4 (7-20 kg): 26 - 41 Size 5 (11-25 kg): 29- 46.3 Size 6 (13-27 kg) = 30.7 – 50	Group' Hygiene Communication, 2019

Based on the weight of a diaper, the Dossier Submitter considered the most recent data available from an European industrial association.

Table 63 : Reported diapers weight (Group'Hygiène 2019)

Parameter	Age groups	Value	Reference
Weight of a diaper by age group	0-6 months exclusive	23.1 g	Group'Hygiène (2019) *via* personal communication
	6-12 months inclusive	31.0 g	

	13-18 months inclusive	31.0 g	
	19-24 months inclusive	31.0 g	
	25-30 months inclusive	46.3 g	
	31-36 months inclusive	46.3 g	

The Dossier Submitter would like to underline that the weight of premature babies' diapers are not taken into account in the weight of a diapers by age group due to lack of available data.

B.9.4.8. Conclusion on exposure parameters

The values of the parameters used by the Dossier Submitter to perform the exposure assessment (and calculate the DED) are gathered in the table here under :

Table 64 : values of the parameters used in the exposure assessment

Parameter	Realistic conservative approach		
	Value		Reference
Weight of a diaper by age group (W)	0-6 months exclusive	23.1 g	Group Hygiène (2019) *via* personal communication
	6-12 months inclusive	31.0 g	
	13-18 months inclusive	31.0 g	
	19-24 months inclusive	31.0 g	
	25-30 months inclusive	46.3 g	
	31-36 months inclusive	46.3 g	
Daily frequency of use (average) (F)	0-6 months exclusive	7.98	UK Environment Agency, 2005b (average daytime frequency + one diaper/night)
	6-12 months inclusive	6.66	
	13-18 months inclusive	6.75	
	19-24 months inclusive	5.95	
	25-30 months inclusive	5.85	
	31-36 months inclusive	4.70	
Dermal absorption rate (Abs_{skin})	50%		ANSM (2010)
Body weight (BW)	0-6 months exclusive	5.2 kg	BEBE-SFAE (2013)
	6-12 months inclusive	7.5 kg	
	13-18 months inclusive	9.6 kg	
	19-24 months inclusive	10.9 kg	
	25-30 months inclusive	12.0 kg	
	31-36 months inclusive	12.0 kg	

B.9.4.9. Workers exposure

Not relevant

B.9.4. Other sources (for example natural sources, unintentional releases)

Not relevant

B.9.3. Overall environmental exposure assessment

Not relevant

B.9.4. Combined human exposure assessment

Not relevant.

B.10. Risk characterisation

RAC box

RAC reached different conclusions than the Dossier Submitter concerning the risk characterisation of the restriction proposal. RAC undertook a sensitivity analysis using more realistic conditions of use and concluded that either the RCRs were below 1 or that the risks could not be reliably characterised because of the lack of a reliable exposure assessment.

The details of the RAC evaluation are reported in the RAC opinion, together with the justification for the conclusions on the characterisation of risks.

B.10.1. Manufacturing

B.10.1.1. Human health

Not relevant

B.10.1.2. Environment

Not relevant

B.10.2. Use: Traditionnal single-use baby diaper

B.10.2.1. **Human health**

To reduce the risk for the infants and children wearing a single-use baby diaper from exposure to formadehyde, DL-PCB, PCDD/Fs and PAHs, the exposure to a chemical substance migrated from the material should not exceed a migration limit, considered as safe.

Risk characterisation enables the expected risk in a population to be quantified, taking into account exposure to the substance in question and its effects (toxicity). Risk characterisation is the final QHRA phase and consists in calculating the expected risk level for the chosen type of effect, based on the calculation of:

- a Risk Characterisation Ratio (RCR) for substances with a threshold effect,

- an Individual Excess Risk (IER) for substances with a no-threshold effect (carcinogenic effect).

For substances with a threshold effect, meaning formaldehyde, PCDD/Fs and DL-PCBs, and for substances with a no-threshold effect (mainly genotoxic carcinogens, in this restriction dossier, PAHs), the risk level is expressed by the RCR, which is the ratio between the daily exposure dose (DED) and the appropriate internal DNEL or dermal DMEL expressed for 10^{-6} risk level. The numerical value of this ratio is used to determine whether or not the dose received exceeds the $DNEL_{in}$ or $DMEL_{dermal}$.

$RCR = DED/\ DNEL_{in}$ or $DMEL_{dermal}$	equation 3

The numerical value of the RCR is interpreted as follows: an RCR greater than 1 means that the toxic effect may occur, without it being possible to predict its likelihood of occurrence in the exposed population, whereas an RCR lower than 1 indicates that no toxic effect is theoretically expected in the exposed population , provided that the exposure to the substance is only due to the single use baby diaper.

Single-use baby diapers are not the only source of babies exposure to substances. The intake of chemicals from single-use baby diapers is small in comparison with that from other sources, such as food, air, drinking-water and other consumer products. So some consideration is needed as to the proportion of the DNEL that may be allowed from different sources. This approach ensures that total daily intake from all sources does not exceed the DNEL. This approach is used for example to derive guideline values in drinking water or regulatory thresholds for chemicals in toys.

The value of this allocation factor could be different in different contexts. For drinking water, WHO recommends to use "*wherever possible or in an ideal situation" "data on the proportion of total daily intake normally ingested in drinking-water (based on mean levels in food, drinking-water, consumer products, soil and air), or data on intakes estimated on the basis of physical and chemical properties of the substances of concern*" to derive guideline values for drinking water (WHO, 2018). "*In the absence of adequate exposure data or where documented evidence is available regarding widespread presence in one or more of the other media (i.e. air, food, soil or consumer products), the normal allocation of the total daily intake to drinking-water is 20% (floor value), which reflects a reasonable level of exposure based on broad experience, while still being protective (Krishnan & Carrier, 2013). This value reflects a change from the previous allocation of 10%, which was found to be excessively conservative*" (WHO, 2018).

An allocation factor of 10% is also used for calculation of regulatory thresholds for toys. For example, an allocation of 10 % of the TDI to the intake of formaldehyde from toys was used to derive a migration limit for formaldehyde in toys (Commission Directive (EU) 2019/1929 of 19 November 2019 amending Appendix C to Annex II to Directive 2009/48/EC[31]). According to RIVM (2008), this allocation factor was already used in 1984 by the Scientific Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds to propose

[31] **COMMISSION DIRECTIVE (EU) 2019/1929of 19 November 2019 amending Appendix C to Annex II to Directive 2009/48/EC of the European Parliament and of the Council for the purpose of adopting specific limit values for chemicals used in certain toys, as regards formaldehyde :** https://eur-lex.europa.eu/legalcontent/EN/TXT/HTML/?uri=CELEX:32019L1929&from=EN

thresholds for metals (report EU 12964 EN not available) (RIVM, 2008). CSTEE stipulated that leaching from toys should not contribute more than 10% of the dietary intake. After evaluation of the toxicology of the elements, in particular children's sensitivity regarding toxicity and toxicokinetics (absorption), CSTEE determined whether for individual elements the figure of 10% of normal dietary intake being permissible for leaching from toys, needed adjustment. CSTEE choose different allocation values between 10 and 1% depending on the elements studied. In 2010, the SCHER stated that the total contribution from toys should not exceed 10% of the TRV (2010b; 2010a).

Table 65: Permissible intake of certain elements, derived from Annex 0 of the June 1985 advice by the Scientifid Advisory Committee to examine the toxicity and ecotoxicity of chemical compounds, as published in report EU 12964 EN (from RIVM, 2008)

	Sb	As	Ba	Cd	Cr	Pb	Hg	Se
Adult intake (µg/week)	30	1400	7000	175	400	1000	70	700
Children's intake (µg/week)	15	700	3500	87.5	200	500	35	350
Assumed contribution from toys	10%	0.1%	5%	5%	1%	1%	10%	10%
Children's daily permissible intake from toys in µg	0.2	0.1	25	0.6	0.3	0.7	0.5	5

An allocation factor, expressed as percentage of the toxicological reference value, is one of the criteria considered for derivation of specific release limits (SRLs) for substances in food contact materials and articles. Indeed, food contact materials as one possible source for the human exposure (next to food and dietary supplements). For example, contribution to the total intake of metal ions due to other sources of exposure than metals and alloys used in food contact materials and articles are taken into consideration by applying allocation factors, where appropriate, when deriving SRLs (Council of Europe, 2013[32]).

The possibility of cumulative exposure through other sources (environmental, food, *etc*.) leading to an increase in the total DED is recognized, meaning that the exposure to these chemicals is likely not limited to diapers only. Nevertheless, the share allocated to each source can't be documented. Considering 100% of the DNEL/DMEL for one source of exposure, will lead to underestimate the risks due to cumulative exposure. Given the number of potential or well-known sources of exposure for the chemicals included in the scope of the restriction proposal, it seems reasonable for the Dossier Submitter to allocate only a limited part of the DNEL/DMEL to estimate the risks linked to the use of single use baby diapers.

Therefore, the Dossier Submitter decided to limit the share allocated to single-use baby diapers to 10% of the DNEL/DMEL. In addition this in line with other regulatory contexts (please see above).

[32] https://static1.squarespace.com/static/58b148d6bebafbde4946144b/t/5d14d9a50339890001745b3b/1561647539027/Metals+and+Alloys+used+in+food+contact+materials+and+articles.pdf

B.10.2.1.1 Equation to derive migration limits in single-use baby diapers

To reduce the risk for children and infants from exposure to substances of concern in single use baby diapers, the exposure to a chemical substance migrated from the article should not lead to a RCR higher than 1. As explained before, various exposure routes leading to an increase in the estimated risks could not be ruled out, meaning that the exposure to these chemicals is not limited to only diapers but to another exposure sources (environmental, food *etc*.). **That's why the Dossier Submitter decided to limit the share allocated to baby diapers to 10% of the RCR.**

The limit in single use baby diaper was calculate using the following equation:

- **For substance with a threshold effect :**

$$\mathbf{C_{diaper} = RCR\ x10\%\ x\ BW\ x\ DNEL_{in\ or}\ DMEL_{dermal}\ /\ (W\ x\ F\ x\ Abs\ _{skin}\ x\ TEF)}\quad \textbf{equation 4}$$

With:

- $DNEL_{in}$: internal DNEL (mg/kg bw/d)
- BW: Body weight of a child (kg)
- W: Weight of a diaper (kg)
- F: frequency of use per 24h (number/24h)
- Abs $_{skin}$: fraction absorbed by the skin (%)
- TEF : toxic equivalent factor (only used for PCDD/Fs and DL-PCB and PAHs)
- C_{diaper}: concentration limit of the chemical extracted with a urine simulant from an entire diaper, in relation to the weight of the diaper taking into account the extracted simulant volume (mg/kg of diaper)

During the public consultation, some comments indicated that a rewet factor should be included in the calculation of the exposure(for example, industry stated that a value of 1% could be used as a rewet factor). This rewet factor represents the quantity of urine that is not trapped into the diaper; meaning that is not absorbed by the core of the diaper. This rewet factor can be used as a tool to measure the function of absorption of the diaper (its efficiency). In the exposure calculation performed by the Dossier Submitter in this restriction proposal, no rewet factor has been used. Indeed, the concentration of chemicals found during the analysis performed by the SCL are already measured in the urine simulant extracted from the diaper. Moreover according to the SCL, the objective of their analysis was, to recover the maximum volume of urine simulant to be able to perform the analysis. In other words, it means that the volume recovered in the SCL analysis is higher (around 30%) than the value of rewet proposed by the industry and not comparable to the 1%. **Independently of the volume obtained, the objective was to measure the quantity of chemicals that is not trapped in the diaper's core.**

Finally, regarding the real value of a rewet factor, if one should have been included, a bibliography search performed in ANSES, 2018 shows that several industrial studies have estimated this parameter based on the location of the chemical in the parts of single-use diapers (Krause *et al.*, 2006*; Erasala *et al.,* 2007*; Rai *et al.*, 2009*; Kosemund *et al.*, 2009*; Dey *et al.*, 2016a*):

- Chemicals in direct contact with the skin (topsheet, lotion, leak guards, belt section) can be transferred to the skin directly or by solubilisation in sweat, urine, faeces or sebum. Only a fraction is transferred to the skin during use. According to Odio *et al.* (2000*), 7% is actually transferred to the skin. This figure was estimated based on the transfer of a tracer ingredient (stearyl alcohol) found in lotions in the topsheet whose objective is precisely to be transferred to the skin. This transfer factor for lotions was also used by default for most of the ingredients in the topsheet and elastics. It was deemed conservative by the authors since a lotion is intended to be transferred to the skin, unlike other ingredients;

- For substances in indirect contact with the skin (acquisition layer, SAP, core, nonwoven material surrounding it, glue), transfer can occur by extraction or solubilisation in body fluids followed by migration to the topsheet and release onto the skin under pressure (reflux). In the absence of data, the authors recommend a reflux value of 100%. The highest reflux value would be 0.223% after testing diapers that can be worn through the night with a high urine load. The authors selected the value of 0.25%, which they considered conservative (Rai *et al.*, 2009*). This value is recommended by EDANA (2005). A new method for calculating reflux has been developed to more realistically simulate the wearing of diapers: Prolonged Exposure Rewet Method in Diapers (PERMID). This method uses a gravimetric approach where collagen is used as a skin mimic. It takes into account the pressure a child may apply to a diaper, the urine load during diaper wear, the gap between urine voids, the exposed surface area, and diaper wear time (Dey *et al.*, 2016a*). This pressure was measured in 174 children between the ages of two weeks and 56 months, in four positions (sitting up straight, lying on the stomach, lying on the back, and falling on the buttocks). Thanks to this new method, an average reflux factor of 0.46% (0.32-0.66%) was adopted, considering 50% of the diaper surface area since in real conditions of use, only a small portion of a diaper is under pressure;

- The authors assumed skin contact to be negligible for the backsheet, printed surfaces, fastening system and ear tabs.

Table 66 : Transfer from the material to the skin and reflux ratio

Reference		Comment
Krause *et al.* (2006)*	Direct contact of the material with the skin: 10-20% Indirect contact (reflux): 0.25-2.5% Negligible contact: 0%	-
Rai *et al.* (2009)*	Direct contact: 7% Indirect contact (reflux): 0.25%	Default factor
Dey *et al.* (2016a)*	Direct contact: - 4% after three hours of wear - 3% after six hours of wear - 4.3% after a night Indirect contact (reflux): 0.46%	PERMID method

The concentration of the **available** substance expressed in mg/kg of diaper cannot be directly measured. It is proposed to be determined after extraction of said substance from an entire diaper with a urine simulant. It is thus related to the weight of the diaper, and to the extracted simulant volume. The concentration limit of available substance expressed in mg/kg of diaper can thus be transformed into a limit concentration of the **available** substance expressed in mg/L of urine simulant using the following equation:

$$C_{\text{urine simulant}}\ [\text{mg/mL urine}] = (C_{\text{diaper}}\ [\text{mg/kg diaper}] \times \text{weight of the diaper}\ [\text{kg}]) / \text{extracted volume}\ [\text{mL}] \qquad \text{equation 5}$$

Example : Here is presented an example of the calculation of the RCR for formaldehyde starting from the concentration of urine simulant obtained for one of the references tested.

After the analysis has been performed :

- A concentration of $C_{\text{urine simulant}} =$ 0.096mg/L urine simulant has been obtained (that can be also expressed as 0.000096 mg of substance/mL of urine simulant).
- The weight of the diaper was : 0.0211 kg
- The extracted volume (meaning the volume of urine simulant obtained after having pressed out the diaper)was : 230 mL

By using the equation 5,the concentration of formaldehyde for the reference tested, expressed in mg of substance/mg of diaper is :

C_{diaper} = 0.000096*230/0.0211= **1.046 mg/kg of diaper**

Then the calculation of the RCR regarding formaldehyde for this reference for the class of age 0-6 months is :

$DED_{0\text{-}6} = (C_{\text{diaper}} \times F \times W \times Abs_{\text{skin}}) / BW = 1.046 \times 7.98 \times 0.0231 \times 50\% / 5.2 = 0.0186$ mg/kg/day

RCR = **$DED / DNEL_{in}$ = 0.0186/ 0.075 = 0.247**

The Dossier Submitter would like to indicate that even if the risk assessments are performed while using concentrations of chemicals measured through a dedicated analytical method were urine simulant are added to the parts of the diapers that are in contact with the skin (to be the more realistic), chemicals can migrate from the other parts of the diapers (due to urine simulant, the sweat or to the ability itself of the chemicals to migrate). In conclusion, the limits proposed by the Dossier Submitter here after will be applicable for the whole diaper, all the sizes of the diapers available on the market and all the category of ages(explanations given in Annex B and in 1.2.6 of the main report).

B.10.2.1.2. Formaldehyde

Approximate level in diapers

In the studies performed by SCL in 2018 and 2019, formaldehyde was quantified 22 times and detected 17 times over 51 references analysed.

The 95th percentile of the concentration out of the 51 references is 1.767 mg/kg (As explained in section B.5), the internal human reference value for formaldehyde retained by the Dossier Submitter is 0.075 mg/kg bw/d.

By applying the exposure equation described in Annex B.9, and for the class of age from 0 to 6 months excluded, the DED will be:

$DED_{0\text{-}6} = (C_{diaper} \times F \times W \times Abs_{skin}) / BW = 1.1767 \times 7.98 \times 0.0231 \times 50\% / 5.2 = 0.0314$ mg/kg/day

Consequently, the RCR for fomaldehyde quantified in single use diapers in 2018 and 2019 in the SCL analysis, will be:

$$\mathbf{RCR_{0\text{-}6} = DED / DNEL_{in} = 0.0314 / (0.075) = 0.42}$$

Single-use baby diapers are not the only source of exposure to chemicals for which reference values have been established and exposure *via* single-use diapers is certainly lower than exposures from other sources such as food or the air. Thus and as already explained, the Dossier Submitter chose to limit to 10% of the DNEL the share allocated to baby diapers for the calculation of threshold concentration which imply that the RCR calculated for formaldehyde is above 0.1 that will ensure safety for babies when exposed to this chemical in diapers.

As already explained, the Dossier Submitter decided, in its risk assessment, to calculate the RCR and using the parameters related to babies aged between 0-6 months, as for this category of age, the ratio BW/W is the lowest and so the RCR will be the worst over the 6 classes of age. Moreover, as mentioned above, the Dossier Submitter decided to limit the share allocated to baby diapers to 10% of the DNEL meaning that the RCR must not be ovec 0.1 ; otherwise a risk could not be excluded.

Consequently, and regarding the result of the calculation described here above, it can be concluded, that through the risk assessment performed, sufficient exposure may occur *via* diaper to trigger adverse effects in babies.

Migration limit not to be exceeded in diapers

A $DNEL_{in}$ of 0.075 mg/kg bw/d was retained (see Annex B.5). For infants between 0 to 6 months old excluded, a frequency of use of 7.98; a diaper weight of 23.1 g and a body weight of 5.2 kg were used. No TEF is needed for formaldehyde.

The migration limit of formaldehyde in diapers ensuring that 10% of the $DNEL_{in}$ is not exceeded is:

Migration limit (mg/kg diaper) = 0.1 x 0.075 X 5.2 /(0.0231 X 7.98 X 50%) = **0.42 mg/kg**

The Dossier Submitter proposes a migration limit of **0.42 mg/kg** for formaldehyde in single-use baby diaper.

Because the process and the manufacturing lines are the same, the Dossier Submitter chose to indicate that this limit is proposed to cover all the category of ages and all the sizes of diapers available on the market.

B.10.2.1.3. PCDD/Fs and DL-PCBs

Approximate level in diapers of PCDDs

In the studies performed by SCL in 2018 and 2019, various PCDDs were quantified in the 51 diapers analysed.

In the table below are detailed the concentration (95th percentile), the calculated DED according the equation 2 and the RCR for the class of age 0-6 months excluded.

Table 67 : RCR for each PCDD quantified in the SCL studies

Substances	**95th percentile (ng/kg of diaper)**	**DED_{0-6} in TEQ (ng_{TEQ}/kg/d)**	**RCR_{0-6}**
1,2,3,4,6,7,8 HpCDD	0.2105	$3.73.10^{-12}$	$1.24.10^{-8}$
OCDD	0.185	$9.84.10^{-13}$	$3.27.\ 10^{-9}$
1,2,3,6,7,8 HxCDD	0.0186	$3.29.10^{-11}$	$1.09.10^{-7}$
1,2,3,4,7,8 HxCDD	0.0085	$1.51.10^{-11}$	$5.02.10^{-8}$
1,2,3,7,8,9 HxCDD	0.0155	$2.74.10^{-11}$	$9.16.10^{-8}$
Sum of the quantified PCDDs	0.00414	$7.33.10^{-5}$	0.24

It can be concluded, that through the assessment performed, sufficient exposure may occur *via* diaper to trigger adverse effects in babies for the sum of the quantified PCDDs.

Approximate level in diapers of PCDFs

In the studies performed by SCL in 2018 and 2019, various PCDFs were quantified in the 51 diapers analysed.

In the table below are detailed the concentrations (95th percentile), the calculated DED according the equation detailed above and the RCR for the class of age 0-6 months excluded.

Table 68 : RCR for each PCDF quantified in the SCL studies

Substances	**95th percentile (ng/kg of diaper)**	**DED_{0-6} (ng_{TEQ}/kg/d)**	**RCR_{0-6}**
1,2,3,6,7,8 HxCDF	$1.18.10^{-02}$	$2.08.10^{-05}$	$6.9.10^{-02}$
2,3,4,6,7,8 HxCDF	$2.29.10^{-02}$	$4.05.10^{-05}$	0,14
1,2,3,4,6,7,8 HpCDF	$5.16.10^{-02}$	$9.14.10^{-06}$	$3.3.10^{-02}$
OCDF	$6.76.10^{-02}$	$3.59.10^{-07}$	$1.19.10^{-03}$
2,3,7,8 TCDF	$6.76.10^{-02}$	$1.19.10^{-04}$	0.40
1,2,3,7,8 PeCDF	$6.76.10^{-02}$	$3.59.10^{-05}$	0.12
2,3,4,7,8 PeCDF	$1.21.10^{-02}$	$6.43.10^{-05}$	0.21
1,2,3,4,7,8 HxCDF	$1.01.10^{-02}$	$1.79.10^{-05}$	$5.97.10^{-02}$
1,2,3,7,8,9 HxCDF	$6.87.10^{-03}$	$1.22.10^{-05}$	$4.05.10^{-02}$
1,2,3,4,7,8,9 HpCDF	$8.55.10^{-03}$	$1.52.10^{-06}$	$5.06.10^{-03}$
Sum of quantified PCDFs	$3.11.10^{-01}$	$5.51.10^{-03}$	18.35

It can be concluded, that through the risk assessment performed, sufficient exposure may occur *via* diaper to trigger adverse effects in babies for some of the quantified PCDFs.

Approximate level of DL-PCBs in diapers

In the studies performed by SCL in 2018 and 2019, various DL-PCBs were quantified in the 51 diapers analysed.

In the table below are detailed the concentration (95th percentile), the calculated DED according the equation detailed above and the RCR for the class of age 0-6 months excluded.

Table 69 : RCR for each DL-PCB quantified in the SCL studies

Substances	95th percentile (mg/kg of diaper)	DED_{0-6} in TEQ(mg_{TEQ}/kg/d)	RCR_{0-6}
PCB 77	$7.26.10^{-01}$	$1.29.10^{-06}$	$4.28.10^{-03}$
PCB 81	$6.64.10^{-02}$	$3.53.10^{-07}$	$1.18.10^{-03}$
PCB 123	$3.87.10^{-01}$	$2.06.10^{-07}$	$6.86.10^{-04}$
PCB 118	8.51	$4.53.10^{-06}$	$1.51.10^{-02}$
PCB 114	$2.87.10^{-01}$	$1.53.10^{-07}$	$5.08.10^{-04}$
PCB 105	4.41	$2.35.10^{-06}$	$7.82.10^{-03}$
PCB 126	$7.64.10^{-02}$	1.35.10-^{04}	0.45
PCB 167	$3.69.10^{-01}$	$1.96.10^{-07}$	$6.53.10^{-04}$
PCB 156	$8.92.10^{-01}$	$4.47.20^{-07}$	$1.58.10^{-03}$
PCB 157	$1.68.10^{-01}$	$8.94.10^{-08}$	$2.97.10^{-04}$
PCB 169	$6.51.10^{-02}$	$3.46.10^{-05}$	0.12
PCB 189	$1.81.10^{-01}$	$9.63.10^{-08}$	$3.32.10^{-04}$
Sum of the quantified PCBs	6.47	$1.15.10^{-01}$	381.99

It can be concluded, that through the risk assessment performed, sufficient exposure may occur *via* diaper to trigger adverse effects in babies for some of the quantified DL-PCBs.

The Dossier Submitter would like to underline the statements hereafter:

- When laboratories perform analysis onto diapers, they search for each congener.
- All PCDD/Fs and DL-PCBs were not quantified in each diaper but could be found in some of them leading, when performing the QHRA, to risk ratios higher than 0.1 . These risk assessments showed that risks exist for the chemical groups quantified in single-use baby diaper.
- Moreover, these chemicals have similar toxicological profiles meaning that hazards for each congener can be evaluated by using TEF.

All these statements lead the Dossier Submitter, in terms of regulatory management, to restrain the sum of the quantified PCDDs, PCDFs and DL-PCBs.

Migration limit not to be exceeded in diapers for the sum of the above chemicals

To define the migration limit for the sum of PCDD/Fs and DL-PCBs, the Dossier Submitter followed the approach described in section B.10.2.1.1.

A $DNEL_{in}$ of 0.3 pg/kg bw/d has been retained (See Annex B.5). For infants between 0 to 6 months old, a frequency of use of 7.98; a diaper weight of 23.1 g and a body weight of 5.2 kg were used.

The migration limit of **the sum of PCDD/Fs** in diapers ensuring that 10% of the $DNEL_{in}$ is not exceeded is then:

Migration limit (ng $_{TEQ}$/kg diaper) = 1 X 0.1 X 0.0003X 5.2 /(0.0231 X 7.98 X 50%) = **0.0017 ng $_{TEQ}$/kg**

The Dossier Submitter proposes a migration limit of **10.0017ng $_{TEQ}$/kg** in single-use baby diapers. As explained in section 1.2.6.1. this limit is proposed to cover all the category of ages and all the sizes of diapers available on the market.

DL-PCBs can be found in such articles and as it is commonly known when DL-PCBs can be quantified, NDL-PCBs are likely to co-exist. Even if these chemicals have not been searched for in single use baby diapers, they have been quantified in similar articles, that is to say in incontinence diapers (UFC Que Choisir, 2019). Consequently, the Dossier Submitter, chose to add these chemicals to the restriction proposal and to restrain the sum of the PCBs.

To determine the migration limit, the Dossier Submitter used the same equation (equation 3) and the same values for the parameters like for the calculation of the concentration limit of the sum of the above PCDD/Fs, DL PCBs except for the $DNEL_{in}$. Indeed, the $DNEL_{in}$ that has to be used can't be the same as the one used above (meaning 0.3 pg/kg bw/d) due to the fact that the toxic action mode of PCBs is not the same as the one for DL-PCBs. Consequently, and after a litterature search and exchange with toxicological experts, the Dossier Submitter, retained a HRV of 0.02 µg/kg/d (WHO, 2002) for the PCBs. In the table below are gathered all the information needed to determine the $DNEL_{in}$.

Table 70 : DNEL used to define a migration limit for PCBs

Type of HRV	Organisation (year)	Value	Target organ/critical effect	Oral bioavailability (reference)	internal DNEL
Oral chronic	WHO (2002)	TDI = 0.02 µg/kg/day	immunological and neurobehavioral effects	100%	2.10^{-5} mg/kg/day

The migration limit of **the sum of the total PCBs** in diapers ensuring that 10% of the $DNEL_{in}$ is not exceeded is then:

Migration limit (ng /kg diaper) = 1 X 0.1 X 2.10^{-5} X 5.2 /(0.0231 X 7.98 X 50%) = **112 ng/kg**

The Dossier Submitter proposes a migration limit of **112 ng/kg** of diaper. As explained in section 1.2.6.1. this limit is proposed to cover all the category of ages and all the sizes of diapers available on the market.

The migrations limits of the sum of the quantified PCDD/Fs, DL-PCBs and the sum of total PCBs, in diapers ensuring the safety of children and infant are:

Table 71 : Migration limit not to be exceeded in the entire diapers

Chemical	Migration limit
Sum of the quantified PCDDs, PCDFs and DL-PCBs in **TEQ**	**0.0017 ng_{TEQ}/kg of diaper**
Sum of the quantified total PCBs	**112 ng/kg mg/kg of diaper**

B.10.2.1.4. PAHs

Approximate level in diapers

In the studies performed by SCL in 2018 and 2019, various PAHs were detected in the 51 diapers analysed.

In the table below are detailed the concentration (95th percentile), the calculated DED according the equation detailed above.. As explained in annex B.5.1.11, the Dossier Submitter selected two DMELs (10^{-6} risk level) to assess health risks:

- for PAH mixture, a DMEL of 0.004 ng/kg bw/d (BAuA, 2010, considering only dermal studies) (most conservative DMEL but all DMELs are in the order of magnitude),
- for BaP alone, a DMEL of 0.006 ng/kg bw/d (derived from Knafla *et al.,* 2006) (most conservative DMEL).

So the Dossier Submitter calculated the RCR for each congener of PAHs detected using the $DMEL_{internal}$ from the Knafla study. For the sum of the detected PAHs, the Dossier Submitter calculated the RCR with both $DMEL_{internal}$ (the one from BAuA and the one from Knafla).

Table 72 : RCR (for an excess risk of 10^{-06})for each PAH detected in the SCL studies

Substances	95th percentile (mg/kg of diaper)	DED_{0-6} in TEQ(mg_{TEQ} /kg/d)	RCR_{0-6} (with the $DMEL_{internal}$ from the Knafla study)	RCR_{0-6} (with the $DMEL_{internal}$ from the BAuA study)
Benzo[d,e,f]chrysene	0.68	$1.19.10^{-02}$	1998	
Benz[a]anthracene	0.24	$4.29.10^{-04}$	71490	
Chrysene	0.25	$4.48.10^{-05}$	7473	
5-methyl-chrysene	0.25	$4.48.10^{-05}$	7473	
Benzo[e]acephenanthrylene	0.69	$1.22.10^{-03}$	203096	
Benzo[j]fluoranthene	0.25	$4.42.10^{-04}$	73705	
Benzo[k]fluoranthene	0.25	$4.42.10^{-04}$	73705	
Benzo[e]pyrene	0.77	$1.37.10^{-04}$	22850	
Benzo[g,h,i]perylene	0.68	$1.21.10^{-04}$	20206	
Sum of the detected PAHs	1.08	$1.91.10^{-02}$	3189209	4783814

It can be concluded, that, through the assessment performed, significant exposure may occur *via* diaper to trigger adverse effects in babies for all PAHs detected. The Dossier Submitter retains the DMELinternal from the Knafla study.

As for PCDD/Fs and DL-PCBs, various PAHs have been detected in single-use baby diapers. The risk evaluation has shown cases of risk ratios higher than 0.1 for some of the congeners. The Dossier Submitter would like to underline the statements hereafter:

- When laboratories perform analysis onto diapers, they search for each congener.
- All PAHs are not detected in each diaper but could be found in some of them leading, after QHRA, to risk ratios higher than 0.1. These risk assessments showed that risks exist for the chemical group detected in single-use baby diaper.
- Moreover, these particular PAHs (carcinogenic ones[33]) have similar toxicological profiles meaning that hazards for each congener can be evaluated by using TEF.

All these statements lead the Dossier Submitter, in terms of regulatory management, to restrain the sum of the detected or quantified PAHs (benzo[c]fluorene, benz[a]anthracene, cyclopenta[c,d]pyrene, chrysene, 5-methylchrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[e]pyrene, benzo[d,e,f]chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene, dibenzo[def,p]chrysene, naphtho[1,2,3,4-def]chrysene, benzo[r,s,t]pentaphene, dibenzo[b,def]chrysene)

Migration limit not to be exceeded in diapers for the sums of the above chemicals

To define the migration limit for each of the sum listed above, the Dossier Submitter followed the approach described in section B.10.2.1.1.

A $DMEL_{dermal}$ of 0.004 ng/kg bw/d has been retained (please see Annex B.5).

The migration limit not to be exceeded to ensure that infant and exposed to PAHs in single-use diapers is:

Migration limit (ng/kg diaper) = 1 X 0.1 X 0.004X 5.2 /(0.0231 X 7.98 X 50%) = 0.023 ng_{TEQ}/kg

For the sum of the detected or quantified PAH, the migration limit in diapers ensuring the safety of children and infant is 0.023 ng_{TEQ}/kg of diaper. The Dossier Submitter proposes a migration limit of **0.023 ng_{TEQ}/kg of diaper.**

B.10.2.1.5. Conclusion on human health risk

As a reminder, the Dossier Submitter summarizes all the DED calculated for the class of age 0-6 months and the dedicated RCR for each substance.

Table 73 : RCR for all the substances in the scope

Substances/group of substances	Concentration (95th	DED 0-6 months	RCR

33 benzo[c]fluorene, benz[a]anthracene, cyclopenta[c,d]pyrene, chrysene, 5-methylchrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[j]fluoranthene, benzo[e]pyrene, benzo[d,e,f]chrysene, dibenz[a,h]anthracene, indeno[1,2,3-c,d]pyrene, benzo[g,h,i]perylene, dibenzo[def,p]chrysene, dibenzo[a,e]pyrene, benzo[r,s,t]pentaphene, dibenzo[b,def]chrysene

	percentile) mg/kg		
Formaldehyde	1.1767	0. 0314 mg/kg/day	0.42
1,2,3,4,6,7,8 HpCDD	0.2105	$3.73.10^{-12}$ mg/kg/day	$1.24.10^{-8}$
OCDD	0.185	$9.84.10^{-13}$ ng/kg/day	$3.27. 10^{-9}$
1,2,3,6,7,8 HxCDD	0.0186	$3.29.10\text{-}^{11}$ ng/kg/day	$1.09.10^{-7}$
1,2,3,4,7,8 HxCDD	0.0085	$1.51.10^{-11}$ ng/kg/day	$5.02.10^{-8}$
1,2,3,7,8,9 HxCDD	0.0155	$2.74.10^{-11}$ ng/kg/day	$9.16.10^{-8}$
Sum of the quantified dioxins	0.00414	$7.33.10^{-5}$ ng/kg/day	0.24
1,2,3,6,7,8 HxCDF	$1.18.10^{-02}$	$2.08.10^{-05}$ ng/kg/day	$6.9.10^{-02}$
2,3,4,6,7,8 HxCDF	$2.29.10^{-02}$	$4.05.10^{-05}$ ng/kg/day	0,14
1,2,3,4,6,7,8 HpCDF	$5.16.10^{-02}$	$9.14.10^{-06}$ ng/kg/day	$3.3.10^{-02}$
OCDF	$6.76.10^{-02}$	$3.59.10^{-07}$ ng/kg/day	$1.19.10^{-03}$
2,3,7,8 TCDF	$6.76.10^{-02}$	$1.19.10^{-04}$ ng/kg/day	0.40
1,2,3,7,8 PeCDF	$6.76.10^{-02}$	$3.59.10^{-05}$ ng/kg/day	0.12
2,3,4,7,8 PeCDF	$1.21.10^{-02}$	$6.43.10^{-05}$ ng/kg/day	0.21
1,2,3,4,7,8 HxCDF	$1.01.10^{-02}$	$1.79.10^{-05}$ ng/kg/day	$5.97.10^{-02}$
1,2,3,7,8,9 HxCDF	$6.87.10^{-03}$	$1.22.10^{-05}$ ng/kg/day	$4.05.10^{-02}$
1,2,3,4,7,8,9 HpCDF	$8.55.10^{-03}$	$1.52.10^{-06}$ ng/kg/day	$5.06.10^{-03}$
Sum of the quantified furans (TEQ)	$3.11.10^{-01}$	$5.51.10^{-03}$ ng/kg/day	18.35
PCB 77	$7.26.10^{-01}$	$1.29.10^{-06}$ ng_{TEQ}/kg/d	$4.28.10^{-03}$
PCB 81	$6.64.10^{-02}$	$3.53.10^{-07}$ ng_{TEQ}/kg/d	$1.18.10^{-03}$
PCB 123	$3.87.10^{-01}$	$2.06.10^{-07}$ ng_{TEQ}/kg/d	$6.86.10^{-04}$
PCB 118	8.51	$4.53.10^{-06}$ ng_{TEQ}/kg/d	$1.51.10^{-02}$
PCB 114	$2.87.10^{-01}$	$1.53.10^{-07}$ ng_{TEQ}/kg/d	$5.08.10^{-04}$
PCB 105	4.41	$2.35.10^{-06}$ ng_{TEQ}/kg/d	$7.82.10^{-03}$
PCB 126	$7.64.10^{-02}$	$1.35.10\text{-}^{04}$ ng_{TEQ}/kg/d	0.45

PCB 167	$3.69.10^{-01}$	$1.96.10^{-07}$ ng_{TEQ}/kg/d	$6.53.10^{-04}$
PCB 156	$8.92.10^{-01}$	$4.47.20^{-07}$ ng_{TEQ}/kg/d	$1.58.10^{-03}$
PCB 157	$1.68.10^{-01}$	$8.94.10^{-08}$ ng_{TEQ}/kg/d	$2.97.10^{-04}$
PCB 169	$6.51.10^{-02}$	$3.46.10^{-05}$ ng_{TEQ}/kg/d	0.12
PCB 189	$1.81.10^{-01}$	$9.63.10^{-08}$ ng_{TEQ}/kg/d	$3.32.10^{-04}$
Sum of the quantified DL PCBs (TEQ)	6.47	$1.15.10^{-01}$ ng/kg/d	381.99
Benzo[d,e,f]chrysene	0.68	$1.19.10^{-02}$ mg/kg/day	1998
Benz[a]anthracene	0.24	$4.29.10^{-04}$ mg/kg/day	71490
Chrysene	0.25	$4.48.10^{-05}$ mg/kg/day	7473
Benzo[e]acephenanthrylene	0.25	$4.48.10^{-05}$ mg/kg/day	7473
Benzo[j]fluoranthene	0.69	$1.22.10^{-03}$ mg/kg/day	203096
Benzo[k]fluoranthene	0.25	$4.42.10^{-04}$ mg/kg/day	73705
Benzo[e]pyrene	0.25	$4.42.10^{-04}$ mg/kg/day	73705
Benzo[g,h,i]perylene	0.77	$1.37.10^{-04}$ mg/kg/day	22850

For all the chemicals in the scope of the restriction proposal, the migration limits are far below the highest limits found in single-use baby diapers at point of sale (as indicated in section 1.2.4 and annex B). Therefore, the risks associated with these substances are not adequately controlled. Hence, lowering the limits of these chemicals in single-use baby diapers to the ones proposed above, is considered to significantly reduce the risk. The migrations limits proposed are considered to adequately protect infants and children.

A sensitivity analysis has been performed for the formaldehyde, the sum of the PAH, the sum of the quantified PCDD/F/DL PCBs. This analysis is available in the annex added to the restriction proposal.

The calculated limits in single-use baby diapers (the entire diaper) proposed by the Dossier Submitter are the following ones:

Table 74 : Migration limits not to be exceeded in the entire single-use baby diaper

Substance/group of substances	**Proposed migration limit**
Formaldehyde	
Formaldehyde	**0.42 mg/kg of diaper**
PCDDs/PCDFs/ PCBs	
Sum of the quantified PCDDs, PCDFs **in TEQ**	**0.0017 ng_{TEQ}/kg of diaper**
Sum of the quantified total PCBs	**112 ng/kg of diaper**
PAHs	
The sum for the PAH quantified or detected **in TEQ**	**0.023ng_{TEQ}/kg of diaper**

B.10.2.2. Workers

Not relevant

B.10.2.3. Consumers

Not relevant

B.10.2.4. Indirect exposure of humans *via* the environment

PCDD/Fs, DL PCBs, PAHs and formaldehyde are ubiquitous substances that can be found in various sources of exposure. Indeed, dioxins, furans and DL-PCBS are found in food, air or in the ground. (ANSES, 2017b)

However, indirect exposure of infants and children was not considered for this restriction proposal.

B.10.2.5. Combined exposure

Not relevant.

B.10.2.6. Environment

Not relevant

Annex C: Justification for action on a Union-wide basis

The main reasons for a Union-wide restriction are summarised below.

Severity and extent of health risks

The severity of the possible health risk as documented in section 1.3 and section B.5 of the main report, and the extent of the risk as children are in daily contact with single-use baby diapers call for a Union-wide restriction. A Union-wide regulatory measure would ensure a harmonised high level of protection for human health across the Union.

As best-informed guess, the Dossier Submitter assumes that 90% of the European children and infants wear only single-use baby diapers (EDANA, 2011). According to Eurostat, around 5.2 million babies are born in EU28 every year[34], i.e. there are currently about 16 million babies and infants between 0 and 3 years old in EU28. It is reasonably assumed that all babies and infants in Europe share similar skin properties and similar diapering time until 3 years old (except some extreme cases of late toilet-training or physiological deficiencies). Therefore, it is assumed that around 14.5 million babies and infants in Europe are exposed to the hazardous chemicals targeted in this restriction proposal *via* their single-use baby diapers and thus are potentially at risk.

The free movement of goods

A Union-wide action to address the risks associated with substances of concern in single-use baby diapers is needed to ensure the free movement of goods within the EU. The fact that diapers, imported as well as manufactured in the EU, need to circulate freely once on the EU market, stresses the importance of an EU-wide action rather than action by individual Member States, as these actions could differ significantly from Member State to Member State. In addition, a Union-wide action would eliminate the distortion of competition on the European market between markets with and without national legislation on the chemical composition of textile and leather articles.

Additionally, this EU-wide action will have an effect on the goods produced outside EU. Indeed, the substances of concern in this restriction proposal often bare other hazards, in particular for environment. As their concentration will be limited to enter the EU market, their use will be controlled and limited as well when produced.

[34] Average over 2008-2018 retrieved on June the 9th from: https://ec.europa.eu/eurostat/databrowser/view/tps00204/default/table?lang=en

Annex D: Baseline

This restriction covers substances specified in section 1.1.4 that may be present in single-use baby diapers at points of sale within EEA31. A list of articles relevant for the scope is provided in section 1.1.4.

The baseline, the "business as usual" scenario, is defined as the current and predicted future use of these substances in the articles covered without the proposed restriction and is described as follows:

- The geographical boundaries for the assessment are the countries of EEA31.

- Regarding pending legislative changes of relevance, and as already mentioned above: BaP and formaldehyde will also be the subject of a restriction proposal from Sweden and France, which suggests a concentration limit for textiles, leather fur and hide articles including single use baby diapers. The proposal is targeted at the skin sensitising properties of formaldehyde and BaP. In case certain single use baby diapers can meet the concentration limit proposed in Sweden and France's restriction they would be taken off the market in order to comply with this restriction on single use baby diapers. Some impacts for these diapers may thus occur. However, at this stage, it is difficult to predict them. The Dossier Submitter would like to underline that no overlapping is expected betwenn the skin sens in textiles restriction and the single-use baby diaper's proposal due to the fact that in the current proposal, **it is a migration limit that is proposed while in the skin sens in textile restriction, it is a concentration limit i.e a content limit**. In conclusion, the two restrictions do not have the same objective.

- Regarding other REACH restrictions that might have some overlapping with the present restriction proposal, the Dossier Submitter identified :

    - The entry 50 about restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles. In this entry, BaP, benzo(e)pyrene, benzo [a]anthracene, chrysene, benzo[b]fluorenthene, benzo[j]fluoranthene, benzo[k]fluoranthene and dibenzo[a,h]anthracene are restricted if they are present in any of rubber or plastic components of childcare articles and shall not be contained at a concentration greater than 0.5 mg/kg. If single-use baby diapers are considered as childcare articles, then, it could appear an overlapping but, because the entry 50 and the present restriction proposal do not measure the same part of the article nor propose the same analytical method, the Dossier Submitter considers that no impact may occur, indeed, as explained above in the entry 50, a content limit is proposed while in the current proposal on single-use baby diapers, a migration limit is proposed.
    - The pending restriction about formaldehyde and formaldehyde releaser. This pending restriction is about articles that are produced using formaldehyde that should not be place on the market if the concentration of formaldehyde exceeds 0.124mg/m3. In the present restriction proposal, formaldehyde is not used in the single-use baby diaper manufacturing process but is a contaminant. Moreover, the analytical method proposed in not the same and will measure, in the pending formaldehyde restriction the volume of formaldehyde emitted

while in the present restriction , the formaldehyde measured is the one contained in a urine simulant that can be extracted from a diaper, so for now the Dossier Submitter considers that no impacts may occur, however, at this stage, it is difficult to predict them.

- **Regarding the Persistent organic pollutants (POPs) Regulation:** The PCBs, PCDDs and PCDFs are chemicals that are considered as POP according to the dedicated regulation. PCBs are included in the Annex C (unintentional production) of this regulation that states "Parties must take measures to reduce the **unintentional releases** of chemicals listed under Annex C with the goal of continuing minimization and, where feasible, ultimate elimination." Nevertheless, PAHS and Formaldehyde are not considered as POP. In conclusion, the Dossier Submitter considers that some impacts for these diapers may thus occur for PCBs. However, at this stage, it is difficult to predict them.

- **Concurrently,** voluntary actions from diapers industry as well as labels exist. These schemes are part of the baseline. As explained in section 2.2. of the main report, if properly implemented and monitored, voluntary agreements can be effective and businesses can help to achieve public policy aims. Since they are not regulatory schemes, their efficiency is however difficult to measure. Nevertheless, these actions demonstrate that diaper industry is willing to improve their processes and end products and have already implemented actions for these purposes.

- As shown in Annex A, the single-use baby **diapers consumption** in the EU has been constantly growing since the 1980s and has rapidly increased during the last decade. Based on EU statistics, a part of the diaper production involving chemical substances occurs outside the EU. Based on these trends, it is assumed that the production of single-use baby diapers will keep on growing in the future or at least stay as it is now, and the part of manufacturing occurring outside EU is assumed to remain real, encouraged by low-paid workforce and less stringent workers regulation in the field of textiles in particular.

- The Dossier Submitter has insufficient information to define the actual number of children and infants that wear single-use baby diapers in Europe. As a best-informed guess, the Dossier Submitter assumes that 90% of the European children and infants wear only single-use baby diapers (EDANA, 2011). Nonetheless, some parents choose to use reusable diapers. The choice of diaper type is influenced by family members as well as by income disparity and methods of access to information (Thaman and Eichenfield, 2014). According to Eurostat, around 5.2 million babies are born in EU28 every year[35], i.e. there are currently about 16 million babies and infants between 0 and 3 years old in EU28. It is reasonably assumed that all babies and infants in Europe share similar skin properties and similar diapering time until 3 years old (except some extreme cases of late toilet-training or physiological deficiencies). Therefore, it is assumed that around 14.5 million babies and infants in Europe are exposed to the

[35] Average over 2008-2018 retrieved on June the 9th from: https://ec.europa.eu/eurostat/databrowser/view/tps00204/default/table?lang=en

chemicals targeted in this restriction proposal *via* their single-use baby diapers and thus are potentially at risk.

As a result of these above asumptions, it is assumed that adverse effects linked to the chemicals of concern in single use baby diapers, will steadily increase over time.

Annex E: Impact Assessment

E.1. Risk Management Options

Herein existing regulations on chemicals of concern in single-use baby diapers as well as actions in voluntary schemes are presented. For the presentation of other RMOs, please see section 2.2. of the main report.

E.1.1. French and European regulations

In France and in the EU, baby diapers are not covered by any specific regulations, whether for their composition, manufacture or marketing.

The General Product Safety Directive (2001/95/EC) is the only regulation to which these products are subject; the obligations it imposes on companies include the duty to market safe products for use under reasonably foreseeable conditions by consumers, to undertake a risk assessment, to have at their disposal the corresponding dossier, to provide consumers with information about risks, to ensure the traceability of products, and to have a procedure for withdrawing products from the market.

Manufacturers of such products wishing to include certain chemicals in their products claimed to also comply with the following regulations:

- Regulation (EC) No 1223/2009 on cosmetic products, in particular regarding the substances used in lotions. This regulation lays down a positive list of substances that manufacturers can use in cosmetics,
- Regulation (EC) No 1907/2006 (REACh Regulation) and Regulation (EC) No 1272/2008 (CLP Regulation). According to the REACh Regulation, baby diapers are considered as articles containing substances that may be released (e.g. lotion). To comply with REACH regulation, according to EDANA[36], manufacturers have to:
    - List all the substances that are intented to be released from the material under normal or reasonably foreseeable conditions of use,
    - List all known concentrations of candidates SVHC that are present in the material
    - List all substances on the Authorization list,
    - Declare that the material complies with all applicable requirements of the Annex XVII 'Restrictions List'.
- as well as the advice provided in the EDANA and Group'Hygiène guides.

[36] https://www.edana.org/docs/default-source/absorbent-hygiene-products/safety-and-regulatory-supply-chain-information-for-ahp-aug2018.pdf?sfvrsn=2555b491_2

Germany:

In Germany, baby diapers are considered as commodities and are regulated by the German Food and Feed Code (LFGB). There are no regulations specific to diapers. However, the BfR has issued recommendations related to the materials used for the manufacture of baby diapers, in particular regarding:

- the materials used,
- maximum concentrations for acrylic acid,
- the use of scented oils and conditioning agents,
- the use of chemicals, plastic materials and dyes.

A restriction proposal recently adopted by ECHA's committees on skin sensitisers in textiles, leather, fur and hide articles ("skin sens. in textiles"). In the scope of this restriction single-use baby diapers are covered. It is acknowledged that the restriction proposal calls for an explanation of the under process REACH Annex XVII restriction on skin sensiters in textile, leather fur and hide as ar as formaldehyde and benzo[def]chrysene are concerned. The skin sensitisers in textile, leather, fur and hide restriction aims at restricting the content of formaldehyde and benzo[def]chrysene in, among other articles, single-use baby diapers. It will be enforced through a dedicated analytical method. This restriction deals with the skin sensiting properties of formaldehyde and benzo[def]chrysene only.

E.1.2. Certification labels and standards

At EU level, since 24 October 2014, there has been an Ecolabel certification scheme for single-use absorbent hygiene products (feminine sanitary towels, tampons, nursing pads, baby diapers) (EC, 2014). This EU Ecolabel enables consumers to identify good-quality products meeting high environmental standards. It guarantees a reduced environmental impact throughout the product life cycle, minimal use of hazardous substances, and the implementation of quality and performance tests. The EU Ecolabel is the only official European environmental certification scheme that can be used in all European Union Member States.

In general, some manufacturers draw inspiration, among other things, from the EU Ecolabel's list of substances and migration limits to assess the safety of their products.

As reported in Mendoza *et al.* (2019), this Ecolabel sets rigorous life cycle ecological criteria for baby diapers, including the sourcing, processing and treatment of raw materials. For adhesives, the use of certain chemicals, such as colophony resins, formaldehyde or some types of phthalates (e.g. diisobutyl and diisononyl) is banned, unless they are present in quite low concentrations (e.g. <100-250 ppm). Holt-melt adhesives are exempt from this requirement.

Oeko-Tex standard 100 certifies that all textile articles in every stage of processing, starting from the threads to the finished fabrics and finished articles comply with the standards (including threads, buttons, zippers and linings, prints and coatings). The certification according to Oeko-tex standard by diapers manufacturers mainly aims at preventing irritation and damages to babies' skin. Standards for **Product class I (**Articles for babies and toddlers) set limits for individual chemical to be comply with[37]. Nevertheless, this label is not specific to baby diapers. It only concerns the textile part of a baby diaper.

COSMOS/Ecocert certifies that all the ingredients are from natural origin except a restrictive approved ingredients list (including preservatives) autorised in small quantity. In average, Ecocert certifies products contain 99% ingredients of natural origin[38]. For certified diapers manufacturers, the focus is on organic cultivation when selecting their ingredients, so that their skin care products are not only certified organic, but also environmentally friendly.

Ecocert Greenlife also guarantees that products do not contain artificial colours and mineral oils.

The Nordic Swan Ecolabel, the official ecolabel of the Nordic countries (Iceland, Sweden, Norway, Denmark, Finland), was created in 1978 (Nordic Ecolabel, 2011). It is a seal of approval intended to help consumers choose the most eco-friendly products, within 63 product groups (cleaning products, paper towels, textiles, etc.). Companies using the logo undertake, among other things, to limit certain chemicals that are hazardous to human health, limit greenhouse gas emissions when manufacturing their products, use renewable raw materials, organic cotton, wood from sustainably managed forests, etc.

The **FSC** (Forest Stewardship Council) **certification scheme** is an international environmental certification scheme that ensures that products are sourced from sustainably managed forests, that there is a procedure for tracking timber from the forest to the finished product, and that forestry practices limit environmental impacts on the fauna, flora, natural environment and local populations. There are three different types of FSC certification scheme depending on the composition of the FSC-certified product:

- the FSC 100% certification scheme: the product contains 100% (by weight) FSC-certified virgin fibre;
- the FSC Mix certification scheme: the product contains FSC-certified fibre, recycled fibre and controlled wood;
- the FSC Recycled certification scheme: the product contains 100% (by weight) FSC-certified recycled fibre.

FSC is an international non-profit organisation created in 1993 and based in Bonn (Germany).

PEFC Certification [39] (Programm for the Endorsement of Forest Certification). Forest certification provides a mechanism to promote the sustainable management of our forests and ensures that forest-based products reaching the marketplace have been sourced from sustainably managed forests. Forest certification is a voluntary, market-based instrument, implemented through two separate but linked processes: sustainable forest management certification and Chain of Custody certification. Sustainable forest management certification

[37] https://www.oeko-tex.com/importedmedia/downloadfiles/STANDARD_100_by_OEKO-TEX_R__-_Limit_Values_and_Individual_Substances_According_to_Appendices_4___5_en.pdf
[38] https://www.ecocert.com/en/certification-detail/natural-and-organic-cosmetics-cosmos
[39] People for the Ethical Treatment of Animals

assures that forests are managed in line with challenging environmental, social and economic requirements.

The **TCF (Totally Chlorine Free), PCF (Processed Chlorine Free)** and **SI (Sustainability Index) certification schemes** are proposed by the Chlorine Free Products Association (CFPA)[40]. They certify that a product has been manufactured and bleached without any use of chlorine.

The **OK Biobased** TUV Austria (former **Vinçotte) certification scheme** certifies products based on their concentration of renewable raw materials. It determines the percentage of renewable raw materials used to manufacture products[41]. The OK Biobased certification is tested according to Standard ASTMD 6866 (Test Methods for Determining the Biobased Content of Solid, Liquid, and Gaseous Samples Using Radiocarbon Analysis). It distinguishes carbon resulting from contemporary biomass-based inputs from those derived from fossil based inputs. Certification may apply to finished products or to packaging.

The **International Featured Standards (IFS)** comprise eight different food and non-food standards, covering the processes along the supply chain. IFS does not specify what these processes must look like but merely provides a risk-based assessment of them. More specifically, the IFS HPC[42] is a standard for auditing safe and quality products/processes of suppliers concerning the manufacturing of Household (e.g. detergents, softeners, cleaning agents, aroma sticks, etc.) and Personal Care products (e.g. tampons, tweezers, bath sponges, diapers, etc.). The development of this Standard was made possible thanks to the common work with HPC industries, retailers and certification bodies which took care of the main aspects of this Standard and at all times tried to reflect the evolving needs of the HPC industry. The IFS HPC aims to ensure that products do not represent any hazards for the safety of consumers.

BRC Certification[43] (Global Standard for Consumer Products Personal Care and Household): The BRC Global Standard for Consumer products, published in 2003 by the British Retail Consortium, aims to protect consumers and to increase the quality and safety of consumer goods through consistent quality- and risk management. The standard focuses upon the identification and management of risks and the implementation of preventive measures, with hygiene as a central element of the quality management system. The scope of Consumer Products - Personal Care and Household covers formulated and fabricated products which typically have higher hygiene requirement due to the nature and sage of the products (household cleaners, cosmetics, diapers, food wrap, etc.).

Good manufacturing practices (GMP) are the practices required in order to conform to the guidelines recommended by agencies that control the authorization and licensing of the manufacture and sale of food and beverages, cosmetics, pharmaceutical products, dietary supplements, and medical devices. GMP is a system for ensuring that products are consistently produced and controlled according to quality standards. For example, it is designed to minimize the risks involved in any pharmaceutical production that cannot be

[40] An independent not-for-profit accreditation and standard-setting organisation, located in the state of Illinois, United States
[41] http://www.tuv-at.be/green-marks/certifications/ok-biobased/
[42] https://www.ifs-certification.com/index.php/en/standards/260-ifs-hpc-en
[43] https://www.brcgsbookshop.com/bookshop/global-standard-for-consumer-products-issue-4-(personal-care-and-household)/c-24/p-257

eliminated through testing the final product[44]. Diapers manufacturers may follow those EU-GMP to ensure that their produts are safe.

Various **standards** can be used by manufacturers like ISO 9002, ISO 14001, ISO 13485.

The Dossier Submitter notices that a lot of certification labels and standards are available and nevertheless, single-use baby diapers have shown too high concentrations of substances of concern.

E.1.3. Proposed options for restriction

Please refer to section 2.3 of the main report.

E.1.4. Discarded restriction options

The following additional restriction option was also investigated: Restriction of the same chemicals of the proposed restriction but including also all the 17 congeners of the PAHs, all the congeners of the PCDD/Fs and DL-PCBs (RO2).

As explained in the restriction proposal, congeners of PAHs, PCDD/Fs and DL-PCBs have been searched and assessed when detected or quantified in single-use baby diapers.

Nevertheless all PCDD/Fs and DL-PCBs and all congeners of PAHs are not quantified or detected in each single-use baby diaper but can be found in some of them leading, when performing the QHRA, to risk ratios bigger than 0.1. (see Annex B.10). Moreover,for each group of chemicals, the congeners have similar toxicological profiles meaning that hazards for each congener is evaluated by using TEF. Finally, when laboratories perform analysis onto diapers, they search for each congener.

So even if the risk assessment performed onto the congeners showing that some risks exist for the chemical quantified or detected in single-use baby diaper, the Dossier Submitter concluded that it is not the most efficient, proportionate and enforceable way to reduce the risks linked the presence of all the congeners in single use baby diapers.

E.1.5. Other Union-wide risk management options than restriction

Please refer to section 2.2 of the main report.

[44] For example for medicinal products : https://ec.europa.eu/health/documents/eudralex/vol-4_en

E.2. Alternatives

E.2.1. Description of the use and function of the restricted substances

E.2.1.1. Good practices to keep single-use baby diapers safe

Diaper production follows high-quality control standards. The companies consulted from the diapers industry have reported the following good practices followed by the actors of the market. These practices are common shared knowledge in the supply chain for absorbent hygiene products. Among others, EDANA has developed specific guidance documents, outlining `best practices` to help their members define what is needed from suppliers to ensure safety and regulatory compliance[45.]

1. Raw materials information and quality controls
    a. Raw materials and primary packaging are traceable based on their batch identification number.
    b. Requirements from diapers manufacturers of certain pieces of information to suppliers related to the raw materials supplied (material type, intended end-use, technical specifications, specific composition including all intentionally-used ingredients and impurities, details of any known 'ingredients of the ingredient' based on sub-supplier information, including the original manufacturer, Safety Data Sheet,safety certificate, general status such as animal derived or organic, etc., compliance with REACH Regulation, Biocidal Products Regulations, alignment with the German Federal Institute for Risk Assessment (BfR) Guidelines for the Evaluation of Personal Sanitary Products from 1996[46], etc.)[47].
    c. Requirements from diapers manufacturers of annual declarations of conformity of raw materials from their suppliers (attached with associated independent chemical toxicological risk analysis).
    d. The use of any new raw material in the manufacturing process shall be approved and tested by independent institute from suppliers
    e. For raw materials selection: analysis to find the most reliable raw material, based on systematic evaluation of components.

2. Finished Products information and quality controls at production site:
    a. Quality controls: they are carried out on products weights; test of rewet (once a week); test of retention (e.g. retention capacity of products with fluff); removal of elastic in oven; microbiological monitoring (one bag per production line per month); visual monitoring of products; manual tests of welding resistance; checking of metals detectors; Some manufacturers monitor the diapers by cameras and sensors to ensure quality during the production process.

---

[45] https://www.edana.org/docs/default-source/absorbent-hygiene-products/safety-and-regulatory-supply-chain-information-for-ahp-aug2018.pdf?sfvrsn=2555b491_2
[46] https://bfr.ble.de/kse/faces/resources/INTENGLISCH.pdf
[47] https://www.edana.org/docs/default-source/absorbent-hygiene-products/safety-and-regulatory-supply-chain-information-for-ahp-aug2018.pdf?sfvrsn=2555b491_2

   b. Requirements that the finished products are compliant with REACH Regulation, Biocidal Products Regulation and the General Product Safety Directive 2001/95/EC (GPSD)
   c. Certification of finished products by competent and independent institutes (for more details please refer to Annex E.1)

3. Additional controls tests on finished products at the distribution site to assess the impact of transport and storage downstream (mainly triggered by French RMOA and restriction intention).

4. Manufacturing process quality controls:
   a. HACCP - Hazard Analysis Critical Control Point (mainly triggered by French RMOA and restriction intention).
      HACCP is Good Manufacturing Practices (GMP) (HACCP for Non Food Consumer Goods**):** HACCP, is a preventive approach to safety that identifies physical, allergenic, chemical, and biological hazards in the production processes and designs measurements to reduce any detected risks to a safe level.
   b. Controls according to standards such as IFS, BRC, GMP
   c. Quality management system (e.g. ISO 13485, Medical Devices[48], for more details please refer to Annex E.1)
   d. Regular temperature controls on production lines
   e. Regular air controls (mainly triggered by French RMOA and restriction intention)

5. Additional controls tests of transportation trucks (visual and olfative controls)

6. Routine compliance testing on raw materials, finished products (independent laboratories) and packaging based on:
   a. Regulations (REACH, SVHC, GSD, Food, etc.)
   b. Internal voluntary chemicals blacklist
   c. Requirements from certified labels (Oeko-text, Nordic Swan etc.)

7. Implementation of hygiene and safety measures on site:
   a. Air filtration and dust management systems are in place at production site to help reduce levels of airborne pollutants. Materials are covered in protective packaging materials until they are delivered to the production line to be used. Indoor air is centrally filtered to guarantee certain air quality (blockage of pesticides and reduction of other potential chemical traces such as dioxins, furans, PCB from outdoor air)[49]
   b. Forklifts are electrical to avoid evacuation gases indoor
   c. Cleaning of the production and storage areas, walls and floor washing etc..

8. Implementation of hygiene and safety measures from staff:
   a. Hands washing and disinfection for the staff who handle materials

---

[48] ISO 13485 *Medical devices* – Requirements for regulatory purposes, is an internationally agreed standard that sets out the requirements for a quality management system specific to the medical devices industry, https://www.iso.org/iso-13485-medical-devices.html

[49] Example of air filter used F7 : https://www.ksklimaservice.cz/en/classification-of-filters-filter-properties-and-typical-examples-of-use

b. Gloves worn by staff in case of products reconditionning
c. Smoking areas only allowed outside[50] (smoking residus in the air can be the source of nicotine and phenanthrene)
d. Cleaning working clothes: cleaning procedure and cleaning working clothes are not yet standardized. Some companies are implementing standardization regarding cloths to be worn during operations (uniforms, hair nets, etc.) as well as their changing and cleaning.

E.2.1.2. Identification of contamination sources and critical steps

Subsequently to the publication of the French RMOA, single-use baby diapers manufacturing and supplying companies have implemented the following actions:

- Analysis of raw materials
- Investigation of possible cross contaminations during the manufacturing process with sometimes, environmental examination inside and outside the manufacturing site
- Investigation of the potential impact of the manufacturing process in contamination of the products with a particular focus on temperatures
- Analysis of finished products at production site and at distribution site (after transport)

The results of these analyses and investigation by industry have been shared with the Dossier Submitter at French level. Based on those results, some conclusion about possible sources of contamination could be drawn. All the information collected is presented below.

E.2.1.2.1. Possible contamination sources for PAHs

The French RMOA on single-use baby diapers showed that certain levels of PAHs were found in those products likely to generate health risks. This conclusion has triggered investigation in manufacturing and supplying companies of single-use baby diapers in order to find where those PAHs may come from given that they are not used or added in the manufacturing process of the products. The Dossier Submitter has consulted those companies and the information collected is presented below.

- **Regarding raw materials and materials used in the manufacturing**

One assumption made in the French RMOA explaining the presence of PAH in diapers is related to high temperature during the manufacturing process and/or the production of raw materials themselves. PAHs may be formed unintentionally due to very high processing temperatures. As reported in Abdel-Shafy and Mansour (2016), pyrogenic PAHs are formed whenever organic substances are exposed to high temperatures under low oxygen or no oxygen conditions. The destructive distillation of coal into coke and coal tar, or the thermal cracking of petroleum residuals into lighter hydrocarbons are pyrolytic processes that occur

[50] as a follow-up of the French RMOA and restriction intention, some diapers manufacturers indicated that they have banned smoking areas inside their manufacturing building. The Dossier Submitter does not know whether this is the case for all manufacturers.

intentionally. Meanwhile, other unintentionally processes occur during the incomplete combustion of motor fuels in cars and trucks, the incomplete combustion of wood in forest fires and fireplaces, and the incomplete combustion of fuel oils in heating systems. The temperatures at which the pyrogenic processes occur are ranging from about 350°C to more than 1200°C.

According to the diapers industry, PAHs are not intentionally added to raw materials and materials, such as SAP, elastic films, elastic thread, adhesive fasteners, frontal tape, (non woven) distribution layer.

However, some oils and resins from glues as well as construction and elastic glues or elastic components used during the process have been reported to contain PAHs traces. Several companies analysed glues and noted PAHs traces in those materials. For instance one company consulted reported that in 2017, naphthalene was detected above background noise in diapers backsheet. In 2018, the adhesive was reformulated, which allowed an important decrease of naphthalene in diapers backsheet (< x1000). The usual level of naphthalene has been stabilized between 0-10 µg/kg for the last two years.

In principle, if raw materials are manufactured themselves with temperatures above 350°C, they may contain some levels of PAHs. However, diapers industry reports that:

- The manufacturing of adhesives is carried out at high temperatures but which do not exceed 200°C, under atmospheric pressure and do not reach pre-combustion level.
- During the public consultation, some industry claimed that if a too hot temperature is used while using hotmelt adhesives, this will result in PAHs formation but instead in a reduction in performance of the adhesive. Another industry claimed that glues are heated to 90-170°C, meaning that no PAHs can be generated.
- The manufacturing of SAP does not operate above 200°C.
- The manufacturing of elastic film does not operate above 210°C, is performed under atmospheric pressure and does not reach pre-combustion level and should not generate PAHs.
- The manufacturing of non woven materials does not operate above 260°C. Moreover, fibers are technically treated without chemical addition but with a "dry" process. For more details about production of non wovens, please refer to Annex A.1.
- Fluff is prepared based on mechanical process which does not involve heating.

Some wetness indicators are reported as containing PAHs: although no PAH is detected in his finished products, one manufacturer indicated that he is currently looking for an alternative for his wetness indicator that contains PAH.

- **Regarding the manufacturing process:**

The companies consulted have also investigated the likelihood of having very high temperatures (above 350°C) during their manufacturing process through thorough audits, diagnosis and further control points on the production line since 2019. As presented in Annex A.2, during the assembling of the materials to make the diaper, some gluing and thermowelding operations occur. During these operations, some heating is required and temperatures increase. The information collected by the Dossier Submitter and the outcome of those investigations are presented below.

- Too hot pieces may lead to combustion and to PAHs contamination during materials processing in the manufacturing machine or during cores forming or gluing operations (nozzles cleaning) even though several manufacturers stated that combustion is not part of normal processing.
- Bad adjustement of glue tank and temperatures above 200°C may lead to uncontrolled combustion and PAHs contamination during gluing operations. Under good practice and normal manufacturing conditions, average temperature of glue tanks is 140°C (according to the information collected from manufacturers). To this respect, one manufacturing company has reported tests on glues (based on voluntary overheating of glues) and did not observe PAH generation from it. Glue operations are controlled automatically as well as by a control operator. On suppliers websites, application temperatures recommended for glues provided to baby diaper manufacturers are between 130-200°C[51].
- During thermo-welding operations, it seems to be unlikely that temperatures exceed 350°C since thermo-welding is done below 180°C and during a very short period of time (between 115°C and 180°C according to the information collected from manufacturers). Thermo-welding operations are controlled automatically as well as by an control operator.
- During materials processing in the manufacturing machine and during folding/compressing: the diapers industry state that those steps do not generate PAHs and are compliant to REACH and German regulations (0.2 mg/kg)
- During ultrasound embossment it seems to be unlikely that temperatures exceed 350°C since normally this step is carried out below 50°C.

Manufacturers of diapers indicate the following steps in the processing when heating or high temperatures are involved, according to the type of diapers.

As indicated by industry, temperatures seen in diaper production (Table 75) are lower than the temperatures indicated above for formation of PAHs making this as an unlikely source for potentially detected PAHs. Temperatures seem to be not high enough to create "incomplete combustion" and generate "pyrogenic PAH". Even the highest temperature seen on a diaper production line does not reach the pre-combustion levels.

---

[51] http://www.hotmeltpsaadhesive.com/quality-10687081-baby-diaper-multi-purpose-hot-melt-glue-raw-material-manufacturer
http://www.hotmeltpsaadhesive.com/sale-10726639-baby-diaper-psa-hot-melt-glue-adhesive-positioning-wing-dot-hot-melt-material.html
http://www.fjxingyuan.com/structure-hot-melt-glue-for-baby-diaper_p47.html
https://www.qzniso.com/hot-melt-glue-for-making-baby-diaper_p1074.html

Table 75 : Temperatures in diaper production

Diaper technologies		
Systems put in temperature	**Temperature range**	**Materials subject to temperature**
Adhesive application system	90 – 170°C	adhesives, nonwovens, films, elastics
Ultrasonic welding	40 – 50°C	nonwovens, films, adhesives
Grinding process of cellulose pulp	30 – 45°C	cellulose pulp

- **Regarding cleaning:**

Some of the companies consulted have also investigated the detergents and cleaning products used on the production line and in the production site as a potential source of hazardous chemicals such as PAHs.

One company identified that process aids used to clean equipment may be the source of contamination and has replaced their cleaning products to minimize the risks.

However, the companies consulted report that cleaning products used on production line are compliant with REACH SVHC and do not contain PAHs. Some manufacturers report also that cleaning sprays used are all compliant with food Regulation and Food standards (such as silicone sprays). They consider that they cannot contain PAHs or any hazardous chemicals targeted in this restriction.

- **Regarding environmental contamination:**

PAHs are naturally present in the environment, through events such as volcano explosion, forest fires, erosion, bacteria degradation of foliage (Abdel-Shafy and Mansour, 2016). They are ubiquitous substances. Finished products during the manufacturing process may be contaminated by production environment. Raw materials may have been also contaminated by environment before being supplied to the manufacturers.

- **Regarding transport and storage:**

No information was provided to the Dossier Submitter suggesting that transport or storage can be (or not) a source of contamination of single use baby diapers by PAHs.

- **Conclusion:**

Therefore, according to the companies consulted, given that manufacturing process temperatures should not exceed 180°C-200°C and are strictly controlled, it seems unlikely that PAHs come from over-heating on the production line. Nevertheless, even though processing temperatures usually do not exceed 180°C – 200°C under normal conditions of manufacturing, it cannot be excluded that very high temperatures and over-heating may occur at certain critical points of the manufacturing process (e.g. during transitional paces of a heating press while starting and maintening temperatures or bad adjustments of glue tanks). Unvoluntary incident cannot be excluded (even if some industry claimed that instead of PAHs formation, overheating of adhesives will result in a reduction of performance) . As a consequence, the Dossier Submitter is of the view that excessive temperatures cannot be discarded as one of the possible causes of contamination of the products during the manufacturing process and should be further controlled. The other possible contamination source is assumed to be raw materials since some of them are reported to contain some levels of PAH due to their own manufacturing (e.g. wetness indicator and glues) or due to combustion residues (cellulose). No information was provided regarding transport or storage. Cleaning products may be a source of contamination.

Table 76 : Summary of the possible PAH contamination sources

Possible sources of PAH contamination	**Quick description of the possible source identified**	**Likelihood of the possible contamination source according to the information available to the Dossier Submitter**
Raw Material and their manufacture • glues and elastics • wetness indicator	If temperature is too high (>200°), PAH may be formed	++
Manufacturing process of a diaper	Bad adjustment of glue tank and if T>200°C Thermowrlding	+
Cleaning process	Detergents and cleaning products may be a source	-
Environmental contamination	Ubiquitous substances	+
Transport and storage	No information available	

E.2.1.2.2. Possible contamination sources for PCDD/Fs

The French RMOA on single-use baby diapers showed that certain levels of PCDD/Fs were found in those products likely to generate risks for babies' health. This conclusion has also triggered investigation in manufacturing and supplying companies of single-use baby diapers in order to find where those chemicals may come from, given that they are not used or added in the manufacturing process of the products. The Dossier Submitter has consulted those companies and the information collected is presented below.

- **Regarding raw materials and materials used in the manufacturing:**

According to the diapers industry, PCDD/Fs are not intentionally added to raw materials and materials such as SAP, elastic films, fluff pulp, elastic thread, adhesive fasteners, frontal tape, (non woven) distribution layer. Moreover, one company analysed printing ink of external sheet used in the assembling of single-use baby pants only and reported no chlorine content.

However according to one company a green pigment used in aesthetic printing may be the source of OCDF and OCDD in external sheet and external film: in 2018 the green pigment was reformulated. In general more than 10,000 modifications related to improved raw materials have been implemented. These changes now allow for non detectable levels of PCDD/Fs. The Dossier Submitter has no knowledge about whether the other manufacturers also made the same change.

Another company reported detectable levels of PCDD/Fs in ECF cellulose fluff, non-wovens and laminated external sheet.

Additionnally, it is assumed that raw materials may contain some traces of PCDD/Fs when high temperatures are involved in their own manufacturing above 200°C.

In the call for evidence, one company stated that PCDDs may come from glues but without any more specifications.

There are two main mechanisms proposed regarding the formation of PCDDs that occur during the incineration (combustion) of municipal solid waste: 1) pyrosynthesis and 2) de novo synthesis. The two mechanisms can occur simultaneously and/or independently and result in the formation of substances with unique fingerprints (Altarawneh *et al*., 2007).

- Pyrosynthesis involves the formation of PCDDss by polycondensation of precursors (e g. polychlorophenols, polychlorobenzenes, PCBs). This mechanism occurs in the gas phase at temperatures between 300°C and 600°C. It is generally believed that the surface catalyzed formation of these species is a major contributor to PCDD/Fs in the incineration processes. The products thus formed have a PCDF/PCDD ratio well below 1 (Everaert and Boeyens 2002).
- The de novo synthesis involves the presence of carbon in a solid phase along with oxygen. This mechanism occurs at temperatures between 200°C and 400°C. The PCDF/PCDD ratio is usually higher than 1 (Everaert and Boeyens 2002).

As a consequence, in principle, if raw materials are manufactured themselves with temperatures above 200°C, they may contain some levels of PCDD/Fs. To this respect, as explained above, diapers industry reports that:

- The manufacturing of adhesives is carried out at high temperatures but does not exceed 200°C, under atmospheric pressure and do not reach pre-combustion level.
- The manufacturing of SAP does not operate above 200°C.
- The manufacturing of elastic film does not operate above 210°C which could then be a cause of dioxins or furans.
- The manufacturing of non woven materials does not operate above 260°C: it could then be a cause of contamination of furans and dioxins.

Moreover, it is reported that during the manufacturing of fluff pulp, PCDD/Fs may appear with the presence of chlorine and concurrently temperatures above 300°C (Dossier Submitter Personal Communication). However, diapers industry states that no chlorine is added to the material when manufactured.

Finally, one company stated that wood used in diapers manufacturing can be inevitably in contact with particules charged with PCDDs coming from nearby combustion processes. As a result, the environmental particles generated by wood combustion can lead to the presence of these undesired contaminants in finished diaper products.

- **Regarding manufacturing process:**

Manufacturers of diapers report that PCDD/Fs can be detected in finished diapers (non wovens elements, external sheet, laminates, cellulose fluff) but their presence can not be explained by the manufacturing process itself which involves temperatures lower than 200°C (see above, PAHs section).

According to the diapers industry, PCDD/Fs are mainly linked to incineration processes (and main affect fluff pulp when high temperatures). However, under good practice and normal manufacturing conditions, manufacturers of diapers report that there is only heating operations and no combustion. As explained above, temperatures should not exceed 170°C.

PCDD/Fs are possibly assumed to come from bleaching but given that the PCDD/Fs detected (specific congeners 1,2,3,6,7,8 HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD, 1,2,3,6,7,8 HxCDF, 2,3,4,6,7,8 HxCDF, 1,2,3,4,6,7,8 HpCDF, 1,2,3,4,7,8,9 HpCDF, and OCDF) are highly chlorinated, some manufacturers state that it is more likely that they are produced from combustion than bleaching. To this respect, literature reports (De Vito et Schecter,2002) that, after analysis of four baby diapers, including three single-use baby diapers and one cotton diaper, screened for 17 PCDDs and PCDFs, only five of the 17 PCDDs were detected in the diapers (LD = 0.1 - 0.2 ppt). There were similar concentrations in the single-use baby and re-usable diapers. Total PCDD/F concentrations in the diapers ranged from 1.8 to 3.7 pg/g, i.e. from 0.0042 pg $_{TEQ}$/g (cotton diaper) to 0.023 pg $_{TEQ}$/g (single-use baby diaper). The study concluded that dioxins are presents in fluff pulp based and cotton diapers suggesting that dioxins may be presents due to background contamination and not from the pulp manufacturing process.

Still, bleaching TCF process is reported to allow for reduction of highly chlorinated dioxins (but is reported to still contain traces of PCB). The Dossier Submitter would like, to underline that "*ECF bleaching is capable of reducing 2,3,7,8-TCDD and 2,3,7,8-TCDF to undetectable levels. However, the complete elimination of dioxins in ECF-bleached effluents is a question of kappa*[52] *number and purity of ClO_2. With a high kappa number and impure ClO_2 (i.e. high concentration of Cl_2) the probability of forming dioxins increases. The production of ECF pulp is common practice in pulp mills in Europe. All mills combine the available stages and processes in order to optimise the bleaching process producing the best pulp quality and yield (depends on species and final application). However, the overall impact of the bleaching process can be lessened by reducing energy and water consumption and the impact of the liquid effluent." JRC, 2015)*

- **Regarding cleaning:**

[52] kappa number gives an indication of the residual content of lignine for a pulp paper.

One company identified that process aids used to clean equipment may be the source of contamination and has replaced their cleaning products to minimize the risks.

The companies consulted report that cleaning products used on production line are compliant with REACH SVHC and do not contain PCDD/Fs. Some manufacturers report also that cleaning sprays used are all compliant with food Regulation and Food standards (such as silicone sprays). They consider that they cannot contain PCDD/Fs of any hazardous chemicals targeted in this restriction.

- **Regarding environmental contamination:**

PCDD/Fs are ubiquitous subtances that are naturally present in very small amounts in the environment . As the manufacturing process of baby diapers is not carried out in clean rooms, according to single-use baby diapers industry they may come from fresh contaminated air during internal transport for production or all steps of the production itself (loading, processing, pulp defibering, cores forming, gluing operations, embossment, cutting, folding/compressing, ultrasound embossment. Raw materials may have been also contaminated by environment before being supplied to the manufacturers[53].

- **Regarding transport and storage:**

No information was provided to the Dossier Submitter suggesting that transport or storage can be (or not) a source of contamination of single use baby diapers by PCDD/Fs.

- **Conclusion:**

Therefore, according to the companies consulted, given that manufacturing process temperatures should not exceed 180°C-200°C and are strictly controlled, it seems unlikely that PCDD/Fs may come from over-heating on the production line. Nevertheless, even though processing temperatures usually do not exceed 180°C – 200°C under normal conditions of manufacturing, it cannot be excluded that very high temperatures and over-heating may occur at certain critical points of the manufacturing process (e.g. during transitional paces of a heating press while starting and maintening temperatures). Unvolontary incident can not be excluded. As a consequence, the Dossier Submitter is of the view that excessive temperatures cannot be discarded as one of the possible causes of contamination of the products during the manufacturing process and should be further controlled. The other possible contamination source is assumed to be raw materials since some of them are produced with temperatures equal or above 200°C (SAP, non-wovens and elastic films) and some may contain residues from combustion (cellulose). Some pigments have been suspected to be the source of dioxins such as a green pigment. Raw materials should be better selected and controlled. Air contamination may also be a possible cause since PCDD/Fs since they are natural contaminants. Further filtration and controls should be carried out following the best pratices. No information was provided regarding transport or storage. Cleaning products appear not to be, according to companies consulted, a source of contamination but the Dossier Submitter does not have sufficient evidence to draw a conclusion on this possible source**.**

Table 77 : Summary of the possible PCDD/Fs contamination sources

Possible sources of PCDD/Fs contamination	**Quick description of the possible source identified**	**Likelihood of the possible contamination source according to the information available to the Dossier Submitter**
Raw Material and their manufacture	• Cellulose fluff • Pigments • Maybe glue • Non woven • High temperature (if >200°)	++
Manufacturing process of a diaper	Bleaching process	++
Cleaning process	Detergents and cleaning products may be a source	-
Environmental contamination	Ubiquitous substances	+
Transport and storage	No information available	

E.2.1.2.3. Possible contamination sources for DL-PCBs

The French RMOA on single-use baby diapers showed that certain levels of DL-PCBs were found in those products likely to generate risks for babies health. This conclusion has also triggered investigation in manufacturing and supplying companies of single-use baby diapers in order to find where those chemicals may come from given that they are not used or added in the manufacturing process of the products. The Dossier Submitter has consulted those companies and the information collected is presented below.

- **Regarding raw materials and materials used in the manufacturing:**

According to the diapers industry, DL-PCBs may be detected in cellulose fluff, non-wovens and laminated external sheet.

Diapers industry also specifies that DL-PCBs are not intentionally added to raw materials and materials such as SAP, elastic films, elastic thread, adhesive fasteners, frontal tape, (non woven) distribution layer.

Similarly to PCDD/Fs, it is assumed that raw materials may contain some traces of DL-PCBs when high temperatures are involved in their own manufacturing (above 200°C). Likewise, according to diapers industry information, elastic film (manufactured below 210°C) and non woven materials (manufactured below 260°C) may be the cause of DL-PCB. However, here again, during the manufacturing of fluff pulp, diapers industry states that no chlorine is added to the material when manufactured and no heating is involved.

- **Regarding manufacturing process:**

As indiated by industry, PCBs have no function and are not intentionally added. Use of PCBs is banned in EU and US since 1985 and 1979 respectively.

It may be assumed that DL-PCBs may come from high temperatures during the manufacturing process: however, again, according to the information collected from manufacturers of diapers, under good practice and normal manufacturing conditions, there is only heating operations and no combustion. As explained above, temperatures should not exceed 170°C. (Table 75)

It may be also assumed that DL-PCBs may come from chlorine process: indeed, it has been reported by diapers industry that bleaching ECF process seems to generate less PCBs than TCF process although leading to traces of highly chlorinated dioxins.

- **Regarding environmental contamination:**

DL-PCBs are ubiquitous subtances. PCBs have been detected in virtually all environmental compartments (indoor and outdoor, surface and ground water, soil and food). Most likely any detected PCB in diapers stem from the environment. The types of PCBs' congeners pointed out as problematic in the ANSES report on diapers (105, 126 and 118) are all typically generated in incineration (Rodenburg *et al.,* 2015). Since the manufacturing process of baby diapers is not carried out in clean rooms,(DL-)PCBs in finished products may come from fresh contaminated air during internal transport for production or during production (loading, processing, pulp defibering, cores forming, gluing operations, embossment, cutting) may be the source. Raw materials may have been also contaminated by environment before being supplied to the manfacturers.

- **Regarding transport and storage:**

No information was provided to the Dossier Submitter suggesting that transport or storage can be (or not) a source of contamination of single use baby diapers by DL-PCBs.

- **Conclusion:**

Therefore, again, according to the companies consulted, given that manufacturing process temperatures should not exceed 180°C-200°C and are strictly controlled, it seems unlikely that DL-PCB may come from over-heating on the production line. Nevertheless, even though processing temperatures usually do not exceed 180°C – 200°C under normal conditions of manufacturing, it cannot be excluded that very high temperatures and over-heating may occur at certain critical points of the manufacturing process (e.g. during transitional paces of a heating press while starting and maintening temperatures). Unvolontary incident can not be excluded. As a consequence, the Dossier Submitter is of the view that excessive temperatures cannot be discarded as one of the possible causes of contamination of the products during the manufacturing process and should be further controlled. Like for PCDD/Fs, the other possible contamination source is assumed to be raw materials since some of them are produced with temperatures equal or above 200°C (SAP, non-wovens and elastic films) and some may contain residus from combustion (cellulose). Air contamination may also be a possible cause since PCBs are natural contaminants. Further filtration and controls should be carried out following the best pratices. No information was provided regarding transport or storage. Cleaning products appear to not be, according to companies consulted, a source of contamination but the Dossier Submitter does not have sufficient evidence to draw a conclusion on this possible source**.**

Table 78 : Summary of the possible DL-PCBs contamination sources

Possible sources of DL PCBs contamination	**Quick description of the possible source identified**	**Likelihood of the possible contamination source according to the information available to the Dossier Submitter**
Raw Material and their manufacture	• Cellulose fluff • Non woven • High temperature (if >200°)	+
Manufacturing process of a diaper	Bleaching process High temperature (if >200°)	+
Cleaning process	Detergents and cleaning products may be a source	-
Environmental contamination	Ubiquitous substances	+
Transport and storage	No information available	

E.2.1.2.4. Possible contamination sources for formaldehyde

The French RMOA on single-use baby diapers showed that certain levels of formaldehyde were found in those products likely to generate risks for babies' health. This conclusion has also triggered investigation in manufacturing and supplying companies of single-use baby diapers in order to find where formaldehyde may come from given that it is not used or added in the manufacturing process of the products. The Dossier Submitter has consulted those companies and the information collected is presented below.

- **Regarding raw materials and materials used in the manufacturing:**

According to the diapers industry, formaldehyde and formaldehyde releasers are not intentionally added to raw materials and materials such as SAP, elastic films, elastic thread, adhesive fasteners, frontal tape, (non woven) distribution layer.

However, one company reported detected formaldehyde in the cellulose fluff used to produce single-use baby diapers.

Formaldehyde is reported to be often used in water-based glues to prevent microbiological contamination. From the experts consulted during the preparation of the restriction proposal, it appears that formaldehyde is unlikely to be released from glues and adhesives used during the gluing steps because these are hot-melt adhesives, not water-based, and consisting of thermoplastic adhesives (which do not contain formaldehyde).

Concerning the (non woven) distribution layer, it has been reported that water-based fibers bonding systems may be employed, as presented in Annex A.1. In the formulation of those systems, a certain amount of additives is added and some of them may be formaldehyde releasers.

- **Regarding manufacturing process:**

Industry reports that formaldehyde or formaldehyde releasers have no functional role in single-use baby diapers and are not added intentionally.

- **Regarding environmental contamination:**

Formaldehyde is an ubiquitous subtance that is naturally occurring organic compound (ANSES, 2017b). As the manufacturing process of single-usebaby diapers is not carried out in clean rooms, formaldehyde in finished products may come from contaminated ambient air. Finished products during the manufacturing process may be contaminated by production environment. Raw materials may have been also contaminated by environment before being supplied to the manufacturers.

- **Regarding transport and storage:**

No information was provided to the Dossier Submitter suggesting that transport or storage can be (or not) a source of contamination of single use baby diapers by formaldehyde.

- **Conclusion:**

Therefore, the Dossier Submitter was not able to define where the contamination from formaldehyde comes from.

Table 79 : Summary of the possible formaldehyde contamination sources

Possible sources of formaldehyde contamination	**Quick description of the possible source identified**	**Likelihood of the possible contamination source according to the information available to the Dossier Submitter**
Raw Material and their manufacture	• Cellulose fluff • Water based glues	+\-
Manufacturing process of a diaper	Formaldehyde not involded	
Cleaning process	No information available	

Environmental contamination	Ubiquitous substances	+
Transport and storage	No information available	

E.2.1.2.5. Conclusion about possible sources of contamination and recommendations

Based on the analyses and investigation actions carried out by industry in 2019, some conclusion about possible sources of contamination can be drawn:

- In general, the nature of the contamination (nature of the contaminants found) is similar regardless of the product.
- The Dossier Submitter was not able to define where the contamination from formaldehyde comes from.
- Regarding raw materials, cellulose, non woven and glue are reported to likely be the main sources of contaminants.
- The contamination due to the manufacturing process or environment is not zero but much lower than the one due to the initial contamination of the raw materials.
- In general, based on their own HACCP and chemical analyses of raw materials and manufacturing process, several companies report a significant correlation between the levels of chemical traces detected or quantified in raw materials and the levels of chemical traces detected or quantified in finished products: according to these companies, this correlation allows discarding the risk of physical or chemical contamination during the manufacturing process.
- Moreover, given the maximum temperatures reached on the production lines, all of the companies discard any formation of PAH during the process.
- Regarding transport and storage, no information has been made available to the Dossier Submitter,
- With regard to PCDD/Fs, the nature of the substances found suggests that they rather come from heating processes released into the environment than bleaching treatments,
- Wetness indicator have been reported to be possible source of PAHs,
- Some pigments have been reported to be possible sources of PCDDs.
- Finally, although most ingredients and raw materials in diapers are synthetic and derived from crude oil (which contains PAH according to the article from Abdel Shafy *et al.*2016), the process to manufacture these ingredients go through various distillation/ refining/ hydrogenation polymerization / purification processes that reduce the concentration of PAH to undetectable levels in synthetic urine.

As a conclusion, based on the information presented above, the Dossier Submitter is of the view that:

- Raw materials are one of the possible source of contamination given that:
    - some of them are produced at temperatures above temperatures considered as "safe" (SAP, non-wovens and elastic films in particular)
    - some raw materials may contain residues from combustion (cellulose)
    - some others are reported to contain contaminants and hazardous chemicals (glues, pigments and wetness indicator).
    - cellulose pulp manufacturers may adopt TCF bleaching processes to limit production of chlorinated PCDD/Fs. The Dossier Submitter does not have any study available to compare the levels of chlorinated products in pulp and single use baby diapers to be sure that the searched levels of chlorinated products are similar. It is therefore necessary to undertake assays on cellulose derivatives. Eventually **the Dossier Submitter would like to underline that the choice of a bleaching process (ECF versus TCF) may not be as clear as it seems to reduce the presence of the chlorinated chemicals (PCDD/Fs and DL-PCBs).**
    In brief, in order to comply with the migration limits proposed in this restriction proposal in the finished products (section B.10.2.2), the raw materials used to manufacture single-use baby diapers should be better selected and further tested and controlled. The development of stricter specifications for raw materials should be also implemented. The raw materials which do not have any technical function, are not necessary to manufacture a single-use baby diaper and are possible sources of contamination, may be removed and no longer be used.

- **Manufacturing process** is another possible source of products contamination. As the substances subject to this restriction are not intentionally used as "ingredients" for diapers during the manufacturing process, reformulations using alternative substances is not a viable option for diapers manufacturers. However, different technical measures could be implemented to further reduce contamination of products:
    - Even though processing temperatures usually should not exceed 180°C – 200°C under normal conditions of manufacturing, and despite suppliers recommend similar temperatures applications for their raw materials (e.g. glues), it cannot be excluded that higher temperatures and over-heating may occur at certain critical points of the manufacturing process (e.g. during transitional paces of a heating press while starting and maintaining temperatures). Involuntary incidents can not be excluded. **Excessive temperatures cannot be discarded as one of the possible causes of contamination of the products during the manufacturing process and should be further controlled.**
    - Regarding glues as potential sources of contamination during the process, as mentioned in Annex A.1, some diapers manufacturers now produce so-called 'glueless' baby diapers based on alternative bonding technologies. This innovation could be of interest in terms of human health protection and it would worth investigating further. However, to the Dossier Submitter's knowledge,

these diapers are procuded by only one company in Europe that did not provide any information during the preparation of this restriction proposal in spite of Dossier Submitter's requests. The Dossier Submitter is therefore not in a position to recommend this technology as a possible solution to glues contamination. For more details about glueless diapers, please see Annex E.2.2.2.2.

  - Additionally to further reducing and controlling temperatures, diaper manufacturers should **make all possible efforts to improve in general their manufacturing processes** to minimize presence of chemical substances (dioxins, furans, DL-PCBs, formaldehyde, PAHs) in products.

- Air contamination may also be a possible cause since the contaminants targeted in this restriction proposal are natural contaminants. **Further air filtration, air controls and higher frequency of dust clean-up should be carried out following the best practices.**

- No conclusion can be made on the impact of transport and storage as a possible source of contamination.

All these recommendations are further developed in Annex E.2.2 and E.2.3.

E.2.2. Identification of potential preventive actions and alternative materials and techniques to remove contaminants

Based on the diagnosis performed by single-use baby diapers industry in 2019 on the contamination sources suspected as well as on experts' consulted and literature, the following preventive actions, alternative materials and techniques have been identified and recommended as potential solutions to remove contaminants. Following these recommendations this restriction aims to encourage manufacturers to further find out how the substances are formed in the products and to take relevant measures to reduce their presence. As shown in the ANSES report it is apparently possible to manufacture diapers with lower levels of the substances suggested to be restricted. This shows that there are manufacturers on the market having a good control over the materials and processes they use and that are able to comply already with very low migration limits proposed.

E.2.2.1. Substitution and technical solutions related to raw materials

Based on the information collected from industry and from literature, some critical raw materials such as cellulose (pulp), glues, wetness indicators and pigments have been reported to likely be the main sources of contaminants. Substitution of these materials with safer materials may be one of the solutions to reduce or remove contaminants.

E.2.2.1.1. Moving to totally chlorine-free (TCF) pulp

As explained in Annex A.2, TCF (totally chlorine free) method is a bleaching process which uses hydrogen peroxide, oxygen or ozone (Counts *et al*., 2017 ; JRC, 2015). Literature reports some comparative assessments between ECF and TCF bleaching processes.

- The result of these studies showed that the advantages of TCF bleaching are:
  - Lower brightness reversion,
  - Lower OX content and DCM[54] content in pulp,
  - Lower water consumption,
  - Lower color and AOX[55] content in the bleach plant discharge,
  - Potential to fully close the bleach plant and reduce the effluent discharge to zero,
  - Lower investment and operating costs.
- and that the drawback of TCF bleaching are :
  - lower tear index for some pulps,
  - technical difficulties regarding the enrichment of non-process elements in the water circuits and undesired scaling, especially of oxalates, remains an unsolved challenge for further closure of the bleach plant effluents.

For other pulp properties there were only minor differences between ECF- and TCF-bleached pulps (Wennerström *et al.*). As stated in JRC (2015): "*A comparison of toxic responses of bleach plant and whole mill effluents from mills using different schemes for non-chlorine bleaching, i.e. modern ECF versus TCF bleaching, shows that neither technique consistently produces effluents with a lower toxic potency . No clear difference in the effect pattern and effect intensity between effluents from mills using modern ECF (chlorate reduced) and TCF bleaching has been detected*. " as well as "*The special focus on the question of whether modern ECF or TCF bleaching is better from an environmental perspective seems to be too narrow*".

As reported by several diapers manufacturers, switching to TCF is theoretically and technically feasible but TCF pulp is only used in limited market currently and is not highly available (for more details about availability, see main report, section 2.4.1.1.1 as well as Annex E.2.3.1.1.). On the contrary, in JRC, 2015, it seems that in Europe, most of the pulp mills have switched to TCF pulp. Nevertheless, it is not specified in this document that this statement is accurate for all the pulp mills including the pulp mills used for fluff pulp in single-use baby diapers.

In the single-use baby diapers market, 5% of the manufacturers have already chosen TCF cellulose over ECF cellulose for a long time (Counts *et al.,* 2017). From the publication of the ANSES' 2019 expertise and the French RMOA, several French and European companies have informed the Dossier Submitter that they have switched from ECF cellulose to TCF cellulose already or are about to do it. Most of them however are making this change more by precaution than based on proven chemicals-contamination evidence.

[54] DCM: Dichloromethane OX: Oxygene

[55] Adsorbable Organic Halogen

Some other diapers manufacturers are more skeptical about the benefit of moving from ECF to TCF cellulose to reduce contaminants in the cellulose and thus the final products: as presented in Annex E.2.1.2.2. above, some report that bleaching TCF process allows for reduction of highly chlorinated dioxins in pulp but still contain traces of PCB while in JRC,2015 it is stated that ECF bleaching is capable of reducing 2,3,7,8-TCDD and 2,3,7,8-TCDF to undetectable levels.*"However, the complete elimination of dioxins in ECF-bleached effluents is a question of kappa number and purity of ClO_2. With a high kappa number and impure ClO_2 (i.e. high concentration of Cl_2) the probability of forming dioxins increases. The production of ECF pulp is common practice in pulp mills in Europe. All mills combine the available stages and processes in order to optimise the bleaching process producing the best pulp quality and yield (depends on species and final application). However, the overall impact of the bleaching process can be lessened by reducing energy and water consumption and the impact of the liquid effluent." JRC, 2015)"* On the contrary, bleaching ECF process seems to less generate PCBs than TCF but pulp contains traces of highly chlorinated dioxins.

Eventually, according to these companies, the move to TCF pulp, is costly (for more details about costs see main report, section 2.4.1.1.1). Additionally, some companies report that TCF process is more energy- and raw materials-consuming (but no details have been provided). From an environmental point of view (waste waters, etc.), they consider that performance of TCF process over ECF is not proven (but again no details have been provided by the companies consulted, nevertheless, according to JRC, 2015, "*The special focus on the question of whether modern ECF or TCF bleaching is better from an environmental perspective seems to be too narrow".*

More information on availability, technical and economic feasibility is provided in Annex E.2.3.1.5 below and in the main report, section 2.4.1.1.1. Based on the information at hand, **it is difficult for the Dossier Submitter to have a clear-cut conclusion about the better capability of TCF pulp to address the health concerns targeted in this restriction proposal over ECF pulp**. Within all the possible solutions to reduce contamination in baby diapers identified, moving to TCF pulp could be an option but given the uncertainties associated to its benefits to human health and its technical and economic feasibility, **the Dossier Submitter can not strongly recommend this substitution without reservation**. Nevertheless, if industry would decide to switch to TCF pulp, the information presented in this restriction proposal would be useful to anticipate the possible impacts on industry and consumers.

E.2.2.1.2. Substitution of types of glues used

As presented in Annex A.1, glues used to assemble the different parts of a single-use baby diapers are generally hot melt adhesives, i.e thermoplastic adhesives in solid form, designed to be melted by a heating element to provide it with adhesion properties. The main resins used in hot-melt adhesives are ethylene-vinyl acetate copolymer, polyamides, polyolefins (mainly polyethylene) and polyesters. Glues can also be copolymer rubber (e.g. SBR, EPDM) and starch.

Several diapers manufacturers consulted reported that glues may contain PAHs traces (especially resins from glues as well as construction and elastic glues; see Annex E.2.1.2.1). Unfortunately the exact composition of any of these glues could not be obtained from suppliers due to confidentiality and business secret.

According to the experts and chemists consulted by the Dossier Submitter, glues are not expected to be the source of contamination *per se*, but they could be when heated during the manufacturing process if temperatures exceed 200°C.

Based on those findings, substitution of glues used to manufacture single-use baby diapers is not considered as a solution to reduce contamination of finished products and may not be necessary.

E.2.2.1.3. Removal or substitution of wetness indicator

As explained in Annex A.1, a wetness indicator is a common feature in many single-use baby diapers and toilet training pants. It is a feature that reacts to exposure of liquid as a way to discourage the wearer to urinate in the training pants, or as an indicator for parents that a diaper needs changing. One diaper manufacturer indicated that wetness indicator can contain PAH even though wetness indicator is not in contact with the baby skin and no PAH has been detected in their finished products. For this manufacturer, the detection of PAH in the wetness indicator used has lead to the remplacement with a non-detectable PAH-level wetness indicator. The Dossier Submitter has not further information about this substitute. Moreover, the Dossier Submitter does not have the percentage of single use baby diapers with a wetness indicator that are sold on the European market.

Regardless of substitution cost due to the replacement of wetness indicators, the acceptability of using such a material in the finished products may be questioned given that wetness indicators do not have essential technical function to manufacture a single-use baby diaper. They are only used for parents' conveniency reasons and may be considered as marketing assets only. **If they may be one of possible sources of contamination of finished products, one option to reduce contamination could be that they are no longer used in single-use baby diapers. Having single-use baby diapers without wetness indicators available on the market would not affect their basic function as absorbent of baby urine and faeces.**

E.2.2.1.4. Removal or substitution of pigments

As reported in Annex A.1, according to one company, a green pigment used in aesthetic printing may be the source of OCDF and OCDD in external sheet and external film. This company informed the Dossier Submitter that reformulations of the green pigment allowed to reduce levels of PCDD/Fs to non detectable level. However the Dossier Submitter does not know whether the other companies in diaper industry have also implemented the same change. (if concerned)

Similarly to wetness indicators, and regardless of substitution cost due to the replacement of this type of pigment, the acceptability of using pigments in the finished products may be questioned given that pigments do not have essential technical function to manufacture a single-use baby diaper. They are only used for aesthetic reasons and may be considered as marketing assets only. **If they may be one of possible sources of contamination of finished products, one option to reduce contamination could be that they are no longer used in single-use baby diapers. Having only white and plain single-use baby diapers available on the market would not affect their basic function as absorbent of baby urine and faeces.**

E.2.2.2. Alternative techniques to manufacturing process

Based on the information collected from industry and from literature, some critical steps in the manufacturing process can also be sources of contaminants. Alternative techniques or technical adjustments are expected to be other solutions to remove contaminants.

E.2.2.2.1. Further controlling process temperatures

As explained above, for PAHs to be generated during processing, temperatures should exceed 350°C (Abdel-Shafy and Mansour, 2016). According to information collected from manufacturers, no step in the manufacturing process implies temperatures higher than 170°C or 200°C and the whole process is strictly controlled. High temperatures are thus not considered as the likely cause of the presence of PAHs in the diapers due to manufacturing process. The only possible contamination source is thus assumed to be raw materials.

According to the manufacturers consulted, and as mentioned above, the temperatures indicated in Table 75 in Annex E.2 are not likely to generate PCDD/Fs or DL-PCB substances during the process. The generation of dioxins and furans may occur with temperatures exceeding 200°C.

In conclusion, according to the information collected from manufacturers and reported above (complemented with information from Annex E.2.1.2), processing temperatures may not be in principle expected to be the source of contamination since manufacturing process should not exceed 200°C under normal and controlled conditions.

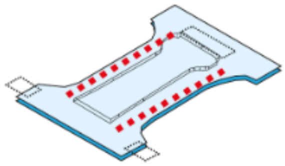
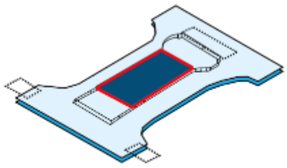
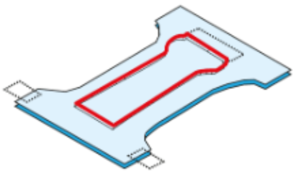
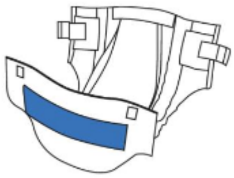
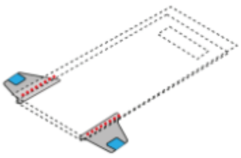
E.2.2.2.2. Moving to glueless diapers

As explained above, according to Mendoza *et al*. (2019a and 2019b), glue represents less than 3% (<1g) of the diaper weight (Mendoza *et al.,* 2019a; 2019b). Despite the small amount per product, the high consumption of diapers in the EU means that 25,200 tonnes of glue are consumed annually. In addition to material resources, glue-based bonding of diaper materials is an energy intensive process, involving glue melting and pumping through tempered pipes to glue applicators at different points in the manufacturing line. Additionally, Mendoza *et al.* (2019a) reports that maintenance requirements in diaper manufacturing are highly influenced by glue contamination during the process. Glue applicators have to be cleaned using solvents as well as vacuuming residual dust from raw materials between production cycles. Consequently, the time spent on glue-related maintenance affects the efficacy and cost efficiency of the process and increases its environmental impacts, including global warming potential and human toxicity (Mendoza *et al.*, 2019a).

Following a series of industrial innovations by Fameccanica[56], glue-based bonding can be completely avoided or notably reduced by using a novel bonding technology for diaper manufacturing. This includes thermal, thermo-mechanical and ultrasonic bonding. Additionally, fluff pulp consumption can be reduced significantly by optimising the design of the absorbent core of the products.

[56] https://glueless.fameccanica.com/en/#Achievements

Fameccanica states that glue bonding can be completely avoided or notably reduced by using alternative bonding technology in five crucial unit processes: elastics entrapment by cuffs, ADL application on the topsheet, absorbent core building, frontal tape application on backsheet and ears reinforcement (Figure 18). This can involve the use of thermal, ultrasonic and themo-mechanical bonding and has no negative effects on the final product. However, elimination of glue in other unit processes and product layers could compromise the performance of the diapers during use.

Unit processes	Diaper layout	Glueless innovations
Glueless™ intermitent elastics		• Cuff elastics mechanically fixed between two layers of nonwoven in intermittent mode • Equivalent results in terms of tension-elongation of the standard application with glue • Process stability up to 450 m/min or 1000 ppm
Glueless™ adquisition and distribution layer (ADL)		• ADL welded on topsheet by using ultrasonic bonding equipment and a properly designed pattern. • Equivalent or improved results in terms of acquisition time and wetback of the final diaper element assembly • Process stability up to 450 m/min or 1000 ppm with 100% of flawless products
Glueless™ absorbent core		• Core welded between two nonwoven layers using thermo-mechanical bonding equipment and a properly designed pattern • Material optimisation of the core • Equivalent or improved results in terms of fluid acquisition and core Integrity
Glueless™ frontal tape construction		• In line creation of a backsheet with loop frontal tape, using ultrasonic bonding equipment • No compromise of the backsheet impermeability • Process stability up to 450 m/min or 1000 pieces per minute • Confirmed strength of the welding through the peel test. • Use of glue applicators [a]
Glueless™ back ear application		• Ears thermal application without glue reinforcement • Equivalent results in terms of strength of the side seal • Welding strength higher than the breaking point of the ear itself • Use of glue applicators [a]

[a] Glue applicators are still required to ensure the integrity of the bonding. However, they are used to a lesser extent.

Figure 18 : Innovations in the manufacture of glueless baby diapers (based on Fameccanica 2018)

The innovations in the production of glueless diapers include a combination of raw materials and bonding pattern selection, design of an optimised quilted absorbent core, technology design and development and process engineering and optimisation. For instance, a quilted absorbent core was designed to bond the upper and lower tissues thermo-mechanically, which entailed the re-engineering and optimisation of the pad-forming drum. In the standard process, the surface of the pad-forming drum is flat, whereas in the glueless process it has a number of dots used to create areas where the pad is not formed so that the NW tissues of the pad can be bonded thermo-mechanically. However, an air-trough bonded (ATB) nonwoven should be also incorporated in the glueless quilted absorbent core to entrap SAP particles and preserve the core integrity. Additionally, the material optimisation of the diapers' absorbent core by changing the fluff pulp/SAP ratio from 40/60 to 20/80 (w/w) entailed the development of a new SAP injection and forming chamber system to control better the SAP and fluff pulp mixture.

Regarding the economic feasibility of glueless diapers, Mendoza *et al.* (2019) states that the final price of glueless diapers could not be determined due to confidentiality but it can be assumed that their retail price would not be much higher than the conventional products, particularly since glueless diaper manufacturing is less costly than the conventional process. The “glueless” innovations can cut the life cycle costs by 11% compared to standard diaper manufacturing. They also reduce the environmental impacts by up to 67%.This could also help to encourage consumers to select glueless diapers and, potentially, other AHPs produced in a similar way.

If glues may be potential sources of contamination during the process, these so-called ‘glueless’ baby diapers based on alternative bonding technologies may be of interest in terms of human health protection. To the Dossier Submitter knowledge, these diapers are procuded by only one company in Europe that did not provide any information during the preparation of this restriction proposal in spite of Dossier Submitter’s requests. It would worth investigating what types of chemicals are used during this alternative process, and what type of investments and costs such a technology would require in case other companies would like to access to it. A deeper analysis would be needed in order to assess this potential alternative. Some information is available on the company’s website but details remain unclear. **Due to a lack of information, the Dossier Submitter is unfortunately not in a position to recommend this technology as a possible solution to glues contamination.**

E.2.2.2.3. Moving to Fluffless diapers

For a few years, all baby diaper manufacturers have been looking for new and more efficient core structures. Up to now, as presented in Annex A.1, the majority of cores are made of a mix of fibers (generally fluff) and superabsorbent polymer (SAP). The former represent the matrix to stabilize the latter and keep it more or less fixed into the core. Moreover fibers have the function to distribute fluid along the core and in contact with SAP where they are absorbed. After last developments and new SAP generations this fluff function has became less and less important. Therefore a goal for all hygiene absorbent product producers is to eliminate the use of fluff and obtain a core made of SAP only. This leads to a thinner core and a less expensive product. Development stream to obtain a fluffless core is the positioning of SAP in small spot on 2 different webs. Afterwards these spots are covered with a glue and bonded together. The result is a sandwich of 2 webs with SAP in the middle. Number of spots and their positions can be varied along the core obtaining a very low SAP grammage in the back and high density in the central part where capacity is more needed. Currently, some manufacturers in Eastern Europe as well as in China commercialize already low-fluff or fluffless baby diapers.

Due to a lack of information and possible higher pollution (according to experts consulted during the elaboration of the proposal) using fluffless diapers, the Dossier Submitter is unfortunately not in a position to recommend this technology as a possible solution.

E.2.2.3. Technical changes related to packaging

All companies consulted during the prepration of the restriction proposal stated that they have implemented, as a preventive measure, the removal of vent holes on their diapers packaging to make them more "air contaminant-proof" during storage and transport.

The purpose of vent holes is to eject air more easily during the packaging of baby diapers.

After having consulted experts, the Dossier Submitter would like to underline that removal of vent holes could prevent release of other chemical substances like volatile organic compounds.

Figure 19 :Example of vent holes on single-use baby diapers packaging

E.2.2.4. Other changes and measures to remove contaminants

E.2.2.4.1. Further decontamination of indoor air

Chemicals in the scope are ubiquitous substances and can thus be suspected to come from contaminated environment and air. As a good practice, single-use baby diapers manufacturers are using air filtration and dust management systems to help reduce levels of airborne pollutants at the production site. Better air filtration and higher frequency of dust clean-up could theoretically help further reduce the presence contaminants. Industry reports that for instance PCFD/Fs levels in the air can be high enough to trigger detection of trace quantities in diapers if the air is insufficiently filtered from particles. Based on their own air analysis at production site, a very few companies consulted conclude that further indoor air filtration may be achieved through generalising central air filtration to reduce as much as possible (not eliminate) the presence of outside air pollutants indoor such as the ones in the scope of this restriction proposal.

However, producing in clean rooms is considered as not feasible. Most of companies consider that given variability in air quality, absolute filtration cannot be reasonably guaranteed in these kinds of industrial processes. The merits of attempting to do this specifically for the materials used in diapers is regarded by these companies as not appropriate given that consumers are exposed to air of similar quality during their entire lives. Morevoer, most of manufacturing sites are expected to currently already follow good or best practice in terms of indoor air filtration and most of the companies consulted during the preparation of the dossier do not seem to consider this technical measure as the most relevant and cost-efficient to achieve the decontamination goals set by the restriction proposal.

Finally, some diapers companies have reported the closure of indoor smoking areas in production sites as a step further decontamination of indoor air.

E.2.2.4.2 Good practices for storage and transport

No information is available to the Dossier Submitter about good practices for storage and transport.

E.2.3. Risk reduction, technical and economic feasibility, and availability of alternatives

E.2.3.1 Assessment of moving to TCF pulp

E.2.3.1.1. Availability of TCF pulp

From the industry consulted and the information collected on TCF pulp supply in Europe, there seems to be one supplier of TCF pulp for an application in single-use baby diapers and another supplier who purchases TCF pulp to the former in order to make the fibers thiner and supply the thiner pulp fibers to diapers manufacturers. In the end, there seems to be only one supplier of TCF pulp on the EU market currently. The availability of TCF pulp is thus very low compared to ECF pulp in Europe. The Dossier Submitter does not have information of supply of TCF from outside EU that could be imported within the EU market to complement domestic supply, or information about the capability of European TCF pulp market to increase its current capacity.

E.2.3.1.2. Human health risks related to TCF pulp

As indicated above, some other single-use baby diapers manufacturers are skeptical about the benefit of moving from ECF to TCF cellulose to reduce contaminants in the cellulose and thus the final products: as presented in Annex E.2 some indeed report that bleaching TCF process allows for reduction of highly chlorinated dioxins in pulp but still contain traces of PCBs. On the contrary, bleaching ECF process seems to less generate PCBs than TCF but pulp contains traces of highly chlorinated dioxins. The human health benefits of TCF pulp over ECF pulp are thus not consensual.

E.2.3.1.3. Environment risks related to TCF pulp

As indicated in Annex E.2 and in JRC, 2015, "*A comparison of toxic responses of bleach plant and whole mill effluents from mills using different schemes for non-chlorine bleaching, i.e. modern ECF versus TCF bleaching, shows that neither technique consistently produces effluents with a lower toxic potency . No clear difference in the effect pattern and effect intensity between effluents from mills using modern ECF (chlorate reduced) and TCF bleaching has been detected*. " as well as "*The special focus on the question of whether modern ECF or TCF bleaching is better from an environmental perspective seems to be too narrow. A TCF bleaching sequence is the more advantageous alternative for further water system closure. However, technical difficulties regarding the enrichment of non-process elements in the water circuits and undesired scaling, especially of oxalates, remains an unsolved challenge for further closure of the bleach plant effluents.".* The environment risks related to ECF pulp versus TCF pulp are thus not so obvious.

E.2.3.1.4. Technical and economic feasibility of TCF pulp

Using TCF pulp is technically feasible since some single-use baby diapers manufacturers already use it. However, some companies report that performance and treatment efficiency are lower with TCF pulp than with ECF pulp. Indeed, a higher amount of TCF pulp seems to be needed to get the same level of performance of the finished product. Moreover, TCF pulp is claimed to be more complicated to treat due to the fiber features. Comparative assessment from the literature show also technical differences between both pulps (see E.2.1.1.1).

Regarding economic feasibility, industry reports extra-costs due to the use of TCF pulp, mainly due to its lower availability and higher price on the EU market currently. Using TCF pulp is also more expensive because of the higher quantity of raw material needed to reach the same level of performance and it is more costly to treat due to technical challenges. As a consequence extra-investment are also reported to be necessary to switch to this raw material. Industry provided some estimate for some of those costs and some others are not quantified. For more details about these extra-costs, see the main report, section 2.4.1.1.1 and Table 17 in the Main report. from those costs, the Dossier Submitter considers that switching to TCF pulp may be economically feasible, at least for big companies and provided that they have sufficient time to operate this move. However, SMEs might have more difficulties to move to TCF pulp depending on the capability of the TCF pulp market to increase its supply while controlling the price increase of TCF pulp to a sustainable level for all market actors. Finally, moving to TCF pulp may economically impact consumers in case the extra-costs are passed onto the final price of diposable baby diapers (for further details, see section 2.4.3.1 of the main report).

E.2.3.1.5. Conclusion on moving to TCF pulp

Based on the information at hand, it is difficult for the Dossier Submitter to have a clear-cut conclusion about the better capability of TCF pulp to address the health concerns targeted in this restriction proposal over ECF pulp. Within all the possible solutions to reduce contamination in single-use baby diapers identified, moving to TCF pulp could be an option but given the uncertainties associated to its benefits to human health and its technical and economic feasibility, the Dossier Submitter can not strongly recommend this substitution without reservation. Nevertheless, if industry would decide to switch to TCF pulp, the information presented in this restriction proposal and especially this part would be useful to anticipate the possible impacts on industry and consumers.

E.2.3.2 Assessment of removal or substitution of wetness indicators

E.2.3.2.1. Availability of alternative wetness indicators

Many single-use baby diapers that contain a wetness indicator seem to use a chemical called bromophenol blue (CAS: 115-39-9). The Dossier Submitter does not have information about other pH indicators available on the market that would be also used for this function as wetness indicators in single-use baby diapers.

E.2.3.2.2. Human health risks related to alternative wetness indicators

As already stated above, wetness indicators are not in contact with the baby skin but one manufacturer stated that wetness indicator can contain PAH and no PAH has been detected in their finished products. Given that the Dossier Submitter does not have information about other pH indicators than bromophenol blue, no information on human health risks is available.

E.2.3.2.3. Environment risks related to alternative wetness indicators

Given that the Dossier Submitter does not have information about other pH indicators than Bromophenol Blue that would be used as wetness indicators in single-use baby diapers, no information is available about their environment risks.

E.2.3.2.4. Technical and economic feasibility of alternative wetness indicators

Given that the Dossier Submitter does not have information about other pH indicators than Bromophenol Blue that would be used as wetness indicators in single-use baby diapers, no information is available about their technical and economic feasibility.

E.2.3.2.5. Technical and economic feasibility of removing wetness indicators

Removing wetness indicators from single-use baby diapers would basically consist in processing fewer raw materials during the manufacturing process without impeding the overall process and without affecting the essential absorbing function of the finished products. As a consequence, the Dossier Submitter considers that this change would be in principle technically feasible at no cost. Removal wetness indicators could even decrease the production costs due to lower raw materials costs. Companies using this material in their products however may claim that a competitive advantage would be lost. For more details about these potential extra-costs, see the main report, section 2.4.1.1.1.

E.2.3.2.6. Conclusion on removing or substituting wetness indicators

Based on the information at hand, the Dossier Submitter considers that wetness indicators should no longer be used in the single-use baby diapers given that they dos not meet any essential technical function in single-use baby diapers. Their removal would not affect the essential absorbing function of the finished products and would cause no direct cost to industry. It could even generate some raw materials costs saving. The Dossier Submitter can not take position on eventual loss in sales and profits which may occur due to the loss of a so-called competitive advantage.

E.2.3.3 Assessment of removal or substitution of pigments

E.2.3.3.1. Availability of alternative pigments

Most of the diapers available on the market are colored onto their external sheet to make them more attractive and fancy. The Dossier Submitter does not have information about all pigments used in the diapers industry and their possible alternatives. As indicated in Annex E.2.1.2.2., according to one company, a “green pigment” used in aesthetic printing may be the source of OCDF and OCDD in external sheet and external film: the company explained that the green pigment was reformulated so that the changes now allow for non- detectable levels of PCDD/Fs. However, the Dossier Submitter has been provided neither with details about this reformulation nor with what is the exact substance called “green pigment”.

E.2.3.3.2. Human health risks related to alternative pigments

As already stated above, pigments are not in contact with the baby skin but one manufacturer stated that a green pigment can contain OCDD/OCDF in external sheet and external film by one company. Given that the Dossier Submitter does not have information about other pigments than this green one, no information on human health risks is available.

E.2.3.3.3. Environment risks related to alternative pigments

Given that the Dossier Submitter does not have information about other alternative pigments than the green one that would be used as pigment in single-use baby diapers, no information is available about their environment risks.

E.2.3.3.4. Technical and economic feasibility of alternative pigments

Given that the Dossier Submitter does not have information about all pigments used in the diapers industry and their possible alternatives, no information is available about their technical and economic feasibility. In particular, regarding the “green pigment” claimed to be source of OCDF and OCDD in external sheet and external film by one company, the Dossier Submitter has no further information about the technical or economic feasibility of reformulations that have been needed to reach non-detectable levels of dioxins and furans.

E.2.3.3.5. Technical and economic feasibility of removing pigments

Similarly to wetness indicators, removing pigments from single-use baby diapers would basically consist in processing fewer raw materials (raw pigments and pigments mixtures) during the manufacturing process without impeding the overall process and without affecting the essential absorbing function of the finished products. As a consequence, the Dossier Submitter considers that this change would be in principle technically feasible at no cost. Removal pigments could even decrease the production costs due to lower raw materials costs. Companies using pigments to color their products however may claim that a competitive advantage would be lost. For more details about these potential extra-costs, see the main report, section 2.4.1.1.1.

E.2.3.3.6. Conclusion on removing or substituting pigments

Based on the information at hand, the Dossier Submitter considers that pigments should no longer be used in the single-use baby diapers given that they do not meet any essential technical function in single-use baby diapers. Their removal would not affect the essential absorbing function of the finished products and would cause no direct cost to industry. It could even generate some raw materials costs saving. The Dossier Submitter can not take position on eventual loss in sales and profits which may occur due to the loss of a so-called competitive advantage.

E.2.3.4 Assessment of moving to best practices regarding raw materials

See main report, section 2.4.1.1.1.

E.2.3.5. Assessment of further controlling manufacturing process

See main report, section 2.4.1.1.2.

E.2.3.6 Assessment of changes in packaging

See main report, section 2.4.1.1.3.

E.2.3.7 Assessment of further indoor air decontamination

See main report, section 2.4.1.1.4.

E.2.3.8. Conclusion about alternatives

Different solutions have been explored above to further reduce contaminants in single-use baby diapers. As already explained, this restriction aims to encourage manufacturers to further find out how the substances are formed in the products and to take relevant steps to reduce their presence, should it be in the raw materials or during the manufacturing process and any other relevant sources identified. The solutions and further actions recommended by the Dossier Submitter to be implemented by industry are a combination of:

- moving to TCF pulp,
- removing wetness indicators and pigments,
- moving to best practices, changes in packaging, indoor air decontamination and changes in packaging.

All the alternatives assessed seem to be reachable for the industry but, the Dossier Submitter can not have a clear cut position on each alternative assessed due to a lack of data especially on human health and environmental impacts. Meanwhile, the Dossier Submitter presents in the table below an overview of the information available on the packaging of the first 19 samples tested by the SCL:

Sample number	Information available on the packaging and description of the diaper
1	White diaper with coloured patterns, with elastics around the thigh. Ultra absorbent. Manufactured in EU. Diapers white and green.
2	White diaper inside and multicolored outside. Absorbent canals helping the repartition of the humidity to have a better absorption.Manufactured in Germany. Softern and extensibles fasterners, Microabsorbent pearls.
3	Anti leaks, repositionable fasteners, super absorbent film, fancy patterns..Manufactured in Germany
4	White diaper with animals patterns.Extensible fasteners. Manufactuered in France. Maxi absorbent anti-leak core. 50% of biodegradable raw materials, Micro airy extern sheet,100% natural latex, without chlore or fragrances. High protection against leaking. Absorbent core coming from sustainable forest.
5	Manufactured in Switzerland, No chlore, no colorant in direct contact with the skin, no petrolatum, no allergen, no paraben no phenoxyethanol, white diaper, almost 50% of biodegradable raw materials, no preservatives,no lotion in the film in direct contact with the skin, elastic ears, respirable, waterproof external sheet
6	White diaper with blue and green patterns, repositionable, soften and externsible fasteners, barriers to prevent leaking, anatomic core, acquisition layer coloured, external layer respirable and soften
7	Manufactured in Gernmany. White and blue diapers with patterns. Soften as cotton, absorbent micropearls, super absorbent layers, Absorbent canals helping the repartition of the humidity to have a better absorption.
8	Manufactured in Germany. Presence of petrolateum,
9	Manufactured in Czech Republic,blue diaper with patterns,anti leaking barriers, repositionable fasterners

10	FSC. Manufactured in the EU. White diaper with patterns. Soften External sheet , repositionalble ears,45% of biodegradable raw materials, cellulose from the core is bleached without chlore or derived chemcals
11	FSC. Manufactured in France. 50% of biodegradable raw materials. Respirable and waterproof, elastic ears, without latex,
12	Manufactured in the EU. White and green diaper, cellulose form sustainable forest,
13	White diaper with blue and green patterns, micro aerated layer, anti-leak barriers, micro sensors for an optimal abosprtion, flexible ears
14	Recommended by the asthma and allergy Swedish society,developed in Sweden, FSC,manufactured in Turkey,white diaper with patterns, naturally transpirable, no chlore no fragrance, film with corn starch,external sheet without chlore, natural raw materials, core 100% without chlore,
15	PEFC,without latex, white and green diaper with patterns, repositionable and self-sticking ears,
16	Manufactured in France, white diaper, extensible ears, anti leaking barriers, micro sensors ultra absorbent, external sheet micro aerated,
17	Manufactured in the EU, white diaper with patterns, anti leaking systems, extensible and soften ears, respirable external sheet, very soften internal sheet,
18	Made at La Réunion, white diaper with patterns, repositionable ears
19	Made at La reunion, white diaper with coloured patterns, elastic ears,

E.3. Restriction scenario(s)

The two restriction scenarios further assessed, and presented in sections 2.4 and 2.5 of the main report, differ mainly in terms of substances included in the scope. RO1 and RO2 have been assessed and compared in terms of risk reduction capacity, substitution costs, enforceability and impacts on industry (please refer to Main Report section 2.5). The following sections focus on the impacts of RO1 (the restriction proposed).

SEAC box

SEAC found it difficult to reach a conclusion on the possible socio-economic impacts associated with the proposed restriction due to the uncertainties related to e.g. the contamination sources, the feasibility of reducing or eliminating the contamination and what industry would do in the restriction scenario.

The details of the SEAC evaluation are reported in the SEAC opinion.

E.4. Economic impacts

At early stage of the preparation of this restriction proposal, some companies considered that the nature of the traces targeted herein stems from unavoidable environmental background contamination (of the raw materials, the manufacturing process and possibly any stage until distribution) and that a further reduction of the trace levels was considered to be technically not feasible. Since the French RMOA has been published, most of them have implemented further preventive measures for the purpose of reducing contamination either in the raw materials or in the finished products or both. A minor proportion of them consider that dedicating resources for finding alternatives is an impractical effort and does not justify the costs involved (without any specifications). However most of companies provided the Dossier Submitter with extra costs that have been already born due to the measures already implemented recently and extra costs that would be further supported if the present restriction proposal would enter into force. These foreseen measures and the possible technical and substitution solutions identified by industry are overall converging. They are thus considered as likely and this was valuable information to be used in the assessment.

The extra-costs assessed consist in compliance costs of reducing or removing the contaminants targeted in this restriction proposal in finished products onto the single-use baby diapers industry due to the substitution measures and technical changes assessed. These costs are assessed qualitatively or quantitatively. They include direct costs of removing or reducing contaminants from raw materials, manufacturing process and other steps in the supply chain as well as testing costs for industry. They also include testing costs for control authorities as well as economic impacts on consumers.

For more details about these costs, please see sections 2.4.1.1, 2.4.1.2 and 2.4.3.1 and Tables 17-19 in the main report as well as dedicated annexes above on economic feasibility of substitution and technical solutions to reduce or remove contaminants (Annexe E.2.3).

E.5. Human health impacts

Single-use baby diapers can contain hazardous chemicals that may cause diseases in babies and the quantitative human risk assessment performed by the Dossier Submitter showed that health thresholds are exceeded for the substances in the scope under realistic and reasonably conservative assumptions (see annexes B.9 and B10). As a consequence, this proposal aims at protecting babies from developing adverse effects due to the exposure to these chemicals at older ages or in their adulthood by restricting these chemicals. However, due to the lack of epidemiological studies, of robust and extrapolable dose-response relationships, and the substances in the scope being ubiquitous, there is no scientifically-based means to estimate the attributable fraction of babies who would actually develop adverse effects due to their diapers at older ages or in their adulthood. It is thus difficult to estimate the incidence and prevalence of adverse effects in babies likely to be associated to single-use baby diapers wearing and human health imapcts could not be assessed quantitatively. As a consequence, the Dossier Submitter’s approach of the human health benefits in this proposal is qualitative. However, a break even analysis was still performed by the Dossier Submitter to evaluate proportionality of the proposal.

For more details, please see section 2.4.2 in the main report.

E.6. Risk reduction capacity

The restriction proposed is considered to be practical and monitorable. See sections 2.4.3.4 and section 2.4.3.5 in the main report.

E.7. Other impacts, practicability and monitorability

E.7.1. Social impacts

Please see section 2.4.3.2 in the main report.

E.7.2. Wider economic impacts

As indicated in Annex A.2 some single-use baby diapers are imported as finished products from outside EEA31 (e.g. Vietnam) but the amount of imported diapers is not available to the Dossier Submitter's knowledge. In some European overseas territories, up to 50% of diapers are imported from Asia (e.g. Vietnam, China, South Korea, Malaysia…) and other countries (e.g. South Africa, USA). Importers claim to have no information about their composition.

Regarding imported raw materials used in diapers manufacturing, most raw materials come from EU but some raw materials come from outside EU. Likewise, the amount of imported raw materials is not available to the Dossier Submitter's knowledge. It cannot be excluded that some impacts may occur outside EEA31 to some companies supplying raw materials or finished single-use baby diapers in Europe due to the restriction. However, due to a lack of data and information, the magnitude of these impacts cannot be assessed.

E.7.3. Distributional impacts

Please see section 2.4.3.3 in the main report.

E.8. Practicality and monitorability

As explained in the main report and in Annex B, the Dossier Submitter considers various analytical tests performed on the single-use baby diapers. These analytical tests lead to detect or quantify various hazardous chemicals. Three analytical tests were performed in ANSES 2019 by SCL, which are :

- a solvent extraction in a shredded entire diaper;
- an urine simulant extraction in shredded entire diaper;
- an urine simulant extraction in an entire diaper : **which is the analytical method considered by the Dossier Submitter as the most close to the reality of use**

The protocol of <u>the solvent extraction in a shredded entire diaper</u> is in accordance with SCL's internal protocols or with standards specific to each group of substances when such standards were available. The detection limit for the hazardous chemicals detected or quantified are the following :

Table 80 : Limit of detection according to the solvent extraction in a shredded entire diaper analysis

Substances/group of substance	Limit of detection/limit of quantification
PAHs	0.3 µg/kg / -
Formaldehyde	0.11/0.35 mg/kg
PCDDs	-
PCDFs	-
DL-PCBS	-

For PCDD/Fs and DL-PCBs, no limit of quantification (LOQ) is available because it varies according to the test sample.

The protocol of the urine simulant extraction in shredded entire diaper or in an entire diaper is an exploratory one and was performed in order to measure the migration to a urine simulant of the chemicals detected or quantified in shredded whole diapers. The composition of the urine simulant used was based on the publication by Colón *et al.* (2015)

Table 81 : Composition of the urine simulant used (Colón et al., 2015)

Compound	**Concentration obtained**
Urea	9.3 $g \cdot L^{-1}$
Creatinine	2 $g \cdot L^{-1}$
Ammonium citrate	1 $g \cdot L^{-1}$
NaCl	8 $g \cdot L^{-1}$
KCl	1.65 $g \cdot L^{-1}$
$KHSO_4$	0.5 $g \cdot L^{-1}$
$MgSO_4$	0.2 $g \cdot L^{-1}$
KH_2PO_4	1.75 $g \cdot L^{-1}$
$KHCO_3$	0.5 $g \cdot L^{-1}$

No limit of detection nor quantification is available due to the fact that each of these limits are specific to test sample.

For urine simulant extraction in shredded entire diaper analysis, each shredded diaper was brought into contact with the urine simulant in an oven at 37°C (+/- 3°C) for four hours (+/- 10 mins) under stirring.

For urine simulant extraction in an **entire diaper analysis,** the analyses were carried out with whole diapers soaked with urine simulant and then placed in an oven at 37°C for 16 hours. 200 ml of simulant were added to the diaper three times, with a 30-minute rest period between each addition. The tested simulant was extracted by pressing (recovery of 220 to 250 ml). The majority of the 600 ml of urine simulant remained trapped in the SAP. The Dossier Submitter would like to indicate that the part of the diaper that is not in contact with the skin (e.g the backsheet) is not in direct contact with the urine simulant added in the single-use baby diaper meaning, that the chemicals extracted from the urine simulant, should come from the absorbant core or the parts in contact with the skin.

The study explaining in details the methodology used to prepare the samples and dose all the chemicals is available in annex of the restriction proposal. Here under are summarized the major points to be taken into account to better understand the analysis.

- Volume of urine simulant used (600 mL) : The SCL study stated that "*The urine volume of a baby between 1 and 3 years old varies from 600 to 750 ml per day. It has been* *decided to take an initial volume of 600 ml in order to meet the dual objective of saturating the layer and to recover a relevant volume of simulant with regard to the analytical need while maintaining a realistic approach. On these 600 ml, according to the different capacities absorption of the layers, 160 to 190 ml of simulant after pressing are recovered*".

- Time of exposure (16h) : The SCL study stated that "*Beyond 6 months old, most babies can sleep up to 10-12 hours a night, or even more. In the laboratory, a total impregnation time of 16 hours was therefore adopted*". The SCL did not perform some tests to determine if the concentration of chemicals extracted is linear to the duration of time of exposure. The Dossier Submitter is of the view that this uncertainty should not affect the frequency of use proposed in the exposure assessment for the following reasons :
    - o chemicals extracted are organics so it means that generally speaking they should be extracted quickly after being in contact with a solvent,
    - o The amount of chemicals found in urine through various published studies. For example, the European Human Biomonitoring Dashboard[57] shows that the 95th percentile of Benzo[a] anthracene, Benzo[a]pyrene, benzo[g,h,i]perylene in a study performed on southern Spain in 2009-2010 for the general population (adults), is 1.6655 µg/L of urine with a LOQ of 0.05µg/L.
    - o Moreover, the 16-hour-exposure time was chosen by the SCL to represent an one night exposure; meaning that during the day, parents should change their babies more often (please look at annex B.9.2).

- Identification and dosage of the chemicals : In the study linked in the Appendix of the restriction proposal, all the methods used to dose the chemicals, the LOD and LOQ are available, but to help the reader, Table 82 shows the most important ones. According to this study joined in the appendix, the same LOD and LOQ and the same methodology were used for both 2018 and 2019 SCL studies.

Table 82 : Methods used to dose the chemicals

Chemicals	Urine simulant extraction			
	Methods	Principle	LOD	LOQ
PAH	Internal method : IDF.IN.ANA.06	Microwave extraction Column purification SPE GC-MS / MS analysis	Between 0.03 to 0.1 mg/L	Between 0.1 to 0.4 mg/L
Dioxins & furans	Internal method according to EPA 1613	Extraction liquid / solid, extraction liquid / liquid HRGC / HRMS	From 0.05pg/l to 8 pg/l according to the test sample	From 0.05pg/l to 8 pg/l according to the test sample
PCB	Internal method according to EPA 1668	Extraction liquid / solid, extraction liquid / liquid HRGC / HRMS	From 0.25pg/L to 40 pg/L according to the test sample	From 0.25pg/L to 40 pg/L according to the test sample

57 https://www.hbm4eu.eu/eu-hbm-dashboard/

Formaldehyde	Internal method adapted from NF EN ISO 14184-1	Aqueous extraction acidified Coloring Analysis by spectrometry visible	0.02 mg/L	0.06 mg/L

As stated in the SCL study joined in the appendix of the restriction proposal, a simulant blank is carried out simultaneously under the same conditions including all the operations to prepare a diaper but in the absence of a diaper (passage on glassware, press and filtration on filter paper). 3 “blanks tests” have been performed in the 2019 study. The Dossier Submitter does not have the values of the blanks for the 2018 study. The values of the 2019 blanks are summarized in the table below :

Table 83 : Values of the blanks for the 2019 SCL study

Chemicals	Range of Values of the blanks
PAHs	
Benzo[a]anthracene	Non detected (<LOD=0,03 µg/L)
Chrysene	Non detected (<LOD=0,03 µg/L)
5-methyl chrysene	Non detected (<LOD=0,03 µg/L)
Benzo[b]fluoranthene	Non detected (<LOD=0,03 µg/L)
Benzo[k]fluoranthene	Non detected (<LOD=0,03 µg/L)
Benzo[j]fluoranthene	Non detected (<LOD=0,03 µg/L)
Benzo[e]pyrene	Non detected (<LOD=0,03 µg/L)
Benzo[a]pyrene	Non detected (<LOD=0,03 µg/L)
Dibenzo[a,h]anthracene	Non detected (<LOD=0,03 µg/L)
Benzo[g,h,i]perylene	Non detected (<LOD=0,03 µg/L)
Formaldehyde	
Formaldehyde	Non detected (LOD<=0.02 mg/L)
DL PCBs	
PCB 81	Non detected (<0.403 pg/l - <1,831 pg/L)
PCB 77	24.604 pg/L -52,281 pg/L or non detected (<5.314 pg/l)
PCB 123	5.379 pg/L – 17.742 pg/L
PCB 118	290.122 pg/L - 868.437 pg/L
PCB 114	15.009 pg/L6 32.647 or non detected (<2.675 pg/L)
PCB 105	180.624 pg/L - 558.049 pg/L
PCB 126	Non detected (<1.821 pg/ L - <4.552 pg/L)
PCB 167	22.231 pg/L - 26.480 pg/L or non detected (<2.177 pg/L)
PCB 156	42.072 pg/L - 58.145 pg/L
PCB 157	Non detected (<1.935 pg/L - <4.118 pg/L)
PCB 169	Non detected (<2.492pgL - <4.825 pg/L)
PCB 189	Non detected (<0.717 pg/L - <1,688 pg/L)
PDDs/Fs	
2,3,7,8 TCDD	Non detected (<0.115 - <0.325 pg/L)
1,2,3,7,8 PeCDD	Non detected (<0.106 - <0.297 pg/L)
1,2,3,4,7,8 HxCDD	Non detected (<0.078 - <0.294 pg/L)
1,2,3,6,7,8 HxCDD	Non detected (<0.125 - <0.260 pg/L)
1,2,3,7,8,9 HxCDD	Non detected (<0.077 - <0.202 pg/L)
1,2,3,4,6,7,8 HpCDD	0.349 - 0.656 pg/L
OCDD	1.033 - 1.518 pg/L

2,3,7,8 TCDF	0.338pg/L or Non detected (<0.146 - <0.230 pg/L)
1,2,3,7,8 PeCDF	Non detected (< 0.112 - <0.250 pg/L)
2,3,4,7,8 PeCDF	Non detected (<0.116 - <0.233 pg/L)
1,2,3,4,7,8 HxCDF	0.279pg/L or Non detected (<0.081 - <0.223 pg/L)
1,2,3,6,7,8 HxCDF	Non detected (<0.073 - <0.215 pg/L)
2,3,4,6,7,8 HxCDF	0.191 pg/L or Non detected (<0.074 - <0.166 pg/L)
1,2,3,7,8,9 HxCDF	0.202 pg/L or Non detected (<0.086 - <0.138 pg/L)
1,2,3,4,6,7,8 HpCDF	0.684 – 0.959 pg/L or non detected
1,2,3,4,7,8,9 HpCDF	Non detected (<0.086 - <0.365 pg/L)
OCDF	0.264 – 2.376 pg/L

It can be seen that neither formaldehyde nor PAHs were found in the blanks. On the contrary, DL-PCBs, PCDDs/Fs have been found, for some of them, in the blanks. The Dossier Submitter would like to underline, that in the concentration values used to perform the exposure and risk assessment, the blank values for the DL-PCBs, PCDDs and PCDFs have not been removed. Indeed the SCL stated that no European harmonization exists regarding the removal of the blank values when it comes to DL-PCBs/PCDDs or PCDFs. (FAQ of the LNR 2012)

Each congener of PCDDs, PCDFs and DL-PCBs have been searched for individually by the methodology proposed. Regarding the NDL-PCBs, only some of them have been searched for in the incontinence diapers (markors).

A sensitivity analysis has been performed and is available in the appendix joined to the restriction proposal.

As already mentioned in the restriction proposal, the QHRA performed in Annex B was based on the results of hazardous chemicals found in single-use baby diapers after a urine simulant extraction in an entire diaper. This type of analysis was considered by ANSES 2019 and the Dossier Submitter as the most representative scenario of the reality of use.

As a matter of a comparison, the Dossier Submitter prepared a table to compare the levels of PCCD/F/DL PCBs/PAHs and formaldehyde in the environment, the LOD/LOQs of the analysis performed and the proposed concentration limits.

It has to be noted, that the levels found in the environment are difficult to be compared to the LOD/LOQ or the migration limits proposed due to the fact that it does not imply the same media (air, food, water, urine etc…). Nevertheless, the migration limits proposed in this restriction proposal (using a dedicated analytical method by extraction with an urine simulant) have been compared the highest concentrations of the quantified and/or detected chemicals in food as part of the Total Diet Study (Anses 2016). **The routes of exposure to these sources are very different.**

Regarding the levels of PCDDs/Fs and DL-PCBs in the soil or in the air, numerous studies are available.

Table 84 : Comparative values regarding chemicals in the scope in other media

Chemicals	LOD/LOQ of the analysis performed in urine simulant	Maximum Levels found in the air (reference)	Maximum Levels found in the US soil (Urban & al, 2014)	Max Levels found in babies' food (Anses, 2016)	Maximum concentration found in the feminine hygiene products (pads/panty liner - extraction with a solvent, Anses 2018)	Migration limits proposed in the restriction proposal
Formaldehyde	LOD : 0.02 mg/L/LOQ : 0.06 mg/L	-	-	-	Not detected	0.42 mg/kg of diaper
PCDDs/Fs						
1,2,3,6,7,8-HxCDD	LOD : From 0.05pg/l to 8 pg/l according to the test sample/ LOQ : From 0.05pg/l to 8 pg/l according to the test sample	-	-	$1.68 \cdot 10^{-5}$ mg/kg	$29.7 \cdot 10^{-9}$ mg/kg	-
1,2,3,4,6,7,8-HpCDD				$2.61 \cdot 10^{-5}$ mg/kg	$4.9 \cdot 10^{-7}$ mg/kg	
OCDD				$3.33 \cdot 10^{-4}$ mg/kg	$3.9 \cdot 10^{-6}$ mg/kg	
1,2,3,4,6,7,8-HpCDF				$6.42 \cdot 10^{-5}$ mg/kg	$7.7 \cdot 10^{-8}$ mg/kg	
OCDF				$6.33 \cdot 10^{-5}$ mg/kg	$24.8 \cdot 10^{-6}$ mg/kg	
Sum of PCDD/F		$1.41 fg_{TEQ}/m^3$(Cleverly&al, 2017)	1680 ng_{TEQ}/kg	$0.00954 ng_{TEQ}/kg$		
DL PCBs						
PCB-81	LOD : From 0.25pg/L to 40 pg/L according to the test sample/ LOQ : From 0.25pg/L to 40 pg/L according to the test sample	-	-	$1.1 \cdot 10^{-11}$ mg/kg		-
PCB-77				$8.4 \cdot 10^{-11}$ mg/kg		
PCB-123				$1.7 \cdot 10^{-5}$ mg/kg		
PCB-118				$2.33 \cdot 10^{-6}$ mg/kg		
PCB-114				$1.6 \cdot 10^{-8}$ mg/kg		
PCB-105				$6.69 \cdot 10^{-7}$ mg/kg		
PCB-167				$1.78 \cdot 10^{-7}$ mg/kg		
PCB-156				$1.61 \cdot 10^{-4}$ mg/kg		
PCB-157				$8.3 \cdot 10^{-8}$ mg/kg		

Sum of the PCDD/F/DL PCBs		2.9-318 fg $_{TEQ}$/m^3(Lopez& al, 2021)		-		**0.0017 ng$_{TEQ}$/kg of diaper**
Sum of the PCBs				-		**112 ng/kg of diaper**
PAHs						
Benzo[a]anthracene	LOD : Between 0.03 to 0.1 mg/L / LOQ : Between 0.1 to 0.4 mg/L	-	-	$8.4 \cdot 10^{-5}$ mg/kg		
Cyclopenta[c,d]pyrene				-	$8.9.10^{-3}$ mg/kg	**-**
Benzo[k]fluoranthene				-	$10.4.10^{-3}$ mg/kg	
Benzo[g,h,i]perylene				$3.5 \cdot 10^{-5}$ mg/kg	$11.7.10^{-3}$ mg/kg	
Chrysene/ Benzo[j]fluoranthene/ Benzo[b]fluoranthene				$1.44 \cdot 10^{-4}$ mg/kg	Detected	
Benzo[e]pyrene				-	$9,7.10^{-3}$ mg/kg	
Sum of the PAHs				0.683µg/kg (sum of 11 PAH)	$28.9.10^{-3}$ mg/kg (sum of the 17 PAHs)	**0.023ng$_{TEQ}$/kg of diaper**

All these information about the analytical method (and as already said : considered by the Dossier Submitter as the most relevant) used to perform chemicals analysis onto single-use baby diapers may be used as a guideline or a starting point to build a harmonised methodology.

Without a validated method and scientifically sound thresholds, during the public consultation some companies expressed their concern that it will be difficult or even impossible for industry to comply with the restriction and that it may result in a disruption of the market, the supply of diapers for babies and create unwarranted legal liabilities. As mentioned above, some analytical and harmonized tests methods are already existing but they imply using solvents and sometimes a shredded diaper. As already explained, the Dossier Submitter considers that these methods are not the most relevant ones because they do not reflect the reality of use of a diaper.

Indeed, some companies claimed that levels reported by SCL/ANSES can not be reproduced and are of unclear origin. It should be noted that the amount of formaldehyde produced in the human body is significantly higher than SCL/ANSES suggested threshold.

In some cases, the restriction would require to measure levels close to or in some cases even below current LOQ achieveable even by best in class specialized laboratories. Hence, the absence of a validated method combined with the challenge for sensitive detection and quantification limits prone to unintended contamination during product pick-up, transport, sample preparation etc. would present a major barrier for compliance and enforcement. Should a European restriction be proposed, it will require a harmonized European approach that provides clarity on testing methodology to producers and enforcers and as said, the methodology proposed above can be used as a guideline to build one.

Industry consulted also points out that diapers are ‘heterogeneous’ samples comprised of many raw materials. These materials are not evenly distributed in space or by mass. For consistency in testing results – and especially for trace analytical chemistry work – this must be considered. Sample preparation steps must also be reproducible across product forms, sizes. A current best practice is to generate a homogeneous diaper sample *via* grinding, and then to use aliquots of this for analytical testing. Standardized equipment capable of grinding diapers to sufficient chemical and physical homogeneity is available (i.e. Retsch SM300 cutting mill). There are also published methods that describe validated approaches for grinding diapers that are well-suited as a sample preparation step (i.e. EDANA NWSP 404).

According to one company, “Background” amounts of PCDD/Fs can regularly be detected in laboratory water of accredited laboratories that are specialized in dioxin/furan analyses. These background amounts fluctuate over time and are within the concentration ranges that would be required to determine the levels of PCDD/Fs at the limits proposed by ANSES. This can introduce a high risk of “false positive” detections.

In its Stewardship Program for AHPs (on voluntary basis), EDANA has informed the Dossier Submitter that they have planned the development of relevant test methods to determine the presence of substances at trace level and to check that the amount of possible trace impurities in products does not exceed the defined limit values. EDANA also indicated, through the Public Consultation, to be unable to develop the analytical method proposed by the Dossier Submitter while, while an industry claimed to be able to reproduce the sample preparation method and the analytical methods by the end of 2021.

Eventually, the Dossier Submitter is confident that a harmonised analytical method will be in place before the end of the transitional period proposed (24 months). This assumption is confirmed by some comments received during the public consultation.

E.9. Proportionality (comparison of options)

SEAC box
SEAC reached different conclusions than the Dossier Submitter concerning the proportionality of the restriction proposal. SEAC undertook a scenario analysis to consider the key uncertainties and information gaps related to the proposed restriction. It concluded that for none of the scenarios is there any evidence demonstrating that the restriction would be proportionate.
The details of the SEAC evaluation are reported in the SEAC opinion, together with the justification for its conclusion on proportionality.

Please see section 2.4.4 in the main report.

E.10. Comparison of Restriction Options

One restriction option (RO2) has been further assessed to be compared with RO1 which is the restriction proposed. RO2 is assessed under section 2.5 in the main report and this restriction option is compared with RO1 under section 2.7 in the main report.

Annex F: Assumptions, uncertainties and sensitivities

Table below lists the assumptions, uncertainties and sensitivities of the assessment done to support this restriction proposal and their overall impact.

Table 85: Assumptions, uncertainties and sensitivities

Section	**Source of uncertainties**	**Overall Impact on the restriction proposal**
Human health hazard assessment	**Formaldehyde :** The route-to-route extrapolation is questionable because observed effects are correlated with the route of exposure. These are only local effects. Systemic toxicity has not been demonstrated.	The Dossier Submitter chose a precautionary approach due to limited dermal data and lack of dermal data in children.
	PAHs : dermal DNEL calculated by ECHA and expressed in µg/cm²/d but not usable to perform the DED calculation. The DED calculation could have been done if data on surface weight had been made available to the Dossier Submitter.	The Dossier Submitter used internal DNEL instead of dermal ones. The impact on the restriction proposal is not quantifiable. This calculation may be done as a comparison with the current approach used in the restriction proposal.
Exposure assessment	**Test method :** SCL tests with entire diapers, extraction with a urine simulant Representative of normal use enabling the chemicals actually extracted by urine to be identified.	The migration limits calculated are assumed to be protective. The impact on the restriction proposal is not quantifiable.
	Skin Absorption. The Dossier Submitter decided to use a value of 100% for skin absorption assuming that baby skin can be damaged and enhance the penetration. Approach adopted by the SCCS and ANSM for products for the buttocks area due to the frequency of skin diseases in the diaper area in babies.	Can lead to an overestimation of the risk.
Risk assessment	**Risk characterisation.** The calculations to generate cmigration limits are based on worst case scenarios for migration and exposure frequency.	Based on the calculations used in this restriction proposal, the migration levels proposed for single-use baby diapers are likely to be sufficiently protective. All the asumptions chosen by the Dossier Submitter are reasonable and are not leading to an overestimation nor and underestimation of the risk according to the Dossier Submitter.
Analysis of Alternatives	Identification of the contamination sources for the chemicals of concern has been difficult due to lack of data	This can turn lead to the inclusion or exclusion of possible sources that are not accurate. This can lead to the exclusion of possible sources that coulb be accurate.
	Link between FSC certification to get TCF pulp claimed by industry to be a problem to switch to TCF pulp. According to experts consulted, FSC certification is linked to sustainable forest management and not wood transformation.	This can facilitate the use of TCF pulp in order to decrease the traces of PCDD/Fs

Economic Impacts/substitution Costs	Industry reactions to the restriction cannot be anticipated and remain to some degree uncertain; From the publication of Anses 2019 and French RMOA reports, companies on the single-use diapers market state that they have already started to implement technical and substitution measures in order to reduce/remove contaminants in their products. Some costs reported by industry are unspecific, some only concern a part of companies products ranges and some expected costs depend on the companies' size and production or sales volume and may not be representative of the whole market. Some reported costs might present some overlapping between extra-costs already borne due to new measures implemented as a voluntary response from industry since Anses' expertise and French RMOA have been published and extra-costs specifically attributable to this restriction proposal. Costs associated with moving to TCF pulp: based on the information at hand, it is difficult for the Dossier submitter to have a clear-cut conclusion about the better capability of TCF pulp to address the health concerns targeted in this restriction proposal over ECF pulp. Within all the possible solutions to reduce contamination in baby diapers identified, moving to TCF pulp could be an option but given the uncertainties associated with its benefits to human health, its availability in the future and its economic feasibility especially for SMEs, the Dossier Submitter can not strongly recommend this substitution without reservation. Nevertheless, if industry would decide to switch to TCF pulp, the information presented above, in particular regarding economic impacts expected would be useful to anticipate the possible costs associated. Costs associated with the removal or substitution of wetness indicators and the removal or substitution of pigments: the Dossier Submitter does not have information allowing to confirm and quantify any loss in profit consecutively to removal of	The costs associated to the measures that are already implemented to reduce contamination are not attributable to this restriction and are already borne by companies. Due to these uncertainties, the costs associated with industry reactions presented in the proposal are not considered as an actual estimate of the expected costs of the restriction proposal but are provided as an indication of possible economic impacts industry would cope with in case of a restriction and depending on the technical solutions companies would opt for to make their finished products compliant.

	these materials. Industry consulted did not provide any marketing or economic evidence to prove such a loss. It is thus considered as highly uncertain. Moreover, it may be expected that removing these materials from their products would represent cost savings for manufacturers due to fewer materials to purchase and process. Costs associated to further air decontamination: The Dossier Submitter does not have further information allowing for a quantification or specification of these costs. Should implementing further filtration would imply to re-invest in total different air decontamination systems or simply to adjust the system on the spot is uncertain. Nevertheless, this technical measure does not seem to be the most relevant to achieve the decontamination goals set by the restriction proposal due to good and best practice being in principle already in place in manufacturing sites.	
Economic Impacts/testing and enforcement Costs	From the publication of Anses 2019 and French RMOA reports, companies on the single-use diapers market state that they have already started to implement more regular and stricter testing and controls of their raw materials, their finished products and their production lines (additionnally to the tests they already performed beforehand). Whether part of the testing costs reported in the restriction proposal are already borne and internalized by companies (driven by the publication of Anses's risk assessment and the French RMOA) or whether whole or part of them are only attributable to this restriction remains unclear. Due to the lack of harmonized analytical methods and the challenges of measuring very low concentration limits such as proposed herein (lower than the current LoD/LoQ) (see Annex E8), the testing costs may be actually somehow higher than reported during the consultation by the Dossier Submitter. This is a source of uncertainty.	If some part of the testing costs reported in the restriction proposal are already borne and internalized by companies, the impacts may be lower than reported and not entirely attributable to this restriction. As a consequence, the actual costs attributed to the restriction are difficult to estimate. If the transitional period of 24 months recommended would allow to implement a harmonized analytical method with very low LoD, this issue may be solved.

	Regarding enforcement costs for authorities, they are somehow uncertain. Whether these costs will converge to the ECHA's average estimate of 55,600€ enforcement costs per restriction per year in total or whether the costs would be higher remains uncertain. There may be some economies of scale in testing practices and costs in connection with the restriction on skin sensitizing substances in textile, leather, furs and hides. However, here again there may be extra-costs due to the lack of harmonized analytical methods and the challenges of measuring very low concentration limits such as proposed herein (lower than the current LoD/LoQ).	Here again, if the transitional period of 24 months recommended would allow to implement a harmonized analytical method with very low LoD, this issue may be solved.
Economic Impacts/Consumers	Industry claims between +2% and 10% of price increase at point of sale as a consequence of this restriction. This expected price increase has been indicated as a rough estimate by industry without evidence. The Dossier Submitter does not have further information to challenge this price increase estimated by industry and considers it as largely uncertain. Moreover, this increase incurred per baby diaper (if any) is considered overall low and affordable by the Dossier Submitter. This conclusion is strenghtened by competition considerations since competition on diapers market is fierce and largely driven by price. Therefore, the restriction is considered affordable for consumers.	If a price increase would actually occur at point of sale, the low-income families would be more impacted than others. Nevertheless, if the whole diapering period is taken into account, as the number of diapers used decrease while babies grow, the price increase burden would be higher for families of newborns in the very first months after birth, then it would be much lower. In any case, any price increase would only be temporarily borne by consumers since after 3 years old, most kids stop wearing diapers.
Human health impact assessment	The human health impact assessment has not been quantified and monetarized due to uncertainties (no prevalence/incidence data, all DNEL/DMEL used in the risk assessment were derived based on oral route studies, dose-response relationships available for some substances in the scope only built on animal studies, etc.). Although the benefits could not be quantified, a break-even analysis was performed by the Dossier Submitter to evaluate proportionality of the proposal.	These uncertaineies did not allow assessing actual human health impacts and disease burden associated with chemicals contained in single-use baby diapers. The human health benefits expected from this restriction have thus been analysed qualitatively. Nevertheless, the Dossier Submitter considers that this qualitative analysis still demonstrates that the benefits for babies' health would be significant by protecting 14 million babies in Europe from being exposed to hazardous chemicals from their diapers.

Analytical feasibility	No harmonized test method is available for now.	The potential consequence is that enforceability may be difficult.

Annex G: Stakeholder information

This annex aims at transparently documenting the consultations of stakeholders that have been carried out for the elaboration of this restriction proposal and how their views have been taken into account.

The current proposal is targeted at restricting chemical substances that may be present in single-use baby diapers at point of sale. To gather information on the substances in the scope and to understand their purpose in the applications relevant for the scope, ECHA launched a call for comments and evidence. During the preparation of this restriction proposal, stakeholders were also consulted directly by the Dossier Submitter by e-mails or telephone calls. More information on these activities are presented below.

Call for comments and evidence

Between 15 January and 15 April 2020 ECHA hosted a call for comments and evidence on their website to allow interested parties to signal their interest and express their views and concerns on the restriction. Specific questions asked in the call concerned information on use of formaldehyde, dioxins, furans, DL-PCBs and PAHs by ANSES to understand their uses in the diaper supply chain, if they may remain in the finished articles, human health exposure data, potential alternatives available, and relevant socio-economic information for the preparation of this Annex XV restriction proposal. The background note for the call is available at: https://echa.europa.eu/fr/previous-calls-for-comments-and-evidence/-/substance-rev/24701/term

In total, 20 comments were received from individual companies as well as industry and trade associations. The information received has been included to the extent applicable and relevant in this report. For confidentiality reasons, the name of individual companies providing information as part of the call for evidence has not been identified.

Direct consultation with stakeholders

Many stakeholders were also consulted directly by the Dossier Submitter during the preparation of this restriction proposal. The contacts are listed in the table below.

Table 86 : List of Stakeholders consulted by the Dossier Submitter in the preparation of the restriction proposal

Name	**Type of organisation** Company/association/national authority/regional or local authority/Laboratory/Academic institution	**Response received** Yes/no	**Mode of contact** E-mail/phone call/Personal communication/etc
Confidential[58]	Manufacturer of raw materials	Yes	E-mail

[58] Due to confidentiality reasons, the name of the companies consulted can't be revealed. The name of these companies were obtained through the DGCCRF, which is the French General Directorate for Competition Policy, Consumer Affairs and Fraud Control

	Manufacturer of diapers	Yes	E-mail
	Distributor of diapers	Yes	E-mail
EDANA	Association	Yes	E-mail
Group'Hygiene	Association	Yes	E-mail

Annex H: Key elements underpinning the RAC conclusions on information on hazards

RAC Box:

This section provides the key elements underpinning the RAC conclusions on hazards referenced in the RAC opinion.

Formaldehyde

Although formaldehyde is classified for mutagenicity and carcinogenicity, these effects were not seen as critical in the Dossier Submitter's assessment. Since the data on sub-chronic or chronic toxicity of formaldehyde following dermal exposure is limited, the Dossier Submitter chose an oral chronic HRV based on histological changes in the stomach (hyperplasia, hyperkeratosis, ulceration, chronic gastritis) and renal papillary necrosis in male rats exposed to 82 mg/kg bw/day for 2 years via drinking water (Til et al., 1989). At this dose level decreased food and liquid intake, and decreased body weight gain were observed. Applying a factor of 10 for interspecies variability and a factor of 10 for interindividual variability to the NOAEL of 15 mg/kg bw/day, a toxicity reference value (TRV) of 0.15 mg/kg bw/day is derived (or 2.6 mg/L drinking water). Four organisations proposed chronic threshold TRVs based on the same critical effect, the same key study and the same uncertainty factors: ECHA (2017; in the assessment of formaldehyde as a biocidal substance), the US EPA (1990), Health Canada (2001), WHO/IPCS (2005) and ATSDR (1999). It should be noted, therefore, that all these TRVs were based on systemic effects following oral exposure, which in the case of formaldehyde are not as relevant as local skin effects, i.e. skin sensitisation.

On the estimated TRV of 0.15 mg/kg bw/day, the Dossier Submitter applied a factor of 0.5 (based on experimental data on formaldehyde toxicokinetics) to correct for oral bioavailability. The resulting chronic **internal DNEL of 0.075 mg/kg/day** for the general population was, thus, derived. The Dossier Submitter considers that the selected HRV is applicable to children between birth and three years of life and points out that studies during gestation were taken into account by WHO/IPCS in 2005 for the establishment of the TRV.

RAC agrees with the Dossier Submitter to consider the non-mutagenic and non-carcinogenic toxic effects as a point of departure. Namely, as concluded previously by RAC (2012; 2020), formaldehyde is a mutagen and (local) carcinogen, inducing tumours at the site-of-contact after inhalation (nasal tissue) but not at distant sites, and there is no convincing evidence of formaldehyde-induced carcinogenic effects at distant sites or via routes of exposure other than inhalation. Regarding mutagenicity, DNA-protein crosslinks (DPX) are eliminated by spontaneous hydrolysis and/or other DNA repair mechanisms and do not accumulate during prolonged exposure to formaldehyde. Additionally, adduct formation was generally shown to be formaldehyde concentration dependent (RAC, 2020).

The TRV used by the Dossier Submitter covers two types of critical effects: one is local (at the site of first contact, i.e., histological changes in the stomach[59]) and the second one is

[59] The histopathological changes in stomach included papillary epithelial hyperplasia in the forestomach, frequently accompanied by hyperkeratosis located on the limiting ridge or in its vicinity, and focal

systemic (renal effect[60]), and they were observed at the same oral dose level (82 mg/kg bw/day) in Til et al. (1989) study. It is unclear if the systemic effects are primary, i.e., directly resulting from formaldehyde or its metabolites, or secondary to local lesions and inflammatory reactions (ECHA, 2019). The Dossier Submitter decided to derive a systemic reference dose to protect from potential internal effects following prolonged exposure to low concentrations of the active substance. Whereas renal effects are systemic effects which may not be solely as a consequence of local effects, the Dossier Submitter choose to derive an internal DNEL as a conservative approach to assessing the risk.

RAC agrees with the Dossier Submitter that the local effects observed after oral exposure are of questionable relevance for this restriction proposal, considering that dermal route is a relevant exposure route in the restriction's exposure scenario. This is in line with ECHA Guidance (2012) which states that "for DNELs covering local inhalation and local dermal effects route-specific data need to be available". If oral data are selected for deriving internal DNEL, an emphasis should be put on systemic effects induced by exposure to formaldehyde (e.g., nephrotoxicity), noting that there is an uncertainty whether these effects are just a consequence of local effects. Namely, it is unclear, whether formaldehyde induces primary systemic effects in mammals. Formaldehyde is not classified for STOT RE (or STOT SE). As stated in the Annex B.5.3.6. of the Background Document, in experimental studies, formaldehyde induced toxic effects only at the site of first contact after oral or dermal exposure, and general signs of toxicity occurred secondary to these local lesions. No systemic toxicity was observed following repeated exposure to formaldehyde in animals and humans according to NICNAS (2006), and renal toxicity is not unequivocally recognised in humans or in animal studies (ATSDR, 1999; Gelbke et al., 2019)[61].

---

ulcerations; chronic atrophic gastritis in the glandular stomach, in some cases with inflammatory process involving the entire mucosa, and with ulceration. In some rats, bulky plugs of necrotic tissue, inflammatory exudate, mucus and feed particles were seen attached to the damaged mucosa.

[60] The study authors relate decreased food intake and, consequent, decreased body weight gain in top dose animals, to rejection of the drinking water solution (bad palatalability due to high formaldehyde concentration in the solution).

[61] Renal effects have been observed in repeated toxicity studies performed by Til et al. (1988, 1989), and also, at very high dose (5000 mg/L drinking water) in rats in Tobe et al. study (1989). Also, some more recently published studies (which quality, however, has not (yet) been assessed) found renal toxicity following exposure to formaldehyde via oral (Bansal and Uppal, 2011), inhalation (Ramos et al., 2017) or intraperitoneal route (Bakar et al., 2015; Morsy, 2018) in rats and rabbits.
Regarding human data, four cases of nephrotic syndrome after exposure to toxic concentrations of formaldehyde in newly built homes were reported (Breysse et al, 1994). However, the authors found that these patients shared a particular HLA type on the major histocompatibility complex and speculated that the patients were genetically susceptible to "triggering" of immune reactions by formaldehyde exposure. This has not been confirmed by other studies (Formaldehyde. Micromedex, IBM Corporation 2021; Breysse et al, 1994).
Gelbke and co-workers (2019), who performed an assessment of safe exposure levels for potential migration of formaldehyde into food, consider that available literature indicates that formaldehyde could be nephrotoxic. As a potential mechanism, sustained metabolic acidosis produced by formic acid (the first-step metabolite in formaldehyde metabolism), has been proposed (Gelbke et al., 2019). The authors' position is that "as potential long-term consequences of mild, non-life threatening chronic acidosis are unknown and determination of blood pH does not belong to the standard toxicological repertoire, a conservative derivation of safe exposure levels has to consider such a possibility".

In ECHA's assessment of formaldehyde as a biocidal substance (under Regulation (EU) No 528/2012) (ECHA, 2017), it was considered that the submitted repeated dose studies had deficiencies in reporting with respect to organs other than those that come into direct contact with formaldehyde. These deficiencies severely constrained any independent evaluation of systemic toxicity of formaldehyde after repeated administration. It remained unclear if any systemic effect was primary, i.e., directly resulting from formaldehyde or its metabolites, or secondary to local lesions and inflammatory reactions. This uncertainty was reflected by derivation of a systemic reference dose to protect from potential internal effects following prolonged exposure to low concentrations of the active substance. It was considered that the overall NOAEL of 15 mg/kg bw/day for subacute, subchronic and chronic oral exposure based on stomach lesions, renal papillary necrosis and reduced body weight gain observed in rats in the Til et al. study (1989), provides the relevant starting point for derivation of oral and systemic reference doses, regarding dietary exposure to formaldehyde. By setting a default assessment factor of 100 and considering an oral absorption of 100%, a value of 0.15 mg/kg bw/day was defined for acute, medium-term and long-term Acceptable Exposure Level (ECHA, 2017). However, it was also pointed out that "due to the high reactivity of formaldehyde, local effects dominate the toxicity profile of the substance" and that "irritation of the skin and sensitisation were observed following dermal administration of doses considerably lower than the oral NOAEL forming the basis for the Systemic Reference Dose". This has been also pointed out in ECHA's assessment of worker exposure to formaldehyde and formaldehyde releasers, as well as the fact that formaldehyde is an endogenous substance at relatively high concentrations (i.e., about 2.6 mg/L in the blood; total body content of 1.82 mg/kg bw) (ECHA, 2019c; EFSA, 2014).

It should be also noted that toxicokinetic differences between oral and dermal exposure route are unclear but could be significant regarding quantitative differences in formaldehyde-metabolising enzymes (e.g., formaldehyde dehydrogenase, "The Human Protein Atlas" https://www.proteinatlas.org/ENSG00000197894-ADH5/tissue).

To conclude, it is considered that for formaldehyde, local effects (i.e., skin sensitisation), are more relevant than systemic effects for this restriction proposal. Namely, due to formaldehyde's high reactivity at the site of first contact, local effects dominate the toxicity profile of the substance, and skin irritation and sensitisation were observed following dermal administration of doses considerably lower than the oral NOAEL.

PAHs

Although some PAHs (primarily those with a low molecular weight) induce systemic non-carcinogenic threshold effects (mainly kidney, liver and blood disorders) for which HRVs have been established, the Dossier Submitter chose carcinogenicity as a critical effect for PAHs: eight out of 17 PAHs included in the scope of the Annex XV dossier are classified as category 1B (H350) carcinogens; many PAHs share the same genotoxic mechanism of action; and carcinogenicity was chosen as a critical effect in the Annex XV dossier on PAH in granules and mulches used in synthetic turf pitches (ECHA, 2019) as well as in the Annex XV dossier for eight PAHs in consumer articles (BAuA, 2010).

Considering the dermal route as the relevant route for this restriction proposal, and that carcinogenicity data on PAHs following dermal exposure are available, the Dossier Submitter decided to derive a DMEL based on dermal carcinogenicity data.

Several dermal DMELs or cancer slopes built on animal data have been derived by regulatory bodies or are available in the open literature (Sullivan et al., 1991, cited by Knafla et al., 2011; LaGoy and Quirck, 1994; Hussain et al., 1998; Knafla et al., 2006; Knafla et al., 2011; BAuA, 2010; ECHA 2018). Considering the unit of the slope factor (per surface of treated area) and the exposure data available, the Dossier Submitter considered that slope factors derived by Sullivan et al. (1991), Laroy and Quirck (1994) and Knafla et al. (2011; which was used to establish a dose-response relationship for the carcinogenicity of CTPHT, ECHA, 2018b) were not appropriate for use in this restriction proposal. The Dossier Submitter also did not choose the slope factor derived by Hussain et al. (1998) because of the lack of information on the method of derivation.

The Dossier Submitter, therefore, decided to calculate two DMELs, at a 10^{-6} risk level, from the following reports/studies:

- **DMEL of 4 pg/kg bw/day** for **PAHs mixture**, based on dermal studies (Schmähl et al., 1977; Fhl, 1997) assessed by **BAuA (2010)**, in which BaP was applied as a component of PAHs mixture (most conservative DMEL of the range);
- **DMEL of 6 pg/kg bw/day** for **BaP alone**, derived from **Knafla et al. (2006)**, in which only BaP was dermally applied.

In the restriction of PAHs in consumer products, BAuA (2010; restriction entry 50 of Annex XVII to REACH: Polycyclic aromatic hydrocarbons in articles supplied to the general public) derived several dermal DMELs for BaP using T25 or BMD calculations. Only the studies in which BaP was administered as the component of a mixture of PAHs were used. For each of the selected studies (where appropriate) T25, BMD_{10}, and $BMDL_{10}$ estimates were used as dose descriptors, and DMELs were calculated applying both the 'Large Assessment Factor' and the 'Linearised' approach (the latter at both the 10^{-5} and 10^{-6} risk levels and using the 'Probit' as well as the 'Multistage Cancer' algorithms for curve fitting). BAuA (2010) noted that the Multistage Cancer model is the approach recommended by the REACH IR/CSA guidance, and excluded from further calculations the very low values obtained by the Probit approach. When only dermal studies were considered, the following DMEL ranges for PAHs mixture were derived by BAuA:

- range for linearised approach, 10^{-5} risk level: 35 – 115 pg/kg bw/day;
- range for linearised approach, 10^{-6} risk level: 4 - 12 pg/kg bw/day;
- range for large assessment factor: 99 – 323 pg/kg bw/day.

The Dossier Submitter choose the BMD approach because this approach is based on modelling of the experimental data considering all available information on the dose response curve whereas T25 is calculated from one data point on the dose-response curve. The Dossier Submitter choose BMDL as the dose descriptor because it is the lowest statistically significantly increased incidence that can be measured in most studies and would normally require little or no extrapolation outside the observed experimental data.

Knafla et al. (2006) proposed a dermal slope factor of 25 cases per mg/kg bw/day for BaP, based on seven relevant dermal carcinogenesis animal studies (studies based on a two-stage model of carcinogenesis, i.e., initiation–promotion, were not considered). This cancer slope factor was developed using the benchmark dose approach and the linearised multistage model. An average dermal cancer slope factor of 0.55 cases per µg/animal/day was then converted to a dose-equivalent slope factor of 25 cases per mg/kg bw/day, based on an adult mouse body weight of 45 g.

In order to derive a DMEL, both in BAuA (2010) calculations and in case of Knafla et al. (2006) slope factor, allometric scaling factor (7 for mice) was applied, as well as a bioavailability factor in order to account for the assumption of 50% absorption across all routes in animal experiments using organic solvents as vehicle *vs.* 20% absorption in the human exposure situation (dermal absorption from a sweat matrix). Since a linearised approach was applied (with a standard high-to-low extrapolation factor), no additional assessment factors were used, in line with ECHA Guidance (ECHA, 2012).

The toxicity of other PAH substances was estimated based on toxic equivalency factors (TEFs).

RAC agrees with the Dossier Submitter's DMEL derivation but regarding the use of TEFs notes that either the EFSA PAH8 or the REACH-8 PAHs approach would have been preferred to be in line with previous restrictions.

In the available animal studies with dermal exposure to PAHs, systemic tumours were not investigated, so the potential for induction via the dermal route could not be adequately assessed. Nevertheless, as stated in ECHA 2018b, "based on current knowledge dermal exposure in humans is related with cancers in areas of first contact with the body and its effect is rather local than systemic", and "limited evidence exists that PAHs may induce tumours at sites other than at the site of application, i.e., other than respiratory tract cancers after inhalation exposure or skin cancers after dermal exposure". RAC also notes that since the DMELs derived by the Dossier Submitter are two orders of magnitude lower than DMELs derived from oral studies using the same approach (i.e., Multistage Cancer modelling, linearised approach, 10^{-6} risk level) (BAuA, 2010; US EPA, 2017), they are expected to also be protective of the potential risk of systemic tumour development in dermally exposed individuals.

PCDD/Fs and PCBs (DL-PCBs and NDL-PCBs)

These substances have no harmonised classification in the EU presently, but TCDD was classified as reprotoxic category 1B by the Chemical Management Center of Japan National Institute of Technology and Evaluation. Some of these substances are self-classified in the EU (predominantly for repeated toxicity). The hazards and risks they pose to human and animal health were reviewed within various risk assessment frameworks and by various international committees (ATSDR, 1998; ATSDR, 2000; ATSDR, 2004 cited in Danish EPA, 2014; Danish EPA, 2014; DGS, 1998; EFSA, 2018; IARC, 1997, 2016; INERIS, 2006; INRS, 2007, 2016; INSERM, 2000; OSAV, 2016; US EPA, 1992; WHO, 2016).

There are no available dermal HRVs derived by any EU or non-EU regulatory bodies. Data on chronic and sub-chronic dermal toxicity in animals exist, but they would first require a thorough analysis in order to decide whether they are appropriate enough for deriving a dermal DNEL.

Since PCDD/Fs and DL-PCBs have similar hazard profile (including hepatotoxicity, epithelial effects, immunotoxicity, reproductive toxicity), the Dossier Submitter decided to select the same critical effect for these substances.

Although several organisations proposed non-threshold oral HRVs for these substances (based on carcinogenicity, i.e., liver tumours), the Dossier Submitter decided to use a chronic threshold HRV. Namely, carcinogenic effects of PCDD/Fs and DL-PCBs are considered to have thresholds, since they are not linked to mutagenic effect or to DNA binding. Also, carcinogenic effects of dioxins/DL-PCBs are observed at higher doses than for other toxic effects (IARC, 2012).

A number of chronic HRVs for dioxins, furans, and DL-PCBs, or only for the most hazardous substance in this class, 2,3,7,8-TCDD, were derived (Table 47 in Annex B.5.12.12.1). All these HRVs, except that of the US EPA and EFSA values, were based on animal studies. Only EFSA's and the US EPA HRVs are based on epidemiological data. The Dossier Submitter considers that in line with ECHA Guidance (Chapter R.8; ECHA, 2012), epidemiological data should be favoured over animal data, and proposes to use EFSA's HRV since it is more recent (from 2018), and it is described clearly and transparently.

EFSA's CONTAM Panel reviewed the data from experimental animal and epidemiological studies and decided to base the human risk assessment on effects observed in humans and to use animal data as supportive evidence. The critical effect observed in human and animal data was on semen quality, following pre- and postnatal exposure. The strongest associations were between the exposure to TCDD during infancy/prepuberty and impaired semen quality, observed in the Seveso population (Mocarelli et al., 2008, 2011) and in the Russian Children's Study (Minguez-Alarcon et al., 2017). The CONTAM Panel selected the Russian Children's Study as a critical study[62].

The Russian Children's Study is a cohort study in 516 boys who were enrolled at age 8 to 9 years and followed for up to 10 years. At 18 to 19 years, 133 young men provided 1 or 2 semen samples, which were analysed for volume, sperm concentration and motility. The results showed that higher quartiles of TCDD and PCDD TEQs were associated with lower sperm concentration, total sperm count, and total motile sperm count (p-trends ≤ 0.05 in linear mixed models), compared with the lowest quartile. Similar associations were observed for serum PCDD TEQs with semen parameters. Although there was no significant association between NDL-PCBs and semen parameters, the association between TCDD and semen parameters became slightly stronger after adjustment for NDL-PCBs. Serum PCBs, furans, and total TEQs were not associated with semen parameters.

NOAEL of 7.0 pg WHO_{2005}-TEQ/g fat in blood sampled at age 9 years based on PCDD/F-WHO_{2005}-TEQs was defined, as median serum level for the sum of PCDD/F- WHO_{2005}-TEQ in the lowest quartile (at which sperm parameters were within the reference range). Using

[62] Contrary to the Seveso studies, in the Russian Children's Study also other PCDD/Fs and DL-PCBs were analysed. Concentrations of TCDD were much lower in the Russian Children's Study than those in the Seveso study. The effects on semen parameters were observed at much lower TCDD levels in the Russian study compared to the Seveso Cohort study. TEQs in Seveso had to be estimated from other studies. In contrast to the two Seveso studies, the Russian Children's Study included two semen samples for most participants. The Russian Children's Study had the advantage of a very narrow age range (18 to 19 years), while the Seveso studies had a broader age range, and the analyses had to be adjusted for age. The reference group in Seveso study (healthy blood donors) may in some respects are not directly comparable with the men from Seveso. In the Seveso studies, semen was collected at home, while in the Russian Children's Study semen was collected in the laboratory.

toxicokinetic modelling and considering the exposure from breastfeeding and a twofold higher intake during childhood, the CONTAM Panel established a **TWI** of 2 pg WHO_{2005}-TEQ/kg bw/week (**0.3 pg** WHO_{2005}-TEQ**/kg bw/day**). Although this TWI is based on findings on PCDD/F-WHO_{2005}-TEQ only, the CONTAM Panel concluded that the TWI should apply to the sum of PCDD/Fs and DL-PCBs.

Among available studies on oral absorption of PCDD/Fs and PCBs, the Dossier Submitter selected an oral absorption fraction based on McLachlan (1993) study, rounded to 100%. In this study more than 90% absorption rates were found for TCDD, penta- (2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD) and hexa-substituted congeners (1,2,3,4,7,8- HxCDF, 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD) in a nursing infant, by determining 12-day mass balance (the difference between the total intake with breast milk and the excretion in the faeces present in the mother's milk). This value is almost identical to 97% oral absorption used in the calculations of EFSA CONTAM Panel. **Internal DNEL**, therefore, remained identical to DNEL of **0.3 pg_{TEQ}/kg bw/day**.

The Dossier Submitter decided to use TEQ concept for PCDD/Fs and DL-PCBs, based on different toxic equivalency factors (TEFs), with "Seveso" dioxin (2,3,7,8-TCDD), as the most toxic congener, assigned a value of 1. TEF values have been defined in 1998 and revised in 2005 by the WHO for PCDD/Fs and PCB-DL (Van den Berg et al., 2006). The Dossier Submitter retained the values of TEF from WHO 2005 (Figure 16 in the Annex B.5.12.12.3.). RAC notes that uncertainties related to TEF concept are identified by EFSA (please see below).

EFSA's HRV is considered applicable to children between the ages of zero and three years since the modelling considered the much higher exposure during infancy from both breast milk and food. Also, according to the CONTAM Panel, derived TWI should be protective towards all endpoints identified by the CONTAM Panel assessment (other reprotoxic effects and higher TSH levels in new-borns).

RAC notes that the data on dermal toxicity of PCDD/Fs and DL-PCBs is rather limited. Therefore, **RAC concurs with the Dossier Submitter's approach to derive internal DNEL based on an epidemiological study in Russian children** (Minguez-Alarcon et al., 2017), in which the primary source of exposure to PCDD/Fs and DL-PCBs was diet, with dermal absorption, inhalation, and hand-to-mouth transfer from contaminated dust and soil as additional exposure routes (Burns et al., 2009).

The uncertainties are well analysed and described in the EFSA report (EFSA, 2018). Some of the uncertainties are around:

- the use of WHO2005-TEFs for all species;
- the studies indicate that the current TEFs require re-evaluation; in particular, PCB-126, which contributes most to the DL-PCB-TEQ level, may be less potent in humans than indicated by the TEF-value of 0.1;
- true exposure in epidemiological study being higher or lower than the estimate of exposure;
- true outcome in epidemiological study more or less prevalent than the estimate of the outcome;
- confounding by other factors;
- low number of epidemiological studies on the critical endpoint at low exposure;
- exposure to other compounds which may impair semen quality;

- uncertainty regarding critical window for effect on semen quality outcome.

Additionally, as pointed out by the authors of the Russian Children's Study, the boy's median serum total TEQ concentrations were relatively high compared to data from the US and Germany, which makes it difficult to investigate the effects of very low exposures.

RAC agrees with the Dossier Submitter that the study is well conducted and reported, with transparent methodology of HRV derivation. The uncertainties are, however, substantial, and although their magnitude cannot be defined, they are expected to lead to a lower (i.e., overprotective) DNEL than necessary.

Total PCBs (DL- and NDL-PCBs)

As stated in the previous section above (3.1.1), the NDL-PCBs have different toxicological activity compared with the DL-PCBs and PCDDs/PCDFs, so the Dossier Submitter considered that a DNEL for total PCBs cannot be the same as the one derived for PCDD/Fs and DL-PCBs.

The Dossier Submitter presented the HRVs for PCBs developed by several international regulatory bodies (Health Canada, RIVM, WHO, ATSDR, US EPA), with values ranging from 0.01 to 0.13 µg/kg bw/day (Annex B.5.12.12.1). Three organisations proposed the same chronic threshold TRV of 0.02 µg/kg/day for PCBs, based on the same critical effect and the same key study: ATSDR (2000), RIVM (2001) and WHO (2003). Only the choice of assessment factors differed between these three organisations (more details are in the Annex B.5.12.12.1). The Dossier Submitter adopted this HRV (0.02 µg/kg/day) since it was established in accordance with high quality standards and considered a set of consistent studies. This HRV is considered applicable to children between the ages of zero and three years.

Applying the same oral absorption factor of 100% as the one used for PCDD/Fs/DL-PCBs, **internal DNEL of 0.02 µg/kg/day** has been derived.

Since in deriving this HRV, it was considered that the limitations of human studies (limited exposure data; inconsistency among some results; the presence of confounding factors, such as co-exposure to dioxins) make it impossible to use them as a basis for quantitative risk estimation, animal data were used for the risk characterisation. Tryphonas et al. (1989, 1991) studies were chosen as critical studies since they were long-term studies (5 years); relatively large number of animals was used (13 to 16 monkeys per group); monkey is a good model for humans; and experimental design and data analysis were good. Female *Rhesus* monkeys receiving daily doses of Aroclor 1254 for several months showed a dose-related increase in liver weight and decreases in the IgG and IgM immunoglobulin response to a sheep red blood cell challenge. No NOAEL was found so the lowest dose studied, 5 µg/kg bw/day, was identified as the LOAEL. Using an uncertainty factor of 300 (factor of 3 for interspecies variation, 10 for intraspecies variation, and 10 for extrapolation from a LOAEL to a NAEL), a **TDI of 0.02 µg/kg bw/day** was derived for mixtures of PCBs. Slight changes in neurobehavioral tests observed at 7.5 µg/kg bw/day (the only dose level tested) in developmental neurotoxicity study in *Cynomolgus* monkeys (Rice and Hayward, 1997), support this TDI, especially for infants[63].

No OECD or EU test method is currently available to investigate immunotoxicity. In Chapter R.8; ECHA (2012) it is stated that the "Health Effects Test Guidelines OPPTS 870.7800 Immunotoxicity" can be referred to. Tryphonas et al. (1989, 1991) studies methodologically deviate from this Guideline (e.g., method of IgM analysis[64]). Nevertheless, the tested outcome (T-cell-dependent antibody response in a form of antibody production against sheep red blood cells, SRBC) is a well-known model in immunotoxicity assessment, including non-human primates (Lebrec et al., 2011), and "became the cornerstone of recent guidelines for assessing the potential immunotoxicity of xenobiotics" (Ladics, 2007). Immunological changes were also observed in human populations exposed to PCBs and manifested as increased infection rates and changes in circulating lymphocyte populations (WHO, 2003).

The assessment factor of 3 for interspecies variation is based on observations from an oral Aroclor study, which confirmed non-human primates as among the most sensitive species (WHO, 2003). This factor is supported by allometric scaling factor of 2 for Rhesus monkeys (Chapter R.8; ECHA, 2012).

For LOAEL to NAEL extrapolation, an assessment factor of 10 was used (no explanation is provided in WHO 2003 document why a maximum value of 10 was selected). Although the Benchmark dose (BMD) approach, which is preferred over the LOAEL-NAEL extrapolation by ECHA Guidance (2012), was not used, RAC considers that factor of 10 is justified, considering a shape of the dose-response curve (i.e., very steep at lower doses, Figure 1).

[63] The PCB mixture given to the monkeys in this study was engineered to mimic the congener pattern in mother's milk.

[64] In Tryphonas et al. (1989, 1991) studies, serum dilutions were reacted with SRBC in the microplate haemolytic complement assay. Titers (IgM) were expressed as the reciprocal of the highest serum dilution showing a 50% haemolysis. On the other hand, in this type of test, anti-SRBC plaque-forming cell (PFC) assay or enzyme-linked immunosorbent assay (ELISA) are usually performed, to determine the effects of the test substance on either splenic IgM PFC response, or serum IgM levels (Health Effects Test Guidelines OPPTS 870.7800; Lebrec et al., 2011; Ladics, 2007).

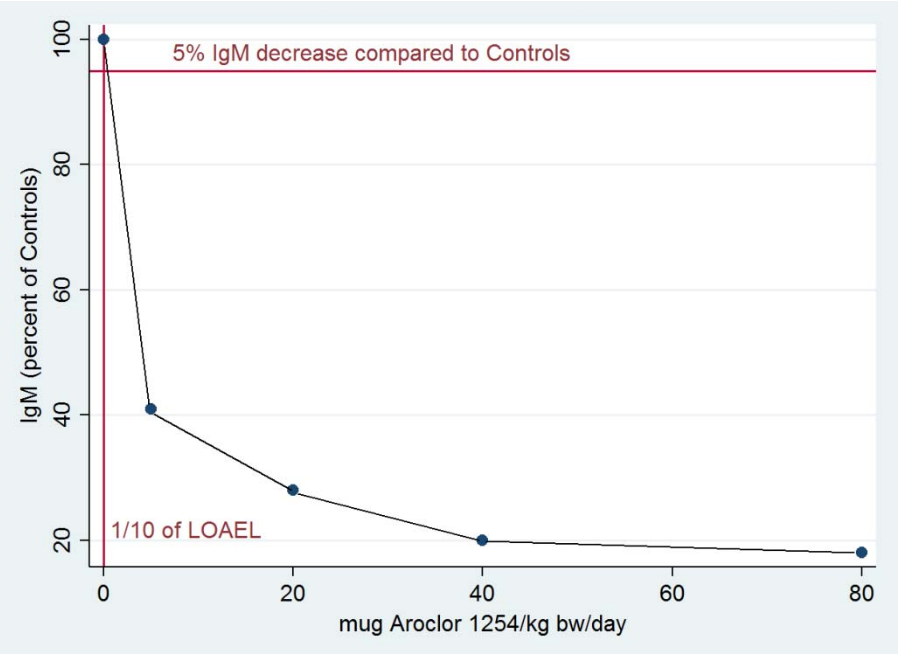


Figure 1: Dose-response curve for anti-sheep red blood cells IgM changes following oral exposure to Aroclor 1254 in monkeys in Tryphonas et al. (1991) study

IgM values are presented as percent of control values, averaged for four assessment periods (once a week during 4-week period following secondary immunisation with SRBC injected on 55th month of the study). **5% IgM decrease compared to Control** corresponds to BMD5, proposed to be comparable to a NOAEL (ECHA Guideline, 2012). **1/10 of LOAEL** represents a value of LOAEL (5 µg/kg bw/day) on which assessment factor of 10 (for LOAEL to NAEL extrapolation) has been applied. As stated in WHO (2003) report, the health risk assessment is based on studies using a limited set of PCB mixtures, mostly Aroclors 1242 and 1254, so when the pattern of PCB congeners is different from the commercial mixtures, another approach could be preferable. RAC notes, however, that NDL-PCBs have not been analysed in diapers, so the pattern of congeners is unknown.

RAC concurs with the Dossier Submitter’s approach to deriving a DNEL for this group.

Annex I: Break-even analysis

SEAC Box:

This section provides the break-even analysis referenced in the opinion of SEAC.

During the opinion-development, the Dossier Submitter carried out a break-even analysis to get a better understanding of the proportionality of the proposed restriction. The analysis aims at illustrating and putting into perspective the health benefits that would be required for the proposal to break even, i.e. to generate benefits that are greater than or equal to costs.

The break-even analysis uses avoided skin cancer cases as a proxy for benefits, considering the other endpoints are too uncertain and vague to be "translated" into precise and valuable diseases. The break-even analysis was performed on the total costs, which implies the costs of changing from ECF to TCF pulp, testing costs and enforcement costs, as these costs are the only ones that have been estimated. Therefore, the break-even analysis does not fully account for the expected benefits and economic impacts of the restriction proposal, but only a part of them. The costs used here are the total annualized costs, over a 10-year period. The column named "Break-even" stands for: Number of skin cancer cases to be avoided each year to break even.

Table 1 Break-even analysis

	Annualized costs	Value of an avoided skin cancer case	Break-even	Number of EU population exposed (in Million)	Skin cancer incidence among exposed babies (cases per Million)	Actual skin cancers incidence rate according to GDP	Actual skin cancers incidence rate converted to in 1 Million, based on EU 27 (447 M people)	Break-even analysis incidence compared to actual incidence (%)
Min	≈€6 000 000	€121 567	49	14.5	3.4	429 837	962	0.4%
Mean	≈€50 000 000	€143 375	349	14.5	24.1	534 018	1 195	2.0%
max	≈€100 000 000	€158 745	630	14.5	43.4	628 967	1 407	3.1%

The Dossier Submitter finds that between 49 and 630 cancer cases would have to be avoided each year for the restriction proposal to break even. The Dossier Submitter has then calculated the incidence per million that is needed for the proposal to break even and compared this to the actual incidence of skin cancer in Europe. The Dossier Submitter concludes that one would need to see a reduction in the actual incidence of 0.4% for the low-cost scenario, 2.0% for the central scenario and 3.1% for the high scenario.

Given the lack of epidemiological data, SEAC considers that in general a break-even analysis could be helpful for considering the proportionality of the proposed restriction. Knowing how many cancer cases would have to be prevented by the implementation of the restriction, for the benefits to be equal to or higher than the costs, could underpin the conclusions on proportionality by considering the likelihood of this reduction in cancer cases actually occurring.

Nevertheless, SEAC does not consider the Dossier Submitter's break-even analysis useful in this case, as there are some very important uncertainties associated with it. In particular:

- The quantified costs used for the break-even analysis are very uncertain. As described in the earlier sections of this opinion, it is currently not fully understood what industry would need to do in order to comply with the proposed restriction and what the associated costs would be. The quantified costs only represent the costs related to switching from ECF to TCF pulp (which may not reduce furans and dioxins based on the available information), testing costs and enforcement costs. There may also be other costs that simply have not been quantified.

- The break-even analysis only focuses on one endpoint: carcinogenicity. SEAC understands why the Dossier Submitter has focused on carcinogenicity, but as there are several potential endpoints, and a lack of information on the relative importance of carcinogenicity compared to the other potential endpoints, it is difficult to draw conclusions from the break-even analysis on the question of proportionality.

- Causes of skin cancer:

    - There is no clear evidence that wearing of diapers could be a cause of skin cancer.

    - Latency has not been considered in the Dossier Submitter's analysis. Seeing as there are many compounding factors leading to skin cancer, it is not clear how exposure to the substances in scope in early life contributes to skin cancer later in life.

    - In the medical literature, it is stated that overexposure to sunlight is one of the major causes of skin cancer. According to WHO[65], experts believe that 4 of 5 skin cancer cases are caused by overexposure to sunlight.

SEAC notes that for all the different cost scenarios, the incidence of skin cancer in the EU is far higher than the incidence needed for the restriction proposal to break even in this analysis. Given that the "break-even analysis incidence" is within the actual incidence it is theoretically possible that the proposed restriction could break even.

In cases where the incidence rates needed for a restriction proposal to break even are far higher than the actual incidence rates, it is possible to draw the conclusion that the cases needed to break even are unlikely to be achieved. But when the situation is the opposite, and

[65] https://www.who.int/activities/raising-awareness-on-ultraviolet-radiation

the actual incidence rates are higher than the levels needed to break even, it is more difficult to draw clear conclusions.

In this specific case, it is uncertain if the costs used in the assessment are representative of the costs of the proposed restriction. Only one of the potential endpoints are used in the break-even analysis and it is unclear if it really is an endpoint, and what relative importance the potential endpoint has. Finally, one may ask whether it is relevant to look at the whole incidence rate of skin cancer, as a major fraction of the skin cancer cases probably is caused by overexposure to sunlight. Based on all these uncertainties, SEAC is not able to draw any conclusions on proportionality from the break-even analysis.

References

(BAuA), B. f. A. u. A. (2010). "Annex XV restriction report proposal for a restriction : benzo[a]pyrene, benzo[e]pyrene, benzo[a]anthracene, dibenzo[a,h]anthracene,benzo[b]fluoranthene,benzo[j]fluoranthene,chrysene."

Abdel-Rahman M, T. R., Skowronski G. (2010). "Effects of soil matrix and aging on the dermal bioavailability of hydrocarbons and metals in the soil : dermal bioavailability of soil contaminants." Dermal bioavailability of soil contaminants 13.

Abdel-Rahman, M. S., et al. (2002). "Assessment of the dermal bioavailability of soil-aged benzo(a)pyrene." Human and Ecological Risk Assessment 8(2): 429-441.

Abdel-Shafy, H. I. and M. S. M. Mansour (2016). "A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation." Egyptian Journal of Petroleum 25(1): 107-123.

ADEME (2012). "Impacts environnementaux des couches pour bébé. Les fiches techniques de l'ADEME. ." 3.

AFSSA (2005). "Dioxines, furanes et PCB de type dioxine : Evaluation de l'exposition de la population française." 57.

AFSSAPS (2010). "Recommandations relatives aux caractéristiques spécifiques à prendre en compte pour évaluer l'innocuité des produits cosmétiques destinés aux enfants de moins de trois ans.": 17.

AFSSE (2003). "Les dioxines dans l'environnement e tla santé." 13.

Agency, U. E. (2005a). "Life cycle assessment of disposable and reusable nappies in the UK. ." 203p.

Agency, U. E. (2005b). "Time to change ? A study of how parents and carers use disposable and reusable nappies." (Project record P1-487/PR): 68.

Agency, U. E. (2008). "Using the science to create a better place. An updated lifecycle assessment study for disposable and reusable nappies. ." (Science report – SC010018/SR2.): 37.

Alderfer.R., S. M., Fingerhut.M., Hornung.R., Wille.K., Fidler.A. (1992). "MEASURES OF DEPRESSED MOOD IN WORKERS EXPOSED TO 2,3,7,8-TETRACHLORODIBENZOP-DIOXIN (TCDD)." Chemosphere 25(1-2): 247-250.

Altarawneh, M., et al. (2009). "Mechanisms for formation, chlorination, dechlorination and destruction of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs)." Progress in Energy and Combustion Science 35(3): 245-274.

Anderson, Y. B., et al. (1993). "Maturational changes in dermal absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (tcdd) in fischer 344 rats." Toxicology and Applied Pharmacology 119(2): 214-220.

ANSES (2011). "CLH Report : Proposal For Harmonised Classification and Labelling : Formaldehyde." 194.

ANSES (2016). "Etude de l'alimentation totale infantile.".

ANSES (2017). "Avis de l'Anses relatif à une analyse de la meilleure option de gestion des risques professionnels générés par le formaldéhyde (n° CAS 50-00-0).".

ANSES (2017a). "Valeurs toxicologiques de réfence. Guide d'élaboration de l'Anses." 186.

ANSES (2017b). "Etude individuelle nationale des consommations alimentaires 3 (INCA 3)." 566.

ANSES (2019). "Anses revised opinion on the safety of baby diapers."

ANSES (2019b). "Draft analysis of the most appropriate regulatory management optio (RMOA) : HAzardous chemicals in single use baby diapers." 55.

ANSM (2010). "Recommandations relatives aux caractéristiques spécifiques à prendre en compte pour évaluer l'innocuité des produits cosmétiques destinés aux enfants de moins de trois ans. ." 17.

Armstrong, B., et al. (2004). "Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: A review and meta-analysis." Environmental Health Perspectives 112(9): 970-978.

Armstrong B., H. E., and Fletcher T. (2003). "Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs) : A meta analysis." Report No. Research Report 068. .

ATSDR (1994). "Toxicological profile for chlorodibenzofurans." 256.

ATSDR (1995). "Toxicological profile for polycyclic aromatic hydrocarbons." 487.

ATSDR (1998). "Toxicological profile for chlorinated dibenzo-p-dioxins." 721.

ATSDR (1999). "Toxicological profile for formaldehyde." 468.

ATSDR (2000). "Toxicological profile for Polychlorinated biphenyls (PCBs)." 948.

ATSDR (2011). "Addendum to the toxicological profile for polychlorinated biphenyls." 44.

Baan R. Grosse Y, S. K., Secretan B (2009). "Special Report : POlicy A review of human carcinogens - Part F : Chemical agents and related occupations." 2.

Baccarelli, A., et al. (2008). "Neonatal thyroid function in seveso 25 years after maternal exposure to dioxin." PLoS Medicine 5(7): 1133-1142.

Banks, Y. A., et al. (1990). "Age-related changes in dermal absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,4,7,8-pentachlorodibenzofuran." Toxicological Sciences 15(1): 163-173.

Banks, Y. B. and L. S. Birnbaum (1991). "Absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after low dose dermal exposure." Toxicology and Applied Pharmacology 107(2): 302-310.
Bartsch, N., et al. (2016). "Skin permeation of polycyclic aromatic hydrocarbons: A solvent-based in vitro approach to assess dermal exposures against benzo[a]pyrene and dibenzopyrenes." Journal of Occupational and Environmental Hygiene 13(12): 969-979.
BfR (2006). "Assessment of the Carcinogenicity of Formaldehyde." 156.
BfR-Herausgegeben von A. Schulte, U. B., S. Madle, H. Mielke, U. Herbst, H.-B. Richter-Reichhelm, K.-E. Appel, U. Gundert-Remy - (2006). "Assessment of the Carcinogenicity of Formaldehyde."
Blot, W. J., Brown, L.M., Pottern, L.M., Stone, B.J. & Fraumeni, J.F., (1983). " Lung cancer among long-term steel workers." Am. J. Epidemiol., 117: 706–716.
Boffetta, P., et al. (1997). "Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons." Cancer Causes and Control 8(3): 444-472.
Bowman RE, H. M., Barsotti DA (1981). "Locomotor hyperactivity in PCB-exposed rhesus monkeys." Neurotoxicology 2(2): 251-268.
Brewster, D. W., et al. (1989). "Comparative dermal absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin and three polychlorinated dibenzofurans." Toxicology and Applied Pharmacology 97(1): 156-166.
Businesscoot (2020). "Le marché des couches pour bébés- France." 66.
C.L, R. P. g. (1991). "oral toxicity of formaldehyde and its derivatives." Critical Reviews in Toxicology 21(5).
Canada, H. (2001). "Liste des substances d'intérêt prioritaire - rapport d'évaluation. Formaldéhyde." 123.
Canada, S. (2018). "Ebauche d'évaluation préalable : Groupe des composés du furane." 63.
Cavret S, L. C., Feidt C, Laurent F, Rychen G. (2003). "Intestinal absorption of C from C-phenanthrene, C-benzo[a]pyrene and C-tetrachlorodibenzo-para-dioxin : approaches with the caco-2 cell line and with portal absorption measurements in growing pigs." Reprod.Nutr.Dev 43: 145-154.
Choisir, U. Q. (2019). "Protections pour incontinence." Septembre: 48-49.
Chu, I., et al. (1996). "Skin reservoir formation and bioavailability of dermally administered chemicals in hairless guinea pigs." Food and Chemical Toxicology 34(3): 267-273.
Colón, J., et al. (2015). "Anaerobic digestion of undiluted simulant human excreta for sanitation and energy recovery in less-developed countries." Energy for Sustainable Development 29: 57-64.
Cordella, M., et al. (2015). "Evolution of disposable baby diapers in Europe: Life cycle assessment of environmental impacts and identification of key areas of improvement." Journal of Cleaner Production 95: 322-331.
Cornu, U. J. F.-P. (1987). "Les polychlorobiphényles : enjeux environnementaux et sanitaures, et mycoremédiation." 100.
Costantino J.P., R. C. K., and Bearden A. (1995). "Occupationally Related Cancer Risk Among Coke-Oven Workers - 30 Years of Follow-Up." Journal of Occupational and Environmental Medicine 37(5): 597-604. .
Counts, J., et al. (2017). "Common Diaper Ingredient Questions: Modern Disposable Diaper Materials Are Safe and Extensively Tested." Clinical Pediatrics 56(5_suppl): 23S-27S.
Counts, J. L., et al. (2014). "Modern disposable diaper construction: Innovations in performance help maintain healthy diapered skin." Clinical Pediatrics 53(9): 10S-13S.
Culp, S. J., et al. (1998). "A comparison of the tumors induced by coal tar and benzo[a]pyrene in a 2-year bioassay." Carcinogenesis 19(1): 117-124.
DeVito, M. J. and A. Schecter (2002). "Exposure assessment to dioxins from the use of tampons and diapers." Environmental Health Perspectives 110(1): 23-28.
Dey, S., et al. (2016b). "Modern diaper performance: construction, materials, and safety review." International Journal of Dermatology 55: 18-20.
Dey, S., et al. (2016a). "Exposure Factor considerations for safety evaluation of modern disposable diapers." Regulatory Toxicology and Pharmacology 81: 183-193.
Dey, S., et al. (2015). "An in vitro skin penetration model for compromised skin: Estimating penetration of polyethylene glycol [14C]-PEG-7 phosphate." Skin Pharmacology and Physiology 28(1): 12-21.
DHI (2007). "Study on enhancing the endocrine disrupter priorit list with a focus on low production volume chemicals." (ENV.D.4/ETU/2005/0028r).
ECHA (2012a). " Opinion proposing harmonised classification and labelling at EU level of Formaldehyde. ." Committee for Risk Assessment (RAC). CLH-O-0000003155-80-01/F. : 50.
ECHA (2012b). "Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1. ." 195.
ECHA (2017a). "Annex XV Report. An evaluation of the possible health risks of recycled rubber granules used as infill in synthetic turf sports fields."

ECHA (2018). "Annex XV Restriction Report : Eight polycyclic aromatic hydrocarbons (PAHs) in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications." 340.
ECHA (2018b). "Note on reference dose-response relationship for the carcinogenicity of pitch, coal tar, high temperature and on PBT and vPvB properties.".
ECHA (2018c). "Implementation and enforcement of restrictions in Member States, unpublished.".
ECHA (2019). "Opinion on an Annex XV dossier proposing a restriction on polycyclic aromatic hydrocarbons (PAHs)." 89.
ECHA (2019b). "Substance evaluation conclusion and Evalaution report for formaldehyde." (EC 200-001-8): 57.
ECHA (2019c). "Annex XV restriction report for formaldehyde and formaldehyde releasers ": 85.
ECHA, R. (2018). "Annex XV restriction report proposal for a restriction : eight polycyclic aromatic hydrocarbons in granules and mulches used as infill material in synthetic turf pitches and in loose form on playgrounds and in sport applications."
EDANA (2005). "Seven decades of disposable diapers." 15.
EDANA (2008). "Sustainability Report 2007-2008 Absorbent Hygien Products." 72.
EDANA (2010). "Quality of Life and Absorbent Hygiene Products. ." 13.
EDANA (2011). "Sustainability Report 2011." 48.
EDANA (2015). "Sustainability Report 4th edition, 2015. ." 48
EFSA (2005). "Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic." The EFSA Journal 282: 1-31.
EFSA (2008). "Polycyclic Aromatic Hydrocarbons in Food - Scientific Opinion of the Panel on Contaminants in the Food Chain." EFSA Journal(724): 1-114.
EFSA (2018). "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food." EFSA Journal 16((11):5333): 331.
EFSA (2019). "Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food." EFSA Journal.
Environnement, F. N. (2011). "Les couches lavables. Etat des lieux, enjeux & pistes pour agir. Dossier de presse. ." 46.
EPA, D. (2009). "Survey and health assessment of the exposure of 2 year-olds to chemical substances in consumer products?Survey N°102, ." 327.
EPA, D. (2014). "Evaluation of health hazards by exposure to polychlorinated biphenyls (PCB) and proposal of a health-based quality criterion for soil." (1485): 334.
EPA, U. (1984). "Health effects assessment for benzo(a) pyrene (BaP)." Report No. EPA-540/1-86-022: 1-42.
EPA, U. (1990). "Chemical Assessment Summary : Formaldehyde."
EPA, U. (1992). "Dermal exposure assessment : principles ans applications." (EPA/600/8-91/011B): 389.
EPA, U. (2005). "Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens." (EPA/630/R-03/003F): 126.
EPA, U. (2012). "Appendix A : Summary of external peer review and public comments and disposition." (EPA/600/R-10/038F): 1521.
EPA, U. (2017). "Toxicological Review of Benzo[a]pyrene." (EPA/635/R-17/003Fa): 234.
Everaert, K. and J. Baeyens (2002). "The formation and emission of dioxins in large scale thermal processes." Chemosphere 46(3): 439-448.
FAO/WHO (2006). " Safety evaluation of certain contaminants in food. Prepared by the Sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives . ." WHO Food Additives Series 55; FAO Food and Nutrition Paper 82.((JECFA, 2006).).
Faqi, A. S., et al. (1998). "Reproductive toxicity and tissue concentrations of low doses of 2,3,7,8-tetrachlorodibenzo-p-dioxin in male offspring rats exposed throughout pregnancy and lactation." Toxicology and Applied Pharmacology 150(2): 383-392.
Food, S. C. o. (2002). "Opinion of the Scientific Committee on Food on the risks to human health of Polycyclic Aromatic Hydrocarbons in food." (SCF/CS/CNTM/PAH/29 Final).
Foth, H., et al. (1988). "Pharmacokinetics of low doses of benzo[a]pyrene in the rat." Food and Chemical Toxicology 26(1): 45-51.
FRC (2018). "Couches-culotte. Au sec et en sécurité. Frc mieux choisir." octobre : 112: 16-17.
G., A. B. G. a. G. (2009). "Exposure-response relationship between lung cancer and polycyclic aromatic hydrocarbons (PAHs)." Occup. Environ. Med. 66(11): 740-746.

Gallagher, R. P., Bajdik, C.D., Fincham, S., Hill, G.B., Keefe, A.R., Coldman, A. & McLean, D.I. (1996). "Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. ." Cancer Epidemiol. Biomarkers Prev. 5: 419–424

Gourmand M., C. J.-M. (1999). "Hygiene : la révolution des superabsorbants. ." Lettre des sciences chimiques du CNRS/l'actualité chimique.: 46-50.

Group'Hygiène (2015). "La couche bébé à usage unique. ." 14.

Grova, N., et al. (2002). "[14C] Milk, urine and faeces excretion kinetics in lactating goats after an oral administration of [14C]polycyclic aromatic hydrocarbons." International Dairy Journal 12(12): 1025-1031.

Gupta, H., et al. (2009). "Performance evaluation of market available diapers." Indian Journal of Pediatrics 76(8): 859-860.

H.E., T. H. P. W. R. A. F. V. J. H. V. H. M. F. (1989). "Two-year drinking-water study of formaldehyde in rats." FD Chem Toxic 27(2): 77-87.

Habs, M., et al. (1984). "Carcinogenic activity of condensate from coloquint seeds (Citrullus colocynthis) after chronic epicutaneous administration to mice." Journal of Cancer Research and Clinical Oncology 108(1): 154-156.

Habs M., S. D., and Misfeld, J. (1980). "Local Carcinogenicity of Some Environmentally Relevant Polycyclic Aromatic-Hydrocarbons After Lifelong Topical Application to Mouse Skin." Archiv fur Geschwulstforschung 50(3): 266-274.

IARC (1983). "Monographs on the Evaluation of Carcinogenic Risks to Humans : Polynuclear Aromatic Compounds, part 1, chemical, environmental and experimental data summary of data reported and evaluation. ." 32.

IARC (1984). "Monographs on the Evaluation of Carcinogenic Risks to Humans . Polynuclear Aromatic Compounds, Part 2: Carbon Blacks, Mineral Oils (Lubricant Base Oils and Derived Products) and Some Nitroarenes. ." 33.

IARC (1985). "Monographs on the Evaluation of Carcinogenic Risks to Humans . Polynuclear Aromatic Compounds, Part 4: Bitumens, Coal-Tars and Derived Products, Shale-Oils and Soots. ." 35.

IARC (1989). "Monographs on the Evaluation of Carcinogenic Risks to Humans. Diesel and Gasoline Engine Exhausts and Some Nitroarenes." 46.

IARC (1997). "IARC Monographs on the evaluation of carcinogenic risks to humans : polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans." 69: 687.

IARC (2010). "IARC Monographs on the Evaluation of Carcinogenic risks to humans : some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures." 92.

IARC (2012). "2,3,7,8-TETRACHLORODIBENZOpara-DIOXIN, AND 3,3',4,4',5-PENTACHLOROBIPHENYL." 40.

IARC (2012b). "Benzo(a)pyrene."

IARC (2016). "Polychlorinated biphenyls and polybrominated biphenyls." 107.

IGHRC (2006). "Guidelines on route-to-route extrapolation of toxicity data when assessing health risks of chemicals. ." 56.

INERIS (2006). "Fiches de données toxicologiques et environnementales des substances chimiques : Dioxines." (INERIS –DRC-02-25590-02DF46.doc): 82.

INRS (2007). "Base de données fiches toxicologiques : biphényles chlorés." (94): 7.

INRS (2016). "Base de données Biotox : Dioxines furanes." 3.

INSERM (2000). "Dioxines dans l'environnement : quels riques pour la santé? Synthèse et recommandations." 66.

INVS (2009). "Etude nationale Afssa-InVS d'imprégnation aux polychlorobiphényles (PCB) des consommateurs réguliers de poissons d'eau douce." 28.

Ishii, S., et al. (2014). "Risk assessment study of dioxins in sanitary napkins produced in Japan." Regulatory Toxicology and Pharmacology 70(1): 357-362.

Ishii, S., et al. (2015). "Investigation of the amount of transdermal exposure of newborn babies to phthalates in paper diapers and certification of the safety of paper diapers." Regulatory Toxicology and Pharmacology 73(1): 85-92.

Jämsä, T., et al. (2001). "Effects of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin on bone in two rat strains with different aryl hydrocarbon receptor structures." Journal of Bone and Mineral Research 16(10): 1812-1820.

JECFA (2001). "Evaluation of certain food additives and contaminants." WHO Technical report series 909.

JRC (2015). "Best available techniques (BAT) reference document for the production of pulp, paper and board." (Report EUR 27235 EN).

Kao, J., et al. (1985). "Skin penetration and metabolism of topically applied chemicals in six mammalian species, including man: An in vitro study with benzo[a]pyrene and testosterone." Toxicology and Applied Pharmacology 81(3 PART 1): 502-516.

Klasmeier, J., et al. (1999). "PCDD/Fs in textiles - Part II: Transfer from clothing to human skin." Chemosphere 38(1): 97-108.

Knafla, A., et al. (2011). "Development and application of a skin cancer slope factor for exposures to benzo[a]pyrene in Soil." Regulatory Toxicology and Pharmacology 59(1): 101-110.
Kociba, R. J., et al. (1978). "Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats." Toxicology and Applied Pharmacology 45(1).
Kosemund, K., et al. (2009). "Safety evaluation of superabsorbent baby diapers." Regulatory Toxicology and Pharmacology 53(2): 81-89.

Krause E., B. A., Conrads-Wendtland A., Heelis D., Martinson P., Mezaiti H., Wicenec C., Hartmann P. (2006). "Exposure-Based Risk Assessment Principles Applied to Baby Diapers. ." Epidemiology 17(6): 563.
Mastrangelo G., F. E., and Marzia V. (1996). "Polycyclic aromatic hydrocarbons and cancer in man." Environmental Health Perspectives 104(11): 1166-1170.
Masuo, T., et al. (1989). "Chronic toxicity study on formaldehyde administered orally to rats." Toxicology 56(1): 79-86.
Mendoza, J. M. F., et al. (2019b). "Disposable baby diapers: Life cycle costs, eco-efficiency and circular economy." Journal of Cleaner Production 211: 455-467.
Mendoza, J. M. F., et al. (2019a). "Improving resource efficiency and environmental impacts through novel design and manufacturing of disposable baby diapers." Journal of Cleaner Production 210: 916-928.
Mínguez-Alarcón, L., et al. (2017). "A longitudinal study of Peripubertal serum organochlorine concentrations and semen parameters in young men: The Russian children's study." Environmental Health Perspectives 125(3): 460-466.
Mocarelli, P., et al. (2008). "Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality." Environmental Health Perspectives 116(1): 70-77.
Moody, R. P., et al. (2007). "Contaminated soils (I): In vitro dermal absorption of benzo[a]pyrene in human skin." Journal of Toxicology and Environmental Health - Part A: Current Issues 70(21): 1858-1865.
Moody, R. P., et al. (1994). "In vitro dermal absorption of pesticides: VI. In vivo and in vitro comparison of the organochlorine insecticide DDT in rat, guinea pig, pig, human and tissue-cultured skin." Toxicology in Vitro 8(6): 1225-1232.
Moolgavkar, S. H., Luebeck, E.G., and Anderson, E.L. (1998). (1998). " Estimation of unit risk for coke oven emissions." Risk Anal. 18(6): 813-825.
Murray, F. J., et al. (1979). "Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet." Toxicology and Applied Pharmacology **50**(2): 241-252.
Nesnow, S., et al. (1983). "Mouse skin tumor initiation-promotion and complete carcinogenesis bioassays: Mechanisms and biological activities of emission samples." Environmental Health Perspectives Vol. 47: 255-268.
Netherlands, H. C. o. t. (2006). "BaP and PAH from coal-derived sources." 204.
Ng, K. M. E., et al. (1992). "Percutaneous absorption and metabolism of pyrene, benzo[a]pyrene, and di(2-ethylhexyl) phthalate: Comparison of in vitro and in vivo results in the hairless guinea pig." Toxicology and Applied Pharmacology 115(2): 216-223.
NICNAS (2006). "Priority Existing Chemical Assessment Report N°28 : Formaldehyde." 389.
NTP (2006). "Studies of 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (TCDD) (CAS NO. 1746-01-6) in female HARLAN SPRAGUE-DAWLEY rats (GAVAGE STUDIES)." NTP TR 521: 240.
OECD (2002). "Forword Introduction : Formaldehyde." 395.
OEHHA (1999). "Chronic RELs and toxicity summaries using the previous version of the Hot Spots Risk Assessment guidelines ".
OEHHA (2010). "Benzo[a]pyrene." PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER: 68.
Ohsako, S., et al. (2001). "Maternal exposure to a low dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) suppressed the development of reproductive organs of male rats: Dose-dependent increase of mRNA levels of 5α-reductase type 2 in contrast to decrease of androgen receptor in the pubertal ventral prostate." Toxicological Sciences 60(1): 132-143.
OSAV (2016). "Substances chimiques présentes dans les protections hygiéniques : evaluation des risques." 6.
OSAV (2018). "Analyse des substances chimiques dans les langes pour nourrissons et enfants.".
Patrizi, B. and M. S. de Cumis (2018). "TCDD toxicity mediated by epigenetic mechanisms." International Journal of Molecular Sciences 19(12).
Poiger, H. and C. Schlatter (1980). "Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD." Food and Cosmetics Toxicology 18(5): 477-481.
Poiger, H. and C. Schlatter (1986). "Pharmacokinetics of 2,3,7,8-TCDD in man." Chemosphere 15(9-12): 1489-1494.
Québec, I. N. d. S. P. d. (2006). "Réévaluation des risques toxicologiques des biphényls polychlorés." 704.

Rai, P., et al. (2009). "Safety evaluation of disposable baby diapers using principles of quantitative risk assessment." Journal of Toxicology and Environmental Health - Part A: Current Issues 72(21-22): 1262-1271.
Ramesh, A., et al. (2001). "Metabolism, bioavailability, and toxicokinetics of Benzo(α)pyrene in F-344 rats following oral administration." Experimental and Toxicologic Pathology 53(4): 275-290.
Rehman, H., et al. (2019). "Neonatal exposure to furan alters the development of reproductive systems in adult male Sprague Dawley rats." Food and Chemical Toxicology 130: 231-241.
ReZero (2019). "The environmental& economic costs of single-use menstrual products, baby nappies and wet wipes." 65.
RIVM (2001). "Tumorigenic effects in Wistar rats orally administered benzo[a]pyrene for two years (gavage studies). Implications for human cancer risks associated with oral exposure to polycyclic aromatic hydrocarbons." (658603 010).
RIVM (2014). "General Fact Sheet : General default parameters for estimating consumer exposure - Updated version 2014." 102.
RIVM (2016). "Assessment of the product limit for PAHS in rubber articles : The case of shck-absorbing tiles." 2016-0184: 66.
Rodenburg L, G., Christie R. (2015). "Polychlorinated biphenyls in pigments : inadvertent production and environmental significance." Colora. Technol. 131: 353-369.
Roy T, H. K., Schaum J. (2008). "Percutaneous Absorption of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) from Soil." Journal of Toxicology and Environmental Health, Part A: Current Issues: 8.
Roy, T. A., et al. (1998). "Studies estimating the dermal bioavailability of polynuclear aromatic hydrocarbons from manufactured gas plant tar-contaminated soils." Environmental Science and Technology 32(20): 3113-3117.
Roy, T. A. and R. Singh (2001). "Effect of soil loading and soil sequestration on dermal bioavailability of polynuclear aromatic hydrocarbons." Bulletin of Environmental Contamination and Toxicology 67(3): 324-331.
Santé, D. G. d. l. (1998). "Circulaire DGS/VS 3/98 n° 98-333 du 11 juin 1998 relative aux recommandations du Conseil supérieur d'hygiène publique de France, section de l'alimentation et de la nutrition, sur la dioxine."
SCCS (2018). "10The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 9th revision." (SCCS/1564/15): 151.
(SCF), S. C. o. F. (2002). "Opinion of the Scientifi Committee on Food on the risks to human helath of POlycyclic Aromatic Hydrocarbons in food." 84.
Schantz, S. L., et al. (1992). "Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on behavior of monkeys in peer groups." Neurotoxicology and Teratology 14(6): 433-446.
Schecter A.J., P. O., Marquardt S. (1998). "Dioxins and Dibenzofurans in USA Sanitary Products: Tampons, Sanitary Napkins, Disposable and Cloth Diapers, and Incontinence Pads." Organohalogen Compd. 36: 281—284
SCHER/SCCP/SCENIHR (2009). "Risk assessment methodologies and approaches for genotoxic and carcinogenic substances. ."
Schmähl D, S. K. G., Habs S (1977). "SYNCARCINOGENIC ACTION OF POLYCYCLIC HYDROCARBONS IN AUTOMOBILE EXHAUST GAS CONDENSATES."
Schneider, K., et al. (2002). "Cancer risk assessment for oral exposure to PAH mixtures." Journal of Applied Toxicology 22(1): 73-83.
Schoenberg, J. B., Stemhagen, A., Mason, T.J., Patterson, J., Bill, J. & Altman, R. (1987). "Occupation and lung cancer risk among New Jersey white males." J. natl Cancer Inst 79: 13-21.
SFAE (2013). "Enquête Nutri-bébé 2013 – extraction des données.".
Shanon A, F. W., James W, Dulberg C. (1990). "Diapers: what do parents choose and why?" Can Fam Physician. 36: 1705-1708.
Shin JH, A. Y., Seo JJ. (2005). "Determination of PCDD/Fs in Disposable Diaper for Infant. 2005." Journal of the Korean Society of Clothing and Textiles 29(6): 814-824.
Shu, H., et al. (1988). "Bioavailability of soil-bound tcdd: Dermal bioavailability in the rat." Toxicological Sciences 10(2): 335-343.
Skowronski.G.A, T. R. M. A.-R. M. S. (2010). "Effects Of Soil Matrix And Aging On the dermal bioavailability Of Hydrocarbons And Metals in the Soil: Dermal Bioavailability Of Soil contaminants." Proceedings of the Annual International Conference on Soils, Sediments, Water and Energy 13.
Slob, W., Bakker M.I., Biesebeek J.D. and Bokkers B.G. (2014). " Exploring the uncertainties in cancer risk assessment using the integrated probabilistic risk assessment (IPRA) approach." Risk Anal 34(8): 1401-1422. .
Sorg, O. (2014). "AhR signalling and dioxin toxicity." Toxicology Letters 230(2): 225-233.
Stamatas, G. N., et al. (2011). "Documentation of impaired epidermal barrier in mild and moderate diaper dermatitis in vivo using noninvasive methods." Pediatric Dermatology 28(2): 99-107.

Stroo, H. F., et al. (2005). "Dermal bioavailability of benzo[a]pyrene on lampblack: Implications for risk assessment." Environmental Toxicology and Chemistry 24(6): 1568-1572.
Suskind R.R., H. P. (1984). "Human Health Effects of 2,4,5-T and Its Toxic Contaminants." JAMA 251(18).
Thaman, L. A. and L. F. Eichenfield (2014). "Diapering habits: A global perspective." Pediatric Dermatology 31(s1): 15-18.
Tryphonas, H., et al. (1989). "Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (Macaca Mulatta) monkey - preliminary report." International Journal of Immunopharmacology 11(2): 199-206.
Tryphonas, H., et al. (1991). "Effect of chronic exposure of PCB (aroclor 1254) on specific and nonspecific immune parameters in the rhesus (Macaca mulatta) monkey." Toxicological Sciences 16(4): 773-786.
Umeh, A. C., et al. (2019). "In vitro gastrointestinal mobilization and oral bioaccessibility of PAHs in contrasting soils and associated cancer risks: Focus on PAH nonextractable residues." Environment International 133.
Union, E. (2008). "European Union Risk Assessment report : coal-tar pitch, high temperature - risk assessment."
Van den Berg, M., Birnbaum. L., Bosveld A.T.C. et al (199_). "Toxic Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife." Environmental Health Perspectives 106(12).
Van den Berg, M., et al. (2006). "The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds." Toxicological Sciences 93(2): 223-241.
Van den Berg, M., et al. (1994). "The toxicokinetics and metabolism of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance for toxicity." Critical Reviews in Toxicology 24(1): 1-74.
Van Der Molen, G. W., et al. (2000). "Estimation of dioxin and furan elimination rates with a pharmacokinetic model." Journal of Exposure Analysis and Environmental Epidemiology 10(6): 579-585.
Van Der Molen, G. W., et al. (1996). "A generic toxicokinetic model for persistent lipophilic compounds in humans: An application to TCDD." Fundamental and Applied Toxicology 31(1): 83-94.
Van Leeuwen R, F. M., Schrenk D, Larsen J.C, Farland W, Younes M. (2000). "Dioxins: WHOÕs tolerable daily intake (TDI) revisited." Chemosphere: 1095-1101.
VanRooij, J. G. M., et al. (1993). "Estimation of individual dermal and respiratory uptake of polycyclic aromatic hydrocarbons in 12 coke oven workers." British Journal of Industrial Medicine 50(7): 623-632.
VITO (2018). "Monitoring of the Belgian market with regard to organic residues in baby nappies. Part 2 : target analyses.": 119.
Warshawsky, D. and W. Barkley (1987). "Comparative carcinogenic potencies of 7H-dibenzo[c,g]carbazole, dibenz[a,j]acridine and benzo[a]pyrene in mouse skin." Cancer Letters 37(3): 337-344.
Weber, L. W. D., et al. (1993). "Tissue distribution and toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats after intravenous injection." Toxicological Sciences 21(4): 523-534.
Weber, L. W. D., et al. (1991). "Key enzymes of gluconeogenesis are dose-dependently reduced in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-treated rats." Archives of Toxicology 65(2): 119-123.
Wennerstrôm M., D. M., Nodén S., Näsholm A.S "The second generation TCF bleaching with HC ozone."
Wester, P. W., et al. (2012). "Carcinogenic activity of benzo[a]pyrene in a 2 year oral study in Wistar rats." Food and Chemical Toxicology 50(3-4): 927-935.
Wester, R. C., et al. (1990). "Percutaneous absorption of [C]DDT and [C]Benzo[a]pyrene from soil." Toxicological Sciences 15(3): 510-516.
Weyand, E. H., et al. (1995). "Differences in the Tumorigenic Activity of a Pure Hydrocarbon and a Complex Mixture following Ingestion: Benzo[a]pyrene vs Manufactured Gas Plant Residue." Chemical Research in Toxicology 8(7): 949-954.
WHO (1987). "Air Quality Guidelines for Europe. ." World Health Organization (WHO) Regional Publications, European Series 23.
WHO (1989). "Formaldehyde : Consice International Chemical Assessment Document 40."
WHO (2000). "Polycyclcic aromatic hydrocarbons (PAHs)." Air quality guidelines - second edition 5.9.
WHO (2001). "Safety evaluation of certain food additives and contaminants."
WHO (2002). "Concise INternational Chemical Assessment -Formaldehyde." 81.
WHO (2003). "Polynuclear aromatic hydrocarbons in drinking-water. Background document for development of WHO guidelines for drinking-water quality." 32.
WHO (2005). "The 2005 World Health Organization Reevaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-Like Compounds." Toxicological Sciences 93(2): 223-241.
WHO/IPCS (1998). "Selected non-heterocyclic policyclic aromatic hydrocarbons. ." Environmental Health Criteria 202: 1-701.
WHO/IPCS (2005). " Formaldehyde in drinking water. Background document for development of WHO Guidelines for Drinking-water Quality." 18p.

Wiberg K., L. K., Glas B., Rappe C. (1989). "PCDDs and PCDFs in consumer'paper products. ." Chemosphere 19(1-6): 735-740

Y., T. M. N. K. K. (1989). "Chronic toxicity study on formaldehyde administered orraly to rats." Toxicology 56(79-86).

Yang, J. J., et al. (1989). "In vitro and in vivo percutaneous absorption of benzo[a]pyrene from petroleum crude-fortified soil in the rat." Bulletin of Environmental Contamination and Toxicology 43(2): 207-214.

Zahm, S. H., Brownson, R.C., Chang, J.C. & Davis, J.R. (1989). "Study of lung cancer histologic types, occupation, and smoking in Missouri." Am. J. ind. Med., 15: 565–578.

Appendix : SCL methodology study

Stratégie d'investigation du Service Commun des Laboratoires (SCL) sur la sécurité des couches pour bébé

Corinne MARC, Laurence DELAIRE, Cécile DUTFOY, Franck GAUDIN, Jessica MASSON, Mathieu VERNET, Sonia PIEUCHOT, Mataëlle ONAPIN, Frédéric SALTRON, Catherine ROSSI

Service Commun des Laboratoires – Laboratoire de Paris – 25 Avenue de la République – 91744 Massy – labo75@scl.finances.gouv.fr

Résumé

Cet article a pour objectif de décrire la stratégie d'investigation mise en œuvre par le SCL dans le cadre des enquêtes menées par la Direction Générale de la Concurrence, de la Consommation et de la Répression des fraudes (DGCCRF) sur la sécurité des couches jetables pour bébé.

Cet article décrit précisément la méthode de préparation des échantillons mis en œuvre (broyage des couches et préparation d'un simulant urine) et fournit les principes d'analyses et leurs limites de détection et de quantification.

Cet article présente une innovation portant notamment sur un mode de préparation inédit de simulant urine dans le but de vérifier une éventuelle migration de substances.

Mots-clés : Couches pour bébé, Simulant urine, Broyage

Abstract

This article aims to describe the investigation strategy implemented by the SCL in the context of investigations conducted by the Directorate General of Competition, Consumption and Fraud Control (DGCCRF) on the safety of disposable diapers for baby.

This article describes precisely the sample preparation method used (crushing of the layers and preparation of a urine simulant) and provides the principles of analysis and their limits of detection and quantification.

The innovation of this article includes a novel method of preparation of urine simulant in order to verify a possible migration of substances.

Key-words: Diaper for baby, urine simulant, grinding of the diapers

1. Contexte

En octobre 2016, un article paru dans le journal Le Parisien se fait l'écho d'une étude [1] sur des couches pour bébé fabriquées par le leader du marché. A partir de tests en laboratoire, la présence d'hydrocarbures aromatiques (HAP), plus précisément le chrysène et le benzo(a) anthracène, a été mise en évidence dans des couches pour bébé à usage unique. Il en résulte en novembre 2016 une pétition [2] à l'initiative d'une consommatrice interpellant ce fabriquant et demandant la suppression définitive des substances cancérigènes des couches.

Début 2017, l'Institut National de la Consommation fait paraître dans la revue « 60 millions de consommateurs » un article mentionnant la présence de HAP mais aussi d'autres contaminants tel que les pesticides (dans une référence dite « bio »), dioxines, furannes et composés organiques volatiles dans 12 références commerciales de couches [3].

Suite aux échanges entre professionnels et aux préoccupations affichées des consommateurs, la Direction Générale de la Santé (DGS), la DGCCRF et la Direction Générale de la Prévention des Risques (DGPR) initient une démarche d'évaluation des risques par une saisine, le 25 Janvier 2017, de l'Agence Nationale de Sécurité Sanitaire alimentation, environnement et travail (ANSES).

L'ANSES est ainsi sollicitée pour

- réaliser une analyse des risques liés à ces substances en particulier dans le cas d'une exposition par contact chez le jeune enfant (public sensible),

- évaluer la pertinence de définir ou non des seuils pour la présence de ces substances dans les couches notamment au regard du temps et du mode d'exposition,

- le cas échéant, émettre des recommandations afin de favoriser un meilleur encadrement des modes de fabrication, de la composition et de l'information au consommateur notamment au niveau communautaire.

En complément de cette demande et afin de disposer de données d'exposition consolidées et de les fournir à l'ANSES, la DGCCRF a lancé une campagne de surveillance sur ces produits qui ont été confiés au SCL pour mener les investigations. 19 prélèvements de couche à usage unique ont été réalisés parmi les références en nom de marque ou de distributeur les plus vendues en France.

En l'absence d'informations publiées sur les méthodes ayant abouti aux résultats présentés dans les medias, le SCL a alors mis en place une stratégie d'investigation inédite qui porte à la fois sur des analyses sur couche entière (broyat) et en situation d'utilisation (simulant urine).

La présente publication relève donc d'une démarche spontanée du réseau des laboratoires officiels de la DGCCRF et de la DGDDI (Direction générale des douanes et droits indirects) de mettre à disposition sa stratégie analytique. Cela couvre la préparation des échantillons, le choix des substances à rechercher, les méthodes analytiques et leurs performances. Cela permettra, une fois connues les méthodologies des autres laboratoires, de comparer les méthodes, les résultats et d'étudier les éventuelles différences, puis de se focaliser sur l'analyse des causes de la présence et du taux d'éventuelles substances indésirables.

2. Réglementation

A ce jour, aucune réglementation européenne ou française ne porte de façon spécifique sur les couches à usage unique, qu'il s'agisse de leur composition, leur fabrication ou leur mise sur le marché. Cependant, il s'agit de produits de consommation courante et à ce titre, elles doivent respecter la directive de sécurité générale des produits 2001/95/CE, transposée en

France dans le Code de la Consommation [4]. Cette législation institue une obligation générale de sécurité, qui implique de mettre sur le marché des produits sûrs pour une utilisation prévue et raisonnable par le consommateur, de conduire d'une évaluation de risque, de tenir à disposition le dossier correspondant, de fournir des informations sur les risques aux consommateurs, d'assurer une traçabilité des produits et de prévoir une procédure de retrait du marché.

Néanmoins, il existe des réglementations pour d'autres types de produits (cosmétiques, dispositifs médicaux) utilisées au niveau de la sphère uro-génitale (par exemple, les protections contre les fuites urinaires). Celles-ci imposent des obligations en termes d'évaluation de la sécurité et de transmission des compositions aux autorités compétentes.

3. Stratégie d'investigation

Une première partie de l'étude a consisté à prendre en compte la totalité des matériaux constitutifs de la couche en travaillant sur des aliquotes du broyat de la couche entière.

Dans un second temps, il est apparu nécessaire d'évaluer, en cas de présence de substances dans les couches entières, la quantité qui pourrait être relarguée lors d'une exposition de l'enfant avec une couche souillée en mettant au point une préparation par imprégnation de la couche entière qui reproduit autant que faire se peut des conditions réelles d'utilisation et d'exposition.

En fonction des familles de molécules à rechercher et des méthodes d'identification et de dosage, les quantités de prises d'essais et les volumes de simulant d'urine ont été déterminés (Cf. Tableau 1).

A noter que pour obtenir 1 L de simulant, il convient de traiter entre 5 et 7 couches.

Substances recherchées	Quantité de broyat de couche requis (g)	Volume de simulant requis (ml)
Phtalates	5	100
Allergènes	50	50
Organo-étains dont TBT (Tri-ButyléTain)	5	Non recherché
COV (Composé organique Volatil)	5	50
HAP (Hydrocarbure Aromatique Polycyclique)	5	50
AOX (Composé halogéné adsorbable)	20	250
EOX (Composé halogéné extractable)	Non recherché	1000
Colorants azoïques	5	Non recherché
Dioxines et Furannes	10	1000
PCB (Polychlorobiphényle)	Non recherché	
Glyphosate et AMPA (acide aminométhylphosphonique)	80	10
Résidus de Pesticides		10
Formaldéhyde	50	250
Total	235 g soit environ 10 couches	2770 ml ≈ 3 L soit environ 20 couches

Tableau 1 : Substances recherchées

4. Préparation des échantillons

4.1. Produits chimiques

Urée (Sophyc),
Créatinine (*98%, Sophyc*),
Citrate d'ammonium (*97%, Sophyc*),
Chlorure de sodium (*99%, Sophyc*),
Chlorure de potassium (*99%, Sophyc*),
Hydrogénosulfate de potassium (*99.5%, Merck*),
Sulfate de magnésium (*99.5%, Sophyc*),
Dihydrogénophosphate de potassium (*99.5%, Merck*),
Hydrogénocarbonate de potassium (*99.5%, Merck*),
Azote liquide (Airliquide)
Acétone (Pestipur®, VWR),
Eau déionisée

4.2. Matériels

Broyeur à rotor avec tamis de 1 cm (Pulvérisette FRITSCH)
Dewar
Flacons ambrés
Papier aluminium
Plaque d'agitation
Etuve
Balance
Pressoir inox
Plateaux, béchers inox
Filtres papiers
Paire de ciseaux en inox
Passoire en inox

4.3 Etude sur couche entière broyée

Dans un premier temps, les couches sont broyées dans leur intégralité (scratch, voile intermédiaire, partie imprimée…). Pour ce faire, elles sont découpées grossièrement en carré de 3 à 5 cm de côté avec une paire de ciseaux inox préalablement nettoyée avec de l'acétone. Ces morceaux de couches sont déposés dans un récipient recouvert de papier aluminium pour éviter tout risque de contamination, notamment à cause du plastique qui est susceptible de relarguer des phtalates et des HAP.

Les morceaux de couches sont trempés quelques secondes dans un Dewar contenant de l'azote liquide. Cette étape est nécessaire pour améliorer le processus de broyage afin de garantir une parfaite homogénéisation des échantillons, d 'éviter une surchauffe et l'agglomération de l'échantillon.

4

Les morceaux de couches sont placés dans un broyeur à rotor équipé d'un tamis de 1 cm. Le broyat de couche obtenu est très fin.

Photo 1 : Découpage des couches avec une paire de ciseaux

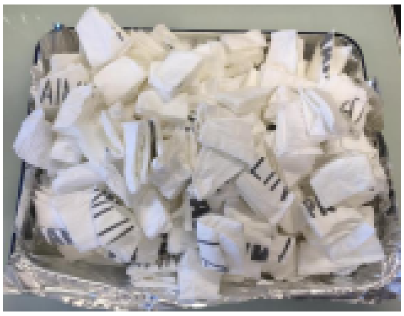


Photo 2 : Couches découpées en carré de 3 à 5 cm.

Photo 3 : Couches plongées dans l'azote liquide

Photo 4 : Couches égouttées dans une passoire en inox

Photo 5 : Broyage des couches

Photo 6 : Récupération du broyat de couche

Dans le but d'éviter tout risque de contamination croisée et de nettoyer correctement le broyeur à rotor, les 10 premières couches broyées sont jetées.

5

Après broyage, les échantillons sont conservés à température ambiante dans des flacons hermétiquement clos à l'abri de la lumière (flacon ambré ou entouré de papier aluminium) et de l'humidité. Une attention particulière est portée sur la fermeture du flacon. En effet, du papier aluminium est placé avant le positionnement du bouchon, notamment dans le cadre des analyses de phtalates et de HAP. Les plastiques des bouchons sont susceptibles de relarguer ce type de molécules.

Photo 7 : Récupération du broyat de couche

4.4. Etude du relargage par imprégnation

4.4.1 Choix des paramètres

4.4.1.1 Nature du simulant

La composition du simulant urine utilisée est basée sur la publication de Colón [5]. Ce simulant a été préféré aux autres formulations disponibles en raison de la présence d'urée et de créatinine qui reflète au mieux la composition du fluide biologique.

Composé	Concentration
Urée	9,3 $g.L^{-1}$
Créatinine	2 $g.L^{-1}$
Citrate d'ammonium	1 $g.L^{-1}$
NaCl	8 $g.L^{-1}$
KCl	1,65 $g.L^{-1}$
$KHSO_4$	0,5 $g.L^{-1}$
$MgSO_4$	0,2 $g.L^{-1}$
KH_2PO_4	1,75 $g.L^{-1}$
$KHCO_3$	0,5 $g.L^{-1}$

Tableau 2 : Composition du simulant

4.4.1.2 Volume du simulant

Le volume urinaire d'un bébé entre 1 et 3 ans varie de 600 à 750 ml par jour. Il a été décidé de prendre un volume initial de 600 ml afin de répondre au double objectif de saturer la couche et de récupérer un volume de simulant pertinent au regard du besoin analytique tout en conservant une approche réaliste. Sur ces 600 ml, en fonction des différentes capacités d'absorption des couches, 160 à 190 ml de simulant après pressage sont récupérés.

Il convient de mesurer précisément le volume récupéré par couche dont on a déterminé préalablement le poids avant imprégnation.

Ces valeurs permettront de ramener les concentrations des substances quantifiées dans le simulant en g par kg de couche.

4.4.1.3 Temps d'exposition

Au-delà de 6 mois, la plupart des bébés peuvent dormir jusqu'à 10/12h par nuit, voire plus.

Au laboratoire, une durée totale d'imprégnation de 16 h a donc été retenue.

Le résumé des conditions de préparation figure au Tableau 3 :

	Conditions réelles	Conditions expérimentales retenues
Fluide	Urine	Simulant urine [5]
Volume	600 à 750 ml/24h - > 6 mois	600 ml par couche
Temps d'imprégnation	Une nuit maximum	16h
Température	Température du corps humain	37°C

Tableau 3 : Conditions expérimentales retenues

4.4.2 Protocole expérimental

Le simulant est préparé selon la composition citée ci-dessus avec de l'eau déionisée. De grands volumes de simulant sont préparés quotidiennement et mis sous agitation pendant au moins 1h.

Photo 8 : Préparation du simulant

Les couches sont placées avec les bords relevés dans des plateaux en inox et maintenues à l'aide de pince en inox.

La méthode d'imprégnation du simulant est la suivante : 3 ajouts de 200 ml espacés de 15 minutes chacun. Ce laps de temps permet qu'après chaque ajout la couche absorbe l'intégralité du simulant. Il convient de bien respecter cette durée et plus particulièrement après le dernier ajout.

Les couches imprégnées sont placées dans une étuve à 37°C pendant 16h.

Pour l'étape de pressage, il est important de positionner le voile de la couche en contact avec le réceptacle où sera récupéré le simulant. La partie extérieure de la couche sera en contact

7

avec la presse. Ce positionnement permet de limiter les risques de contamination pouvant venir de la face extérieure de la couche qui n'est pas en contact de la peau du bébé.

Le temps de pressage est qualitatif de 5 à 10 min. Le but étant de récupérer un maximum de simulant sans que la couche n'éclate.

Le pressoir utilisé est entièrement en inox et se démonte facilement pour un nettoyage optimal.

Le simulant est récupéré par un pressage doux à température ambiante dans un récipient en inox. Cette étape doit être réalisée avec précaution afin d'éviter que la couche éclate et libère le polyacrylate de sodium. Il est ensuite filtré sur papier filtre dans le but d'éliminer le polyacrylate de sodium (cristaux de gel absorbant) éventuellement libéré.

Photo 9 et 10 : mise en place des couches avant ajout du simulant urine

Photo 11 et 12 : Imprégnation des couches

Photo 13 : Etuvage des couches

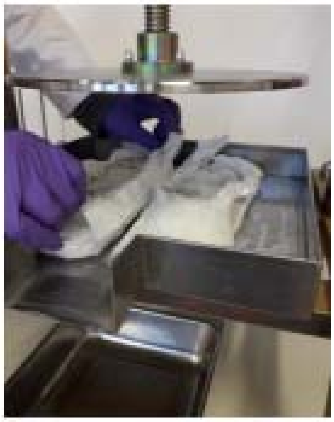


Photo 14 : Positionnement des couches dans le pressoir

Photo 15 et 16 : Pressage des couches

Photo 17 : Couche éclatée où le polyacrylate de sodium est libéré

Photo 18 : Filtration

Quotidiennement, un blanc de simulant est réalisé simultanément dans les mêmes conditions en y incluant l'ensemble des opérations vues ci-dessus mais en l'absence de couche (passage sur verrerie, presse et filtration sur papier filtre).

Après filtration, les échantillons sont conservés à température ambiante dans des flacons hermétiquement clos à l'abri de la lumière et de l'humidité, notamment pour l'analyse des phtalates, des dioxines/PCB/furannes, du formaldéhyde et des HAP.

Une attention particulière est portée sur la verrerie utilisée dans le cadre des analyses de phtalates. Toute la verrerie utilisée pour la préparation et le stockage des échantillons doit-être traitée thermiquement à 400°C pendant au moins 2h puis rincé à l'heptane. Tout contact avec du matériel en plastique est proscrit.

Les plateaux et pinces utilisées pour l'imprégnation des couches, la presse et son bac de récupération sont en inox pour éviter tout risque de contamination croisée.

L'ensemble du matériel inox est nettoyé entre chaque analyse.

Photo 19 : Stockage des simulants urine

Dès lors que le simulant récupéré après pressage est placé dans son flacon de stockage, celui-ci est maintenu au réfrigérateur jusqu'à analyse. Sa durée de stockage ne doit pas excéder 15 jours. Dans le cas contraire, les échantillons sont congelés pour éviter toute détérioration.

5. Identification et dosage

Le tableau ci-dessous résume les méthodes retenues pour chaque paramètre et notamment les limites de détection (LD) et de quantification (LQ) obtenues et validées sur broyat de couches et sur simulant urine après imprégnation sur couche entière.

Dès lors que des méthodes normalisées étaient disponibles, elles ont été strictement appliquées hormis la phase de préparation des échantillons qui relèvent de cette étude. Dans le cas contraire, les méthodes ont été développées et validées par le SCL à partir des données disponibles

Le tableau 4 résume l'intégralité des méthodes utilisées et leurs performances.

Les limites de détection et de quantifications sont présentées sous forme de fourchettes de valeurs pour certaines familles de molécules car chaque molécule a une limite qui lui est propre.

10

Substances	Broyat de couches				Simulant urine				Observations
	Méthodes	Principe	LD	LQ	Méthodes	Principe	LD	LQ	
Phtalates	Norme NF EN ISO 14389 : Textiles - Détermination de la teneur en phtalates - Méthode au tétrahydrofuranne	Extraction par solvant Bain ultra son Re-précipitation des plastiques avec solvant Centrifugation Analyse en GC-MS	Entre 40 et 200 mg/kg	Entre 120 et 600 mg/kg	Méthode interne L33-IN-04-ANA-21 : analyse en GC-MS-MS	Extraction par solvant Concentration par évaporation Analyse en GC-MS/MS	Entre 4 et 20 µg/L	Entre 10 et 50 µg/L	Une attention particuliè est portée sur la verreri utilisée dans le cadre de analyses de phtalates. L matériel en verre est trai thermiquement à 400°C pendant au moins 2h pu rincé à l'heptane. Tout contact avec du matérie en plastique est évitée
Allergènes	Méthode interne adaptée de NF EN 16274	Extraction par solvant Bain ultra son Filtration Analyse en GC-MS	Entre 0,0003 % (m/m) et 0,0015 % (m/m)	Entre 0,0005 % (m/m) et 0,005% (m/m)	Méthode interne adaptée de NF EN 16274	Extraction par solvant Bain ultra son Filtration Analyse en GC-MS	Entre 0,0003% (m/m) et 0,0015% (m/m)	Entre 0,0005% (m/m) et 0,005% (m/m)	
Organo-étains	Méthode interne : IDF.IN.ANA.214	Extraction par solvant Filtration Concentration Analyse en GC-MS	Entre 15 et 30 µg/kg	Entre 40 et 90 µg/kg	Non recherché				
COV	Méthode interne : IDF.IN.ANA.212	Extraction via un espace de tête dynamique Analyse en GC-MS	Entre 0,3 et 3 µg/kg	Entre 1 et 10 µg/kg	Méthode interne : IDF.IN.ANA.212	Extraction via un espace de tête dynamique Analyse en GC-MS	Entre 3 et 0,3 µg/L	Entre 1 et 10 µg/L	
HAP	Méthode interne : IDF.IN.ANA.211	Extraction par solvant Bain ultra son Purification par précipitation sélective	Entre 0,03 et 0,1 mg/kg	Entre 0,1 et 0,4 mg/kg	Méthode interne : IDF.IN.ANA.06	Extraction au micro-onde Purification sur colonne SPE Analyse en GC-MS/MS	Entre 0,03 et 0,1 mg/L	Entre 0,1 et 0,4 mg/L	

11

		Analyse en GC-MS/MS							
AOX	Méthode adaptée de la norme NF EN ISO 9562 (Annexe A)	Filtration SPE si échantillon chargé en sel Elimination des substances minérales par lavage du charbon avec du nitrate de sodium Adsorption des composés organiques halogénés présents dans l'échantillon par du charbon actif Combustion du charbon permettant de former de d'halogénures d'hydrogène (HX) Titrage argentimétrique par microcoulométrie *(mesure d'une quantité d'électricité)*		0,5 mg/kg	Méthode adaptée de la norme NF EN ISO 9562	Filtration SPE si échantillon chargé en sel Elimination des substances minérales par lavage du charbon avec du nitrate de sodium Adsorption des composés organiques halogénés présents dans l'échantillon par du charbon actif Combustion du charbon permettant de former de d'halogénures d'hydrogène (HX) Titrage argentimétrique par microcoulométrie *(mesure d'une quantité d'électricité)*	16.67 µg/L	50 µg/L	
EOX	Non recherché				Méthode DIN 38409 H8	Non communiqué	6.66 µg/L	20 µg/L	
Dioxines et Furannes	Méthode interne selon EPA 1613	Extraction liquide/solide, extraction liquide/liquide HRGC/HRMS	de 0,002 à 1.0 ng/kg en fonction de la prise d'essai	de 0,002 à 1.0 ng/kg en fonction de la prise d'essai	Méthode interne selon EPA 1613	Extraction liquide/solide, extraction liquide/liquide HRGC/HRMS	de 0,05 pg/L à 8 pg/L - en fonction de la prise d'essai	de 0,05 pg/L à 8 pg/L - en fonction de la prise d'essai	

PCB	Méthode interne selon EPA 1668	Extraction liquide/solide, extraction liquide/liquide HRGC/HRMS	de 0,05 à 3.2 ng/kg - en fonction de la prise d'essai	de 0,05 à 3.2 ng/kg - en fonctio n de la prise d'essai	Méthode interne selon EPA 1668	Extraction liquide/solide, extraction liquide/liquide HRGC/HRMS	de 0,25 pg/L à 40 pg/L - en fonction de la prise d'essai	de 0,25 pg/L à 40 pg/L - en fonction de la prise d'essai	
Colorants azoïques	Méthode interne adaptée de NF EN 14362-1	Extraction par solvant Bain ultra son Filtration Analyse en GC-MS	1.7 mg/kg	5 mg/kg	Non recherché				
Glyphosate et AMPA	Méthode adaptée QuPPe – Méthode LRUE	Extraction par solvant en milieu acide Analyse en LC-MS/MS	0.017 mg/kg	0,05 mg/kg	Méthode adaptée QuPPe – Méthode LRUE	Extraction par solvant en milieu acide et analyse par LC-MS/MS	0.017 mg/kg	0,05 µg/ml	
Multi résidus de Pesticides	Méthode interne adaptée de NF EN 12393	Extraction par solvant Purification liquide /liquide Analyse en LC-HRMS, GC-MS/MS et LC-MS/MS	entre 0.00333 et 0.00666 mg/kg	entre 0,01 et 0,02 mg/kg	Méthode interne adaptée de NF EN 12393	Extraction par solvant Purification liquide /liquide Analyse en LC-HRMS, GC-MS/MS et LC-MS/MS	entre 0.00333 et 0.00666 mg/kg	entre 0,01 et 0,02 mg/L	
Formaldéhyde	Méthode interne adaptée NF EN ISO 14184-1	Extraction aqueuse acidifiée Coloration Analyse par spectrométrie visible	0,11 mg/kg	0,35 mg/kg	Méthode interne adaptée NF EN ISO 14184-1	Extraction aqueuse acidifiée Coloration Analyse par spectrométrie visible	0,02 mg/L	0,06 mg/l	

Tableau 4 : Identification et quantification des paramètres

13

6. Résultats

L'ensemble des résultats d'analyse sont disponibles dans le rapport d'expertise collective de l'ANSES de janvier 2019 [6].

Les données du SCL sont cohérentes et complètent les occurrences publiées dans les études de 2017.

7. Conclusion

Cette étude du SCL, transmise à l'ANSES par la DGCCRF, a permis

- de retenir des conditions de préparation des échantillons compatibles avec les volumes nécessaires au dosage tout en conservant une approche réaliste,

- d'atteindre les objectifs fixés de mesure sur couche entière broyée et sur simulant urine après imprégnation sur couche entière,

- de disposer de données consolidées sur la présence d'éventuelles substances indésirables dans des couches pour bébé.

Le 23 Janvier 2019, la DGCCRF, la DGS et la DGPR décident dans un communiqué de presse [7] de retenir toutes les recommandations de l'ANSES et notamment : *« de poursuivre les campagnes de mesures sur l'ensemble des produits du marché, selon le protocole utilisé par le SCL en 2018 (extraction par un simulant d'urine à partir d'une couche entière à usage unique) »*

Complémentairement,

« … les ministres exigent des fabricants et des distributeurs qu'ils prennent avant 15 jours des engagements pour éliminer ces substances des couches pour bébé… »

« … les ministres portent au niveau européen un renforcement des règles protectrices

- la DGCCRF renforce dès à présent ses contrôles et dressera un bilan dans 6 mois … »

« … toutes les études complémentaires demandées par l'Anses seront lancées sans délai … »

La DGCCRF dans la poursuite de gestion du risque va s'assurer de la bonne application de ces recommandations par une nouvelle campagne de surveillance. Les analyses seront réalisées par le SCL selon le protocole décrit dans cet article.

8. Références bibliographiques

[1]. Emilie Torgemen (25 Octobre 2016). Consommation : des produits cancérigènes dans les couches. *Le Parisien*.

[2]. Elodie THONON-DURAND (2017). Pour que Pampers supprime définitivement les substances cancérigènes, de ses couches ! Pétition en ligne sur le site www.change.org

[3]. 60 millions de consommateurs (Décembre 2016). Couches – Attention toxiques !

[4]. Directive 2001/95/CE du Parlement européen et du Conseil du 3 décembre 2001 relative à la sécurité générale des produits.

[5]. Joan Colón, Aaron A. Forbis-Stokes, Marc A. Deshusses (2015). Anaerobic digestion of undiluted simulant human excreta for sanitation and energy recovery in less-developed countries. *Elsevier, Energy for Suitainable Development* **29** (57-64).

[6]. ANSES (Janvier 2019). Avis révisé de l'ANSES – Rapport d'expertise collective sur la sécurité des couches pour bébé.

[7]. DGCCRF. Substances chimiques dans les couches pour bébés : le Gouvernement demande aux professionnels de prendre dans les meilleurs délais les mesures garantissant la sécurité des produits sur le marché. *Communiqué de presse du 23 Janvier 2019*. Disponible sous https://www.economie.gouv.fr/files/files/directions_services/dgccrf/presse/communique/2019/cp-982-couches-bb.pdf