Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Background Document

to the Opinion on the Annex XV dossier proposing restrictions on

1,4-dichlorobenzene

ECHA/RAC/RES-O-0000003486-69-01/F

ECHA/SEAC/RES-O-0000003486-69-02/F

EC NUMBER	CAS NUMBER
203-400-5	106-46-7

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CONTENT

TABLES

FIGURES

BOXES

Preface

1,4-dichlorobenzene was the object of a risk assessment performed under Council Regulation (EEC) 793/93 for existing substances (EU Risk Assessment Report (RAR) 2004, rapporteur: France), now repealed by REACH. A Commission Recommendation and Communication published in 2008 referred to the results of the risk assessment and included a Strategy for Limiting the Risks:

For consumers the risk assessment stated a need for specific measures to limit the risks to **human health**, related to

- *concerns for **carcinogenicity as a consequence of inhalation exposure** arising from the use of moth repellents, air fresheners and toilet blocks.*

For consumers the **Strategy for Limiting the Risks** recommended

- *to consider at Community level **marketing and use restrictions** in Council Directive 76/769/EEC for the use of 1,4-dichlorobenzene **in air fresheners, moth repellents and toilet blocks**.*

For workers the **Strategy for Limiting the Risks** specified that

- *the legislation for workers' protection currently in force at Community level is generally considered to give an adequate framework to limit the risks of the substance to the extent needed and shall apply.*

Commission Decision 2007/565/EC restricted the use of 1,4-dichlorobenzene as **moth repellent** by virtue of the non-inclusion of the substance in Annex I, IA or IB of the Directive 98/8/EC on biocidal products. Therefore, a restriction for this use under REACH is no longer necessary.

On 24/10/2011 the European Commission requested the European Chemicals Agency to consider any new information on the hazards, socio-economic impact and market situation of 1,4-dichlorobenzene and prepare an Annex XV report according to Article 69(1) of the REACH Regulation, taking into account the current state of knowledge. The Annex XV report addressed the uses of the substance in **air fresheners**[*] and **toilet blocks**[†]. These uses lead to exposure of consumers when they use 1,4-dichlorobenzene-based products at home, or when they visit public amenities (mainly toilets) deodorised with these products. In addition, these uses lead to exposure of professional workers (toilet attendants and cleaners) who work in these toilets. The use in public premises by professionals had not been included in the assessment presented in the EU RAR (2004).

The Annex XV report did not address industrial air fresheners and other professional uses of 1,4-dichlorobenzene based products, in accordance with the recommended Strategy for Limiting Risks.

Regarding hazard assessment, exposure assessment and subsequent risk characterisation, DNELs presented in the Annex XV report prepared by ECHA for relevant endpoints were considered by RAC and revised in accordance with expert opinion and the relevant parts of

[*] **Air fresheners** include both domestic use of 1,4-dichlorobenzene-based air fresheners and uses in public toilets or other locations (including, for example, offices).

[†] **Toilet blocks** include both the so-called "urinal blocks" which are used in public toilets, and the toilet rim blocks or in-bowl blocks, which are used both in public toilets and in households.

Annex I of the REACH Regulation and the Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2010a). In addition, based on its review of the uncertainities and comments received during consultations, revised exposure modelling results were assessed by RAC to cover the specific relevant uses and exposed populations

For the assessment of compliance costs of the proposed restriction, but also for the analysis of the alternatives, the main information source used is the report "Socio-economic evaluation arising from a proposal for risk reduction measures related to restrictions on 1,4-dichlorobenzene" (RPA, 2010), commissioned by the European Commission. The results of this report have been complemented by additional literature, to take into account more up to date toxicological and exposure information, and stakeholder consultations carried out by AMEC (2012), commissioned by ECHA. This Background Document also includes new estimates of the costs.

A. Proposal

A.1 Proposed restriction

A.1.1 The identity of the substance

Table A1: Identity of the substance

Substance name	1,4-dichlorobenzene
IUPAC name	1,4-dichlorobenzene
EC number	203-400-5
CAS number	106-46-7
Molecular formula	$C_6H_4Cl_2$
Purity and impurities	the restriction shall apply to 1,4-dichlorobenzene whatever its purity

A.1.2 Scope and conditions of restriction

The opinions of RAC and SEAC concur that a restriction covering the placing on the market and use of toilet blocks and air fresheners containing 1,4-dichlorobenzene will reduce the exposure of consumers and professionals.

The decision to include toilet blocks and air fresheners used in indoor public areas in the scope of the restriction was to provide for a reduction in exposure of both consumers and professionals working in these areas. This type of exposure was not assessed in the EU EU Risk Assessment Report (EU RAR, 2004).

RAC considered exposure to

- Consumers using or being exposed to toilet blocks and air fresheners containing 1,4-diclorobenzene in households
- Users of public toilets where toilet blocks and air fresheners containing 1,4-diclorobenzene are used
- Professionals who work in public toilets where toilet blocks and air fresheners containing 1,4-diclorobenzene are used. This group include in particular toilet attendants and cleaners, but also other groups such as maintenance personnel and plumbers may be exposed
- Consumers and professionals who visit and/or work in indoor areas (other than toilets) where air fresheners containing 1,4-dichlorobenzene are used

Other professional or industrial uses, i.e. which are not related to consumer uses, were not considered. In consequence, industrial use of 1,4-dichlorobenzene-based air fresheners or uses of 1,4-dichlorobenzene in products which are not toilet air fresheners or toilet blocks are not included in the scope of this restriction (see section B.2.2). Finally, the restriction targets the

placing on the market and the use of toilet blocks and air fresheners containing 1,4-diclorobenzene. The restriction shall not apply to the manufacturing of 1,4-diclorobenzene or air fresheners and toilet block products for export.

1. Original restriction proposal from the dossier submitter (ECHA)

Designation of the substance, of the group of substances or of the mixture	**Conditions of the restriction**
1,4-dichlorobenzene EC No. 203-400-5 CAS No. 106-46-7	Shall not be placed on the market or used in[‡] i. Toilet blocks ii. Air fresheners to be used in toilets or other domestic or public indoor areas, or offices

The proposed restriction will apply 12 months after the amendment of the REACH Annex XVII comes into force.

2. Restriction proposal by RAC

Designation of the substance, of the group of substances or of the mixture	**Conditions of the restriction**
1,4-dichlorobenzene EC No. 203-400-5 CAS No. 106-46-7	1. Shall not be placed on the market, or used, as a substance or constituent of mixtures in a concentration equal to or greater than 1 % by weight where the substance or the mixture is intended to be used as an air freshener or to de-odourise toilets, homes, offices and other indoor public areas. 2. Paragraph 1 shall apply from {***date*** corresponding to 12 months after the Commission Regulation amending Annex XVII to REACH Regulation enters into force}.

3. Final restriction proposal by SEAC

Designation of the substance, of the group of substances or of the mixture	**Conditions of the restriction**
1,4-dichlorobenzene	1. Shall not be placed on the market, or used, as a substance or constituent of mixtures in a concentration equal to

[‡] It was not considered necessary to add a concentration limit for this restriction since 1,4-dichlorobenzene is the main active substance and not an impurity. In air fresheners and toilet blocks it is found in concentrations above 70 %.

EC No. 203-400-5 CAS No. 106-46-7	or greater than 1 % by weight where the substance or the mixture is intended to be used as an air freshener or deodoriser in toilets, homes, offices or other indoor public areas. 2. Paragraph 1 shall apply from {***date*** corresponding to 12 months after the Commission Regulation amending Annex XVII to REACH Regulation enters into force}.

Following advice from the Forum working group on enforceability of restrictions (received on 17 May 2013), two additional changes were made to improve readability:

The phrase "to de-odourise" was replaced by "deodoriser" to clarify that the restriction applies to air fresheners (or deodorisers) with a specific use (i.e. in toilets, homes, offices or other indoor public areas) and not e.g. to all air fresheners irrespective of their use.

The word "and" was replaced by "or" (in the phrase "or" other indoor public areas) to clarify that the phrase "indoor public areas" is not meant to include "toilets, homes and offices" but it applies in addition to those.

The proposed restriction should apply 12 months after the amendment of the REACH Annex XVII comes into force to allow distributors and suppliers to sell products in stock.

For the purposes of this Background Document, the term 'air freshener' will be used to describe any products used in toilets or other domestic or public indoor area (e.g. offices, public toilets, workplace toilets) that typically emits fragrance. 'Toilet block' indicates a block used in toilets which slowly dissolves in water. It may be sold in a small holder releasing the substance into the air, but also into the water, when the toilet bowl or urinal is flushed.

A.2 Summary of the justification

Currently, approximately 30,000 t of 1,4-dichlorobenzene are produced in the EU. Whereas more than 3000 t were used in the production of air fresheners and toilet blocks in 1994 (EU12), the current amount used is approximately 800 t, including imports.

A.2.1 Identified hazard and risk

Summary of identified hazards

This Annex XV proposal focuses on the human health hazards of 1,4-dichlorobenzene, since the adverse effect from the uses of concern mainly affects human health. Special attention has been given to endpoints which are directly related to the use of air fresheners and toilet blocks, i.e. adverse effects by inhalation. The hazard assessment carried out by ECHA builds on the work carried out in the context of the EU Risk Assessment Report (EU RAR, 2004), and also takes account of more recent work. The following is an overview of the hazardous properties of 1,4-dichlorobenzene listing all endpoints and conclusions drawn. The literature sources used to draw the main conclusions are mentioned below. More literature sources can be found in the core part of the Background Document.

- The **acute toxicity** of 1,4-dichlorobenzene is low regardless of the route of exposure (EU RAR, 2004).

- 1,4-dichlorobenzene has slight **irritation** properties for skin, eyes and the respiratory system (EU RAR, 2004).

- 1,4-dichlorobenzene is a weak **sensitiser** (EU RAR, 2004).

- Regarding the **repeated dose toxicity**, 1,4-dichlorobenzene is associated with liver toxicity in dogs (oral NOAEL of 10 mg/kg/day) (ATSDR, 2006). There is evidence of kidney toxicity in rats, leading to a NOAEC of 75 ppm for inhalation exposure. It can also cause slight local lesions of the nasal (olfactory and respiratory) epithelium in rats following inhalation exposure which allows establishing a NOAEC of 75 ppm (Aiso *et al.*, 2006). Liver and kidney toxicity was also noted in mice at the highest dose tested following oral exposure (NOAEL of 300 mg/kg/day for both endpoints).

- 1,4-dichlorobenzene is considered a **non-genotoxic substance** (EU RAR, 2004). This conclusion is important as it supports the finding that 1,4-dichlorobenzene is a thresholded carcinogen.

- The **carcinogenic** effects of the substance have been demonstrated as liver carcinogenicity in mice after oral exposure (NOAEL of 300 mg/kg/day), kidney adenocarcinoma in rats (which are not of relevance to humans) after oral exposure (LOAEL of 150 mg/kg/day) and liver carcinogenicity in mice after inhalation exposure (NOAEC of 75 ppm) (EU RAR, 2004). A threshold mechanism for carcinogenicity was considered as the most appropriate in the EU RAR. Recent reviews (ATSDR, 2006; Butterworth *et al.*, 2007) provide further support on the non-genotoxic threshold approach. The carcinogenic effects are considered to be the leading health effect for risk assessment.

- Recent literature contains information on the possible **endocrine** activity of the substance (inhalation NOAEL of 250 ppm in mice and rats, Takahashi *et al.*, 2007).

- Data from a two-generation oral reproductive toxicity study indicate toxicity in offspring at the highest dose tested. Toxicity is also noted at the mid dose in one generation of pups only (NOAEL of 30/mg/kg/day). Data from a two-generation study in rats via inhalation route and four developmental toxicity studies on rats and rabbits via oral and inhalation exposure did not reveal any evidence of reproductive or teratogenic effects in the absence of parental toxicity.

- A reported correlation between blood concentrations of 1,4-dichlorobenzene and **decrease in lung function** was considered (Elliot *et al.*, 2006), however, a causal link between decreased lung function and 1,4-dichlorobenzene exposure cannot be established based on the available data.

Summary of DNEL derivation

DNELs were derived and used for the risk characterisation, as required by the relevant parts of Annex I of the REACH Regulation and further explained in the Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2010). The same experimental studies as used for establishing margins of safety in the EU RAR (2004) were used.

DNELs for different endpoints were derived for consumers, ranging from 0.36 to 0.64 mg/m^3 and for workers, ranging from 2 to 3.62 mg/m^3. For use in the risk characterization, DNELs of 0.64 mg/m^3 for consumers and 3.62 mg/m^3 for workers (Table A2) based on hepatic tumours in mice following inhalation exposure were selected as the most appropriate (despite the lower values for liver effects in the sub-chronic feeding study in dogs), as carcinogenicity is considered as an endpoint of higher relevance for human health assessment and inhalation is the route of exposure of concern.

Table A2: DNELs of 1,4-dichlorobenzene for different endpoints for consumers and workers

Endpoint	DNEL (mg/m^3)		Reference
	Consumers	Workers	
Long-term, Inhalation, Systemic (carcinogenicity)	0.64	3.62	JBRC, 1995
Sub-chronic, Oral, Systemic (hepatotoxicity)	0.36	2	Naylor *et al.* , 1996

Summary of the exposure assessment

The exposure of both professionals and consumers from the uses of 1,4-dichlorobenzene in air fresheners and toilet blocks was estimatedby the dossier submitter. The available measured data were not considered to be representative of the conditions of use. Therefore, exposures were estimated by modelling using the ConsExpo 4.1 tool, which was considered to be the most appropriate tool for this purpose. The available measured data were, however, used to derive some of the modelling parameters and was also compared to the results of the modelling where possible.

The following exposure level estimates were considered by RAC to represent the reasonable worst case and realistic case scenarios:

- Professional workers: estimates of inhalation exposure to toilet attendants and toilet cleaners were calculated. Estimates were calculated for different temperatures, ventilation rates, exposure durations and product usage.

- Consumers: estimates of inhalation exposure were calculated for adults using different temperatures, ventilation rates, exposure durations and assumptions on air concentrations of 1,4-dichlorobenzene in the rest of the house in relation to the toilet.

In addition, the exposure of consumers using a public toilet was estimated.

For both professional workers and consumers exposure estimates, conservative values were chosen for "reasonable worst case scenarios", while "realistic case scenarios" were built on less conservative estimates that are expected to represent average real life conditions. The exposure estimates obtained range from 1.48-13.7mg/m^3 for workers and from 0.33-5.63 mg/m^3 for consumers.

Summary of the risk characterisation

The estimated exposure levels when compared with the DNELs the risk characterisation was greater than 1 for the reasonable worst case consumer scenarios (2.5-8.8) and for one of the realistic case consumer scenarios (1.08). The estimated exposure levels of toilet attendants and cleaners when compared with the DNEL for workers yielded RCR > 1 for reasonable worst case scenarios (1.21-1.64).

In conclusion, the exposure from the uses of 1,4-dichlorobenzene in air fresheners and toilet blocks are not adequately controlled for consumers. The exposure of professionals working in poorly ventilated toilets is also not adequately controlled.

A.2.2 Justification that action is required on an EU-wide basis

While use of 1,4-dichlorobenzene has significantly declined since its classification as a Category 2 carcinogen and its non-inclusion in Annex 1 of the Directive 98/8/EC, additional measures are needed to reduce exposure and to protect the health of consumers, toilet attendants and cleaners working in poorly ventilated environments, exposed to 1,4-dichlorobenzene present in air fresheners and toilet blocks from possible adverse effects (RCRs above 1 were estimated for consumers when exposed for a period of time greater than 16 hours and for workers when exposed for a period of 8 hours). In order to ensure a similar level of protection of human health across the EU, action needs to be taken on an EU-wide basis[§].

A.2.3 Justification that the proposed restriction is the most appropriate EU-wide measure

Health impacts

The following health impact from the use of 1,4-dichlorobenzene in air fresheners and toilet blocks was identified by RAC:

- Possibly some extra cancer cases due to the mitogenic properties of 1,4-dichlorobenzene (a threshold effect).

Population at risk

The use of 1,4-dichlorobenzene in air fresheners and toilet blocks gives rise to concerns for human health following inhalation exposure in consumers and professionals.

The exposure of consumers using 1,4-dichlorobenzene products in reasonable worst case conditions and in one realistic case cscenario at home have been identified to exceed the corresponding DNEL for consumers.

The exposure of professionals (toilet attendants and cleaners) in reasonable worst case conditions has also been identified to exceed the corresponding DNEL for workers.

Consequently, the exposure to these groups from the uses above is not adequately controlled.

Effectiveness in reducing the identified risks

The proposed restriction would remove the human health risks associated with the use of 1,4-dichlorobenzene in air fresheners and toilet blocks from all populations exposed. Adequate consumer products are already commonly used and are considered safer in relation to human health.

Following the implementation of the proposed restriction, 1,4-dichlorobenzene in air fresheners and toilet blocks would not be available on the European market for consumer or professional use. The products should no longer be made available to the market in all Member States within 12 months from the implementation of the restriction.

The exposure to 1,4-dichlorobenzene will cease when all air fresheners and toilet blocks currently on the market are used up, i.e. very soon after the implementation of the restriction.

Proportionality to the risks

The proposed restriction is well targeted to the identified risks and would not unduly affect uses or actors in the supply chain which are not associated to these risks. Different kinds of

[§] Currently one Member State (Sweden) has a national restriction on 1,4-dichlorobenzene.

alternative products for both 1,4-dichlorobenzene air fresheners and toilet blocks are available on the market, and the use of alternative products (with the exception of camphor) and techniques is considered safer from a health viewpoint than the use of 1,4-dichlorobenzene. The technical properties and functioning of 1,4-dichlorobenzene and alternative products differ to some extent, which makes their comparison challenging. The additional costs of alternatives for consumers are estimated to be low, and for some product groups the alternatives are even cheaper.

Different approaches were taken to estimate the costs related to restricting domestic and professional use (in public toilets). For domestic users it was assumed that 1,4-dichlorobenzene products and their alternatives are functionally equivalent (identical). In this case, switching to the alternatives would result in an increase in consumer surplus (i.e. saving) of about €2.8 million per year. For professionals, it was assumed that alternatives to 1,4-dichlorobenzene products have lesser technical properties in terms of odour-masking capability, and hence are imperfect substitutes: the consumer surplus related to this use of 1,4-dichlorobenzene products (which is a measure of their value in use relative to substitutes) is therefore lost as a result of restriction. With this assumption, it is estimated that the loss in consumer surplus (i.e. costs) is around €4 million per year. Consequently, the total cost to society is estimated to be €1.2 million per year. SEAC also considered a separate methodological approach to analysing the costs of the restriction based in the financial costs of switching from 1,4-dichlorobenzene to an alternative (the so called 'substitution cost' approach). Using this approach, as the alternatives in general are less expensive, the financial impact is estimated to be a saving of €1.4 m per year for the combined restriction. The two sets of cost estimates thus appear broadly consistent in terms of showing limited (or even reductions in) costs. The difference in whether costs or savings are derived can be accounted for by how much professional user demand is a function of 1,4-dichlorobenzene's characteristics and how professional users would respond to changes in cost between 1,4-dichlorobenzene based products and their alternatives.

Administrative and enforcement costs are estimated to be low.

A quantitative impact assessment based on decrease in lung functioning due to 1,4-dichlorobenzene exposure was included in the original Annex XV report submitted by ECHA. However, SEAC noted the RAC conclusion that there is insufficient evidence to support the link between exposure to 1,4-dichlorobenzene and reduced lung function. Therefore, SEAC did not consider it appropriate to use the results of the quantitative health impact assessment to inform the SEAC position. Nevertheless, the cost assessment suggests that under the substitution cost approach, any positive (or even zero) value of health benefit would be sufficient to justify the restriction on proportionality grounds, though a higher level of health benefit would be needed in the case of the consumer surplus approach in order to justify the (positive) costs in this case. Taking account of the scale of costs involved across all of the EU (-€1.2 million costs according to the consumer surplus approach and €1.4 million savings according to the substitution costs approach), SEAC considered that a discretionary case may be made for considering the costs of the proposal to not be disproportionate, and hence the restriction overall to be a proportionate measure.

Enforceability

Following comments received from the Forum on exchange of information on enforcement concerning means to ensure harmonised enforcement (Forum 1st advice, October 2012 and Forum 2nd advice, February 2013), a concentration limit of 1 % by weight was included in the restriction proposal.

Practicality and Monitorability

The proposed restriction is implementable. The air freshener and toilet block markets have already moved, to a great extent, to alternative products. It is thus considered that all actors

concerned will be able to comply with this restriction. A transition period of 12 months is considered adequate to allow all market operators to smoothly comply with the proposed restriction without abruptly disrupting the market.

The compliance to the proposed restriction can be followed mainly by verifying if importers, producers and distributors (wholesalers and retailers) still supply these products. The monitoring of the proposed restriction will be done through standard enforcement activities under Market Surveillance activities. No additional monitoring is considered necessary. The proposed restriction is in line with other legal requirements, more specifically the non-inclusion in Directive 98/8/EC on biocidal products for the use of the substance in moth-balls.

The proposed restriction is manageable. The way to implement it (by switching to alternative substances or techniques) is clear and understandable to all actors involved.

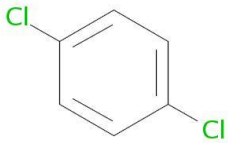
B. Information on hazard and risk

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

The information provided under this section is based on the EU RAR 2004 and the literature search performed by ECHA.

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

Table B3: Name and other identifiers of 1,4-dichlorobenzene

Identifier	Value	Source
EC number	203-400-5	EU RAR, 2004
EC name	1,4-dichlorobenzene	EU RAR, 2004
CAS number	106-46-7	EU RAR, 2004
CAS name	Benzene, 1,4-dichloro-	EU RAR, 2004
IUPAC name	Benzene, 1,4-dichloro-	EU RAR, 2004
Synonyms	p-dichlorobenzene; Paradichlorobenzene; p-chlorophenyl chloride; Dichlorocide;PDB; PDCB; p-dichlorobenzol	EU RAR, 2004
Trade names	Paracide; Paradow; Paradi; Santochlor; Paramoth; Paranuggets; Parazene; Persia-perazol; Para crystals; Globol; Evola; Di-chloricide; Paradichlorobenzol	ATSDR, 2006
Annex I index number	602-035-00-2	EU RAR, 2004
Molecular formula	$C_6H_4Cl_2$	EU RAR, 2004
Molecular weight	147.01 g/mol	EU RAR, 2004
Structural formula		EU RAR, 2004
Smiles code	Clc1ccc(Cl)cc1	RIVM, 2010

B.1.2 Composition of the substance(s)

According to the EU RAR, 2004, the degrees of purity of the products imported or exported within EU vary between 99.7 and 99.9%.

The possible impurities are shown in Table B4.

Table B4: Impurities of 1,4-dichlorobenzene

Substance	EC no	CAS no	Index no (R 1272/2008)	Concentration (%)
1,2-dichlorobenzene	202-425-9	95-50-1	602-034-00-7	≤ 0.1
1,3-dichlorobenzene	208-792-1	541-73-1	602-067-00-7	≤ 0.1
chlorobenzene	203-628-5	108-90-7	602-033-00-1	≤ 0.05
trichlorobenzene	234-413-4	12002-48-1	-	≤ 0.05

Source: EU RAR (2004)

B.1.3 Physicochemical properties

1,4-dichlorobenzene is a moderately volatile solid with a vapor pressure of 1.6 hPa-1.7 hPa at 20 °C equivalent to a saturated vapor concentration of about 1,500 ppm or 0.15 % by volume. The air-water partition coefficient is 10 and a mean odor threshold is 0.18 ppm v/v in air. It is slowly transformed from the solid state to vapors, leaving the very distinctive aromatic (camphor-like) odor (IARC, 1999).

A summary of physicochemical properties is given in Table B5.

Table B5: Physicochemical properties of 1,4-dichlorobenzene

Property	Value	Reference
Physical state at 20°C and 101,3 kPa	Solid, colourless or white crystals (flakes/granular)	EU RAR, 2004
Odour	Distinctive, penetrating aromatic odour, becoming very strong at concentration between 30 to 60 ppm	Merck Index, 2006; HSDB, 2011
Odour threshold	Water: 0.011 mg/L Air: 0.18 ppm (1.1 mg/m^3)	ATSDR, 2006; HSDB, 2011
Melting point	52.8-53.5 °C	EU RAR, 2004; HSDB, 2011
Boiling point	173-174 °C 174,12 °C	EU RAR, 2004; Merck Index, 2006

Density of the liquid	1.25-1.46 g/cm^3 at 20 °C 1.23 g/cm^3 at 70 °C	EU RAR, 2004
Bulk density	0.65 g/cm^3 (granular form) 0.788 g/cm^3 (scale form)	EU RAR, 2004
Vapour pressure	160-170 Pa at 2 °C * 1,330 Pa at 54.8 °C * 0.4 mmHg at 25 °C 80 Pa at 20 °C 170 Pa at 20 °C	EU RAR, 2004; Merck Index, 2006; IARC, 1999; RIVM, 2010
Odour threshold	0.72 mg / m^3 1.1 mg / m^3	RPA, 2010 ATSDR, 2006
Water solubility	60-70 mg/l at 20 °C Practically insoluble in water 90 mg/l at 25 °C	EU RAR, 2004; Padmanabhan *et al*., 2005; INERIS, 2006; Merck Index, 2006; RIVM, 2010
Solubility in organic solvents	Yes, in ethanol, acetone, benzene, chloroform, ethylene oxide and carbon disulfide	ATSDR, 2006; Padmanabhan *et al*., 2005
Henry's law constant	240-262 Pa·m^3/mol (at 20 °C) ** 275 Pa·m^3/mol (at 20 °C)	EU RAR, 2004; RIVM, 2010
Partition coefficient n-octanol-water	log Pow = 3.37-3.39 (experimental) *** log P (olive oil/water)= 3.65	EU RAR, 2004; Merck Index, 2006
Air-water partition coefficient	10	Aronson *et al*., 2007
Flash point	65-66°C (closed cup)	EU RAR, 2004; HSDB, 2011

Flammability	lower = 1.7 (%V) upper = 5.9 (%V) no autoflammability up to 500 °C	EU RAR, 2004
Viscosity, at 55°C	0.839 mPa·s	Rossberg *et al*., 2006
Other properties	Crystals sublimate at ordinary temperatures	Merck Index, 2006; Padmanabhan *et al*., 2005

* Only handbook data or values from safety data sheets are available. As the values differ only slightly from each other, they seem to be accurate.
** The value of 262 Pa·m^3/mol appears to be the most reliable as some data on the test method is available (Ashworth *et al*. 1988, as cited in the EU RAR).
*** Only the value of 3.37 is validated. For further assessment, a rounded value of 3.4 has been used.
Conversion factors: 1 ppm = 6.01 mg/m^3 at 25°C and 760 mmHg (EU RAR, 2004; Patty, 2000)
1 mg/m^3 = 0.166 ppm at 25°C and 760 mmHg (EU RAR, 2004; Patty, 2000)
1 ppm = 6.12 mg/ m^3 at 20°C and 1 atm (air-dispersion, 2011)
1 mmHg = 133.322…Pa (Atkins, 2006)

Chemical properties

Dichlorobenzenes belong to the group of organic halogen compounds replacing two hydrogen atoms in benzene by chlorine atoms, by the chlorination reaction of benzene. This chlorination reaction leads to similar ratio of *ortho- (*1,2-dichlorobenzene) and *para*-dichlorobenzene (1,4-dichlorobenzene), but a small amount of the *meta* isomer (1,3-dichlorobenzene) is still produced. The three isomers have low water solubility and a higher density than water. 1,4-dichlorobenzene is not easily broken down by soil organisms. Like many hydrocarbons, 1,4-dichlorobenzene is lipophilic and accumulates in the fatty tissues (EU RAR, 2004).

Padmanabhan *et al*. (2005) described 1,4-dichlorobenzene as more stable than the corresponding *ortho*- or *meta* isomers. The number and position of the chlorine substituent plays a vital role in deciding the structural stability/reactivity of chlorobenzenes. Chlorobenzenes act as electron acceptors in their interaction with nucleic acid bases/selected base pairs and thereby exhibit their toxic characteristics. The reactive sites in chlorobenzenes identified using the local philicity (*ö*+), the calculated energies, thermodynamic quantities (enthalpy and free energy), and dipole moments of all chlorobenzenes conduct to the conclusion that the *para* isomer (1,4-dichlorobenzene) is the most stable, whereas the *ortho* isomer (1,2-dichlorobenzene) is the least stable. The chlorine substituent at the adjacent positions in chlorobenzenes seems to destabilize the isomers, and the resulting steric effect may be one of the important sources of the relative instabilities of the chlorobenzene isomers apart from the associated electrostatic effects. Also, there is an increase in the value of the electrophilicity index with an increase in the number of chlorine substitutions, indicating an increase in reactivity of more substituted chlorobenzenes. The carbon atom attached to the chlorine atom and the chlorine site shows affinity toward nucleophilic attack in monochlorobenzene and this leads to charge depletion at the carbon sites in the ortho positions. A similar situation prevails in 1,4-dichlorobenzene with non-chlorine-substituted carbon sites predominating in nucleophilic attack.

B.1.4 Justification for grouping

Not relevant for this proposal.

B.2 Manufacture and uses

B.2.1 Manufacture, import and export of a substance

Information collected under REACH and CLP

Registrations and Downstream User reports

Less than ten companies (manufacturers, importers and only representatives) jointly registered the substance at tonnages above 1000 tonnes/year and 100-1000 tonnes/year. The use of the substance in air-care products, by both consumers and professional workers, is included among the registered uses. ECHA has also received one downstream user report (REACH-IT search on 15/03/2012) which relates to the uses of concern (use of 1,4-dichlorobenzene in air care products).

Pre-registrations

Some additional registrations of 1,4-dichlorobenzene might be expected for the following two registration deadlines (in tonnage bands of 1-10 tonnes and 10-100 tonnes), but no accurate estimation of their number can be done based on the available pre-registration data. Approximately 1000 pre-registrations have been received for all tonnage bands.

Historical data on manufacturing, imports and exports

Table B6 shows some historical data on manufacturing, imports and exports of 1,4-dichlorobenzene (EU RAR, 2004) and the latest available manufacturing volume for 2010 (RPA, 2010). It is to be noted that the figures of the table are not directly comparable between them, since they refer to different geographical regions of the EU. The table shows that the quantities manufactured in the EU are maintained in the same order of magnitude (approximately 30000 – 35000 tonnes/year). At a first approximation this is because the quantities destined to support production of mothballs have been "replaced" by quantities destined to export, for the production of polyphenylene sulphide (PPS) (see also next paragraph for more details on these uses).

Table B6: Manufacturing, import and export of 1,4-dichlorobenzene in the EU, in tonnes/year

	1985	1987 - 1988	1991	1995	2010
Manufacturing	n.a.	33000 – 35000*	n.a.	22500 - 30500*	30000
Import	4500	n.a.			
Export	16500			14835	n.a.
EU consumption	22950	20500	16400	15000	

Source: EU RAR (2004), RPA (2010)
n.a.: not available
*ranges given as provided in EU RAR

Production process

1,4-dichlorobenzene is produced by direct chlorination according to a continuous method where liquid benzene is converted with gaseous chlorine in the presence of a catalyst. Through the choice of molar ratio between benzene and chlorine the isomeric ratio of 1,2- to 1,4-dichlorobenzene can be influenced. The chlorination products are separated by distillation.

After crystallisation, the final product can be packaged and transported in solid or liquid form. The corresponding operations are performed in closed systems (EU RAR, 2004).

In practice, 1,4-dichlorobenzene is produced as a by-product of the production of monochlorobenzene. Depending on the ratio of benzene to chlorine chosen, one can achieve either a low rate of benzene conversion and little dichlorobenzene formation, or almost complete conversion of the benzene with a higher degree of dichlorobenzene formation. Which of the two alternatives is favoured depends on a profitability calculation, in which the distillation costs occasioned by the dichlorobenzenes need to be taken into account. The composition of a chlorination mixture containing the highest possible proportion of monochlorobenzene has been given as 4 –5 % unreacted benzene, 73 % monochlorobenzene, and 22 – 23 % dichlorobenzene. Higher concentrations of dichlorobenzene are obtainable in batch processes (Ullmann's Encyclopedia, 2006). In conclusion, a quite high percentage of dichlorobenzene is an unavoidable by-product of the monochlorobenzene production process.

The chlorides on 1,4-dichlorobenzene can be substituted with hydroxyl, amine, and sulfide groups. In a growing application, 1,4-dichlorobenzene is the precursor to the high performance polymer poly(p-phenylene sulfide).

B.2.2 Uses

Uses in Air fresheners and Toilet blocks

Tonnage estimates

The amount of 1,4-dichlorobenzene used in the EU for the manufacturing of air fresheners and toilet blocks is estimated at 800 tonnes/year (RPA, 2010). RPA[5] estimates that 50 % of this amount of 1,4-dichlorobenzene might be imported from non-EU countries (e.g. China and India). The estimated tonnage used in the manufacturing of consumer products is 100 tonnes/year (83 tonnes/year for air fresheners and 17 tonnes/year for toilet blocks in 2009); the rest is allocated to professional uses. These estimates refer to the substance itself and do not include imports of finished products containing 1,4-dichlorobenzene from non-EU countries.

Table B7: Estimated quantities (tonnes) of 1,4-dichlorobenzene used in the production of air fresheners, toilet blocks and moth repellents in the EU

	EU12/1994 (EU RAR, 2004)	**EU15/2003** (RPA, 2010)	**EU27/2008** (RPA, 2010)
Toilet blocks/air fresheners	3170	2285	800
Moth repellents	4070	7095	-
TOTAL	7240	9380	800

Table B7 shows a dramatic decline in the tonnage used for the production of air fresheners and toilet blocks from 1994 to 2008.

[5] RPA (Risk and Policy Analysts) authored the report "Socio-economic evaluation arising from a proposal for risk reduction measures related to restrictions on 1,4-dichlorobenzene" (RPA, 2010). This report was commissioned by the European Commission.

An estimation of the amounts of air fresheners and toilet blocks sold annually in the EU is given in Table B8, broken down to type of use. Domestic use indicates that these products are used by consumers in a domestic environment. Professional use indicates that these products are used by professional workers to deodorize public toilets. They can thereby lead to the exposure of consumers as well. The estimates of Table B8 are used in the socio-economic assessment of the proposed restriction in section F.

Table B8: 1,4-dichlorobenzene air fresheners and toilet blocks sold annually in the EU (tonnes)

Product group	**1,4-dichlorobenzene placed on the market**
Air fresheners (domestic use)*	83
Toilet bowl blocks (domestic use)**	13
Air fresheners (professional use)*	100
Urinal blocks (professional use)**	613
Total	**809**

* Source: RPA (2010)
**Source: AMEC (2012)

Production process

The production process of air fresheners and toilet blocks implies the addition of dye and perfume [6] to 1,4-dichlorobenzene followed by compression of flaked or granular 1,4-dichlorobenzene into disks or blocks. A prior processing of the material is required, either melting/recrystallising and flaking or milling. The next step involves formatting into blocks and packaging and labelling for distribution (RPA, 2010).

Applications in air fresheners

1,4-dichlorobenzene air fresheners are used to deodorise most commonly in toilets and bathrooms, but not exclusively.

For the use as air fresheners the following applications are possible (RPA, 2010; ATSDR, 2006):

- in relatively small size (possibly in the form of a cylindrical tablet) and in solid form[7], 1,4- dichlorobenzene-based air fresheners may be used:
    - inside a plastic box/cage (for instance, made of polypropylene) or paper carton container to deodorise rooms, by hanging on the wall;
    - as deodorisers in diaper pails

[6] The additional fragrance that is added to 1,4-dichlorobenzene products is simply there to make the odour of the product more pleasant as the smell of pure 1,4-dichlorobenzene is a moth ball-like one and is very strong (RPA, 2010).
[7] All known applications of air fresheners and toilet blocks contain 1,4-dichlorobenzene in solid form. There is no information regarding applications of 1,4-dichlorobenzene in aerosols, liquid, gel forms etc.

- in large size (often called 'super blocks' in the US, approximate weight 9 kg) and in solid form, 1,4-dichlorobenzene-based air fresheners may be used in an industrial setting as deodoriser/odour masking blocks for 60-90 days in:
    - sewer systems where they are suspended from manhole covers throughout the sewer line network and prevent/reduce significantly the release of sewer gases into the streets
    - industrial waste collection containers and water treatment facilities
    - lift shafts
- no information on size available:
    - animal holding facilities
    - garbage cans

There is no information indicating their use to de odourise vehicles.

Applications <u>in toilet blocks</u>

For the use as toilet blocks, the following applications are possible (RPA, 2010):

- a solid deodorising cube, sphere, disc, etc. for standing urinals (BUA, 1994 as cited in RPA, 2010), often deposited on a plastic screen;
- a solid block contained in a plastic urinal screen i.e. plastic pliable screen (see pictures of products by JaniSan, 2009, as cited in RPA, 2010)
- a solid block hanging from the rim of a toilet bowl (Grainger, 2010; Bush Boake Allen, 1989 as cited in RPA, 2010; Aronson *et al*., 2007). Rim blocks may comprise:
    - a plastic box with a hanger insider which a cylindrical or cuboid block is placed,
    - a cuboid block upon which a plastic hanger is attached, or
    - a tablet with a hole in the middle through which a plastic or metal wire hook is put through to allow hanging on the rim of a toilet bowl (see pictures of products available in JaniSan, 2009 as cited in RPA, 2010).

1,4 dichlorobenzene is not used in cistern blocks (these are placed in the flushing tank). The substance does not dissolve in water and, therefore, it would be totally ineffective.

The main application of toilet blocks in this area is in the form of urinal blocks in public toilets where urinal bowls are present. On the other hand, the only type of toilet block that could feasibly be used by private consumers at home is toilet rim blocks.

The odour-masking property of the substance, used as air freshener or toilet block, is the main reason for the use in the toilets. However, the presence of the substance in the air may have some additional effects – such as repelling insects. This function, however, may be related to the concentration of the substance in the air, which may or may not be reached when the substance is used as an air freshener.

<u>Other deodorising applications</u>

Other products where 1,4-dichlorobenzene is used are the following (RPA, 2010):

- toilet limescale remover (<0.5 % 1,4 dichlorobenzene – Cannon Hygiene, 2003 as cited in RPA, 2010);

- corrosion inhibitors and odour control agents in tablet form (<8 % 1,4-dichlorobenzene – Momar, 2006 as cited in RPA, 2010); and

- as a granular embalming powder/coffin hygiene agent (30-50 % 1,4-dichlorobenzene mixed with paraformaldehyde – Hizone Brands, undated, as cited in RPA, 2010) where it is sprinkled on the base of a coffin where a body is for long distant transport e.g. repatriation to another country or the powder is sprinkled into bodybags where human remains have decomposed.

Other uses

1,4-dichlorobenzene is used as an intermediate in chemicals production, as a processing aid in the production of grinding wheels, as a monomer for the production of polyphenylenesulphide (PPS) and as a laboratory chemical (Table B9). 1,4-dichlorobenzene also seems to be used (or has been used) in a variety of other uses, but which are not identified uses under REACH: carrier for textile dyes (polyester and wool dyes, but is replaced by alkylnaphthalenes (EU RAR, 2004)), intermediate in crop protection and paper industry, pharmaceuticals, agrochemicals (insecticide on fruit, to control mold and mildew on tobacco seeds leather and fabrics (RPA, 2010; ATDSR, 2006)), cosmetics and others (Lanxess website). The use for the formulation of moth repellents is not authorised anymore in the EU. There are however indications that unauthorised uses of 1,4-dichlorobenzene, i.e. as a moth repellent, might still occur in the EU27. It was found that 1,4-dichlorobenzene-based blocks are marketed as moth balls on certain websites (RPA, 2010).

The use pattern of 1,4-dichlorobenzene has changed in the recent years. When the EU RAR was published most of the manufactured tonnage was used as intermediate, followed by the use in moth repellents, toilet blocks and finally grinding wheels. Currently most of the manufactured tonnage is used as a monomer for polymer production, followed by the use as intermediate, in grinding wheels, toilet blocks/air fresheners and as a laboratory chemical.

Table B9: Identified uses of 1,4-dichlorobenzene

Use setting	**Identified uses**
Uses by workers in industrial settings	Use as a monomer in polymer production
	Use as an intermediate
	Use in processing of grinding wheels
Uses by professional workers	Use as a laboratory chemical
Uses by consumers	Article service life • Vehicles • Machinery, mechanical appliances, electrical/electronic articles

	• Electrical batteries and accumulators • Plastic articles

Source: Information on registered substances:
http://apps.echa.europa.eu/registered/registered-sub.aspx#search (search on 15/03/2012)

Monomer for PPS production

In polymer manufacturing the substance is used as a monomer for the production of polyphenylene sulphide (PPS) (currently in United States, Japan and China). PPS is used in the automotive and aircraft sector, because it enables the replacement of metal parts by lighter polymer components, especially at locations of heavy thermal stress. Due to these uses, small quantities of 1,4-dichlorobenzene can be found as residual monomer in consumer articles (Table B9). Other recent developments include the implementation of PPS in exhaust pipes and high thermo resistant exhaust gas filter bags in coal fired power plants. PPS is currently not manufactured in the EU. EU companies supply 1,4-dichlorobenzene to manufacturers of PPS, which is then re-imported to the EU (RPA, 2010). PPS contains 1,4-dichlorobenzene as an impurity of ca. 0.01 % (EU RAR 2004).

Intermediate

1,4-dichlorobenzene is processed to 1,4-dichloro-2-nitrobenzene, a precursor for dyes and pigments. 1,4-Dichloro-2-nitrobenzene is synthesised in a continuous procedure by nitration of 1,4 dichlorobenzene with nitrating acid (nitric acid/sulphuric acid). After separation of the sulphuric acid and the remaining nitric acid, the raw product is washed with sodium hydroxide and water and is subsequently purified by fractionating crystallisation (EU RAR, 2004).

The use as an intermediate includes the synthesis of agrochemicals, dyestuffs, fragrances and aromas (RPA, 2010).

Grinding wheels

For the production of porous grinding material, a so-called burnout substance is mixed with the grinding material (aluminium oxide, silicium carbide etc.). Material such as cork, naphthalene or 1,4-dichlorobenzene can be used. After mixing and shaping, the grinding wheels are dried and then heated to temperatures of 1,100-1,300 °C. 1,4-Dichlorobenzene can be recovered during the drying process or is thermally destroyed during the heating process (EU RAR, 2004).

When the 1,4-dichlorobenzene flakes are used for the production of grinding or abrasive paper the substance itself is not a part of the end product (RPA, 2010).

B.2.3 Uses advised against by the registrants

No specific use has been advised against by the registrants.

B.2.4 Description of targeting

According to the conclusions of the EU Risk Assessment Report the concerns from the uses of this substance focus on human health risks to workers and consumers (EU RAR, 2004). The hazard assessment and exposure analysis is accordingly targeted to human health[8].

Furthermore, the Strategy for Limiting Risks targets the risks to consumers, and recommends *to consider at Community level marketing and use restrictions… in air fresheners, moth repellents and toilet blocks* (EC, 2008). Moth repellents are not authorised anymore in the EU. Consequently the proposal targets the risks from the use in air fresheners and toilet blocks only.

For workers the Strategy reports that *the legislation for workers' protection currently in force at Community level is generally considered to give an adequate framework to limit the risks.* However, professional use of air fresheners and toilet blocks in public toilets (or other indoor locations) was not examined in the EU RAR and these exposures give rise to exposure of both consumers and workers. This exposure scenario was considered relevant for the scope of this restriction proposal.

In conclusion, the Background Document examines the use of 1,4-dichlorobenzene in air fresheners and toilet blocks by both consumers and professional workers. Consumers can be exposed to the substance at home or when using public toilets. Professional workers can be exposed to the substance in public toilets in their role of toilet attendants or when cleaning, replacing used toilet blocks and air fresheners, doing maintenance work, etc.

The list of known uses (see section B.2.3) contains a number of borderline cases where the products might not be used in toilets, or are used in very specific applications, for example:

- as deodorisers in diaper pails e.g. nursing home
- as coffin hygiene agents

The above uses should not be covered by the scope of the restriction as no exposure scenarios have been presented for RAC to consider and consumer exposure is expected to be minimal.

The following uses, where the products are not used indoors, are in principle out of the scope of the restriction proposal.

- sewer systems where they are suspended from manhole covers throughout the sewer line network and prevent/reduce significantly the release of sewer gases into the streets
- industrial waste collection containers and water treatment facilities
- lift shafts
- animal holding facilities
- garbage cans

[8] For the environment, the conclusion of the risk assessment is that there is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied. This conclusion is reached for the exposure of the aquatic compartment (including the sediment, the atmosphere, the terrestrial compartment, as well as for predators (EU RAR, 2004). Consequently, the environmental risks of the use of 1,4-dichlorobenzene are considered controlled and have not been assessed in this report. Some brief information on environmental hazards of 1,4-dichlorobenzene and alternatives products are presented in section C.2.3.

B.3 Classification and labelling

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

1,4-dichlorobenzene was included under the index number 602-035-00-2 in Annex I to Directive 67/548/EEC as indicated in Table 3.2 - List of harmonised classification and labelling of hazardous substance. Its current classification is presented in Annex VI of Regulation (EC) No 1272/2008, on classification, labelling and packaging of substances and mixtures, in Table 3.1 List of harmonised classification and labelling of hazardous substances.

Table B10: Classification and labelling

Index No: 602-035-00-2 **International Chemical Identification:** 1,4-dichlorobenzene; p-dichlorobenzene **EC No**: 203-400-5 **CAS No:** 106-46-7			
	Classification according to Regulation (EC) No 1272/2008, Annex VI:Table 3.2 *List of harmonised classification and labelling of hazardous substances* from Annex I to Directive 67/548/EEC	**Classification and labelling according to** Annex VI, Table 3.1**,** *List of harmonised classification and labelling of hazardous substances* of Regulation (EC) 1272/2008	
		Hazard Class and Category Codes	Hazard statement Codes
Classification	Carc. Cat. 3; R40 Xi; R36 N; R50-53	Carc. 2: Category 2 carcinogen Eye Irrit. 2: Eye irritation, hazard category 2 Aquatic Acute 1: Hazardous to the aquatic environment, acute hazard category 1 Aquatic Chronic 1: Hazardous to the aquatic environment, chronic hazard category 1	H351: Suspected of causing cancer H319: Causes serious eye irritation H400: Very toxic to aquatic life H410: Very toxic to aquatic life with long lasting effects

Labelling	**Symbols**  **Risk phrases:** R36 Irritating to eyes R40 Limited evidence of a carcinogenic effect R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment, **S phrases:** S2 Keep out of the reach of children S36/37 Wear suitable protective clothing and gloves S46 If swallowed, seek medical advice immediately and show this container or label S60 This material and its container must be disposed of as hazardous waste S61 Avoid release to the environment. Refer to special instructions/Safety data sheets	Pictogram, Signal Word Codes	Hazard Statement codes
		GHS08: Carcinogenicity, hazard category 2  GHS09: Hazardous to the aquatic environment  - Acute hazard category 1 - Chronic hazard category 2 Wng: Warning	H351Suspected of causing cancer H319 Causes serious eye irritation H410: Very toxic to aquatic life with long lasting effects

Source: Regulation (EC) No 1272/2008, on classification, labelling and packaging of substances and mixtures

B.3.2 Classification and labelling in classification and labelling inventory

Industry's self classification(s) and labelling

Approximately 270 notifications were obtained for 1,4-dichlorobenzene (including both notifications from individual companies and bulk notifications), most of them identical with the harmonized classification. The only difference in some of the notified classifications consists of the addition of the GHS07 pictogram.

B.4 Environmental fate properties

Not relevant.

B.4.1 Degradation

Not relevant.

B.4.2 Environmental distribution

Not relevant.

B 4.3 Bioaccumulation

Not relevant.

B.4.4 Secondary poisoning

Not relevant.

B.5 Human health hazard assessment

The assessment of the human health hazards of 1,4-dichlorobenzene is based on the information contained in the EU RAR (2004). In addition, more recent literature has been screened, including a report from RPA (2010) and risk assessments by other organizations such as the ATSDR (2006).

B.5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

B.5.1.1 Non-human information

EU RAR 2004

The EU RAR reviewed several studies in rats and mice via the oral, inhalation and intravenous routes, in rabbits via the oral route and in rats via the subcutaneous route (Hawkins, 1980; Azouz, 1955; Kimura, 1979; Wilson, 1990; Hissink, 1996b; HRC, 1976, as cited in the EU RAR). The main studies are reported below.

Absorption

A study performed in mice and rats via the oral, inhalation and intravenous routes (Wilson, 1990, as cited in the EU RAR) showed rapid but not complete absorption of 1,4-dichlorobenzene in the digestive and respiratory tracts (peak blood levels measured one hour after administration). The absorption varied with the route and species but was not significantly influenced by dose or sex. Absorption was poorer via inhalation than via oral exposure. Absorption via inhalation exposure was higher in mice (59 %) than in rats (25-33 %), while it was similar in rats (72 %) and mice (71 %) after oral exposure. In rats, absorption decreased after repeated oral exposure (62 %). No information was available on percutaneous absorption in animals, but according to the EU RAR it cannot be excluded. The absorption after oral administration resulted in peak blood levels after 1 hour, distribution half-life of 3.5 hours and peak tissue levels after 6 hours.

A study in rats and mice (HRC, 1976, as cited in the EU RAR) reported similar plasma concentrations for both species after 24 hours following oral or subcutaneous administrations.

Distribution

The distribution of 1,4-dichlorobenzene was similar in rat tissues regardless of exposure routes. The substance was found in fatty tissues, kidney, liver, lungs, gonads and muscle

tissues (HRC, 1976, as cited in the EU RAR), with highest concentrations in fat tissue (Hawkins, 1980, as cited in the EU RAR). The liver concentrations of 1,4-dichlorobenzene were higher in female than in male F344 rats, however, kidney concentrations were higher in males than in female F344 rats following inhalation exposure (Umemura *et al*., 1990 and 1992, as cited in the EU RAR).

Metabolism

The metabolism of 1,4-dichlorobenzene has been extensively investigated in rodents. In the EU RAR several studies via the oral and inhalation routes were reviewed. In mice and rats 1,4-dichlorobenzene was mainly hydroxylated to the sulphate and glucuronide conjugates of 2,5-dichlorophenol and also to free 2,5-dichlorophenol.

2,5-dichlorohydroquinone was found in F344 and SD rats but not in Wistar rats and mice.

In rabbits, the major metabolites were the 2,5-dichlorophenol conjugates. Also free 2,5-dichlorophenol and dichlorohydroquinone were formed but no mercapturic acid or catechol (Azouz 1955 *et al.*, as cited in the EU RAR).

In rats 1,4-dichlorobenzene exhibited an enterohepatic cicle with elimination during 24 hours mainly in bile (50 % in SD rats) and a small percent in faeces (0.1 % in SD rats) after a single dose by inhalation (1,000 ppm), oral (250 mg/kg) or subcutaneous (250 mg/kg) exposure (HRC, 1976, as cited in the EU RAR).

In vitro studies

The EU RAR reviewed several *in vitro* studies with mice, rats and human cells.

In vitro conversion of 1,4-dichlorobenzene to 2,5-dichlorohydroquinone by liver microsomes from B6C3F1 mice and Wistar rats has been reported (Hissink, 1997b; Den Besten *et al*., 1992, as cited in the EU RAR).

Another study (Fisher 1995, 1991b and 1990, as cited in the EU RAR) showed quantitatively and qualitatively the same metabolites for 1,4-dichlorobenzene in rat (F344 and SD) and human liver slices: glutathione/cysteine conjugates (major metabolites) and glucuronide and sulphate conjugates.

Den Besten *et al*. (1992, as cited in the EU RAR) reported that Wistar rat liver microsomes metabolised 1,4-dichlorobenzene to 2,5-dichlorophenol and to a lesser extent to 2,4-dichlorophenol, followed by oxidation to its hydroquinone derivative and subsequent oxidation to dichlorobenzoquinone species, 3,5-dichlorocatechol and 1-dichlorobenzoquinone.

Conversion of 1,4-dichlorobenzene was much higher in mouse (16 %) than rat (0.6-1.3 %) or human (0.3 %) liver microsomes (Hissink, 1997b; 1996a, as cited in the EU RAR). The GSH conjugate of the epoxide of 1,4-dichlorobenzene (derived from exogenous glutathion) was higher in rat than in mouse or human microsomes. The addition of cytosol had a marginal effect on mouse and rat microsomes whereas in human liver microsomes it generated a major increase of this GSH conjugate (6 compared to 43 %). Hydroquinone metabolites production (as chlorohydroquinone) in percentage of total conversion was also species dependent: in mice and human liver microsomes it was 16 %, in F344 rats 27 %, and in SD and Wistar rats it was 10 %. The recovery of hydroquinone metabolites increased by addition of ascorbic acid (an inhibitor of hydroquinone oxidation to benzoquinones) and was more pronounced in mice (55 % of total conversion) than in human (28 % of total conversion) while the protein covalent binding was almost completely inhibited (decreased from 21 % to 1.7 % in mouse and from 5.8 to 4.4 % in human). This suggested that the formation of benzoquinone occurs in humans but at very low levels.

In liver microsomes from rats, ascorbic acid inhibited protein binding with 33 % in microsomes from SD and F344 rats and with 80 % in Wistar rats (Hissink 1997b, as cited in the EU RAR).

Relatively more glutathione conjugates of quinones were produced by human and B6C3F1 mouse microsomes (26 and 39% respectively) than by rat microsomes (3 to 22% depending on the strain) (Hissink, 1997b, as cited in the EU RAR).

Elimination

The elimination of the absorbed ^{14}C 1,4-dichlorobenzene was more complete via the oral than the inhalation route and was not significantly affected by dose.

For the oral route the mean cumulative total excretion after 7 days was 80-99 % in F344 rats and male B6C3F1 mice: 55-70 % in urine, 8-15 % in faeces and 10-12 % in the expired air (Wilson, 1990, as cited in the EU RAR). The excretion in urine after 72 hours was more complete after oral exposure (38-42 %) (Klos, 1994, as cited in the EU RAR) than via inhalation exposure (35 % mean cumulative total excretion after 7 days in F344 rats and 55 % in male B6C3F1 mice).

In SD rats 1,4-dichlorobenzene was eliminated in the urine (87 % after oral, 73 % after inhalation and 41 % after subcutaneous exposure) compared to 1.9 %, 2.5 % and 0.1 % in the faeces (HRC, 1976).

In SD rats, means of 97.4 %, 97.1 % and 90.5 % of material excreted during 5 days after exposure were found in urine after inhalation, oral and subcutaneous administration (HRC, 1976, as cited in the EU RAR).

Total elimination occurred in Wistar rat in 4 days after a single oral administration and in 35 days after repeated oral administration (28 days) (Schmidt, 1977a, as cited in the EU RAR). Tissue accumulation of 1,4-dichlorobenzene in Wistar rats was considered to be unlikely after inhalation or oral exposure (Schmidt, 1977a,b; HRC, 1976, as cited in the EU RAR).

Additional information

No additional information was found.

B.5.1.2 Human information

Absorption of 1,4-dichlorobenzene in humans occurs in the gastro-intestinal and respiratory tracts. There are no data available on cutaneous absorption (Pagnotto, 1965; Ghittori *et al.*, 1985, as cited in the EU RAR).

In humans, 1,4-dichlorobenzene is essentially distributed to fatty tissues, but also to liver and milk. Elimination occurs essentially to urine in the form of 2,5-dichlorophenol (Sumino, 1988, as cited in the EU RAR). The elimination of 2,5-dichloroquinol through urine was reported (Hallowell, 1959, as cited in the EU RAR) following accidental ingestion of 1,4-dichlorobenzene by a child. In studies on volunteers (Wallace, 1989; Hill, 1989, as cited in the EU RAR), elimination was shown to occur via the respiratory tract.

Results of occupational studies (workers exposed in manufacturing and packaging) to 1,4-dichlorobenzene, with measurements of 2,5-dichlorophenol in spot samples collected at the end of the workshift, showed that excretion was concomitant with the exposure, attained a maximum level after approximatively 8 hours, and continued for several days. It was established that a concentration of approximately 33 ppm of 1,4-dichlorobenzene in air corresponded to a mean concentration of 100 mg/l in the urine at the end of the workshift (Pagnotto, 1965, as cited in the EU RAR).

In occupational exposures, the quantity of 2,5-dichlorophenol excreted between the beginning and the end of the work shift was well correlated with the intensity of exposure. For an exposure of 10 ppm the concentration of 2,5-dichlorophenol excreted in the urine at the end of the shift was approximatively 45 mg/l (Ghittori *et al.*, 1985, as cited in the EU RAR).

Detectable levels of 2,5-dichlorophenol in urine were also reported in 1,000 U.S. adults (Hill, 1995, as cited in the EU RAR). Another study in Tokyo metropolitan area residents exposed via the environment to 1,4-dichlorobenzene (possible via inhalation and via food with levels of inhalation exposure from 1.5 to 4.2 μg/m^3 (outdoors) and from 105 to 1,700 μg/m^3 (indoors). This exposure resulted in an average concentration of 2.3 μg/g in adipose tissue and 9.5 μg/ml in blood (Morita, 1975a, b, as cited in the EU RAR).

B.5.1.3 Conclusions

The animal studies show that 1,4-dichlorobenzene is rapidly but not completely absorbed via the digestive and respiratory tracts. Also subcutaneous absorption occurs. The distribution of 1,4-dichlorobenzene in animals was concluded to be similar in fatty tissues, kidney, liver, lungs, gonads and muscle tissues regardless of exposure route.

In vivo 1,4-dichlorobenzene is principally metabolized to the sulphate and glucuronide conjugates of 2,5-dichlorophenol and to free 2,5-dichlorophenol in mouse, rat and humans. Some species differences in metabolism is evident as 2,5-dichlorohydroquinone is found in some rat strains and possibly in humans but not in mice.

In vitro the major metabolites are in rat, mouse and human liver microsomes dichlorophenols, hydroquinone metabolites and to a lesser extent glutathione-epoxide and glutathione-quinone conjugates. Species differences included a much higher conversion of 1,4-dichlorobenzene in mouse microsomes than in rat and human microsomes, and production of more hydroquinone metabolites in mouse, F344 rat and human microsomes than in microsomes from Wistar and SD rats. Benzoquinone production seems more predominant in microsomes from mice and rats than from humans.

The majority of 1,4-dichlorobenzene is eliminated through urine and faeces. Tissue accumulation of 1,4-dichlorobenzene was considered unlikely in rats.

In humans, 1,4-dichlorobenzene has been shown to be distributed to fatty tissues, but also to the liver and milk. Elimination occurs essentially through the urine in the form of 2,5-dichlorophenol, but elimination also occurs via the respiratory tract.

B.5.2 Acute toxicity

B.5.2.1 Non-human information

<u>EU RAR 2004</u>

The EU RAR reports the acute effects of 1,4-dichlorobenzene by the oral, dermal, inhalation and intraperitoneal routes. The animal studies taken into consideration for the inhalation route indicated that the 4-hour LC_{50} in rats (EEC method, GLP, limit test) is greater than 5.07 mg/l (845 ppm), with signs of pulmonary irritation (increased respiratory rate up to 4 hours post exposure), piloerection and reversible weight gain losses at Day 2, without macroscopic anomalies (Hardy, 1987 as cited in the EU RAR). In a study with progressive nasal exposure during 7 hours symptoms as tremors, hyporeflexia and instability were observed at Day 1 (Hoechst, 1981, as cited in the EU RAR). Given the available animal data, the EU RAR concluded that 1,4-dichlorobenzene shows low acute toxicity (inhalationLC50>5.07 mg/l; oral LD_{50} >2,000 mg/kg; and dermal LD_{50} >2,000 mg/kg).

<u>Additional information</u>

Information on effects of acute-duration inhalation exposure to 1,4-dichlorobenzene in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth *et al*. 1956). Five rats of each sex and five guinea pigs of each sex were exposed to 173 ppm of 1,4-dichlorobenzene for 7 hours/day, 5 days/week for 16 days (Hollingsworth *et al*. 1956). Mild histological effects of interstitial oedema, congestion, and alveolar hemorrhage were observed in the lungs of male rats and female guinea pigs. The experimental design and report of this study have a number of deficiencies, such that reported observations provide only qualitative evidence of exposure-related respiratory effects.

B.5.2.2 Human information

EU RAR 2004

It was concluded in the EU RAR that data available from a few case reports indicated that the minimum dose that leads to adverse acute effects in humans appears to be greater than 300 mg/kg. However, as the source of this exposure was not clearly explained, this information was not taken into consideration.

Additional information

A limited number of incidents involving intoxication of consumers (usually children) with 1,4 dichlorobenzene-based products (not relating only to air fresheners or toilet blocks) has been reviewed by RPA, 2010. These occurred in Finland, Ireland and Switzerland:

- in Finland, one incident involving an air freshener occurred in 2008 and further six incidences occurred in 2006; no allergic (asthma and allergy associated) reactions were recorded

- in Ireland, one incident involving an air freshener and three involving toilet blocks ingestion were recorded over a 6 year period (2004-2009); most of the effects were asymptomatic and only one case with short breathing for a short time was reported (air freshener ingested by one-year old child)

- in Switzerland, four incidents involving air fresheners and ten involving urinal blocks were recorded over a 15 year period (1995-2009); most of the cases were only slightly harmful and resolved with simple measures. Only in one case slight mucosa irritation of the lower lip in an infant was observed.

Re-Solv, a UK national charity organisation, reported on the effects of 1,4-dichlorobenzene ingestion in humans causing abdominal pain, nausea, vomiting and diarrhoea, breathing problems, burning in mouth, yellow skin (jaundice), slurred speech, headache and weakness. This organization also reported on one case of abuse of 1,4-dichlorobenzene by a 21-year-old pregnant woman who ingested two toilet air freshener blocks each week for an unspecified period of time. The subject developed anaemia, which was resistant to iron therapy (Re-Solv, 2011).

It was concluded by Re-Solv that data on accidental poisoning or abuse of substances like 1,4-dichlorobenzene are difficult to be collected since patients rarely declare that they abuse common household products and physicians rarely ask directly about the use of such substances as intoxicants. There is currently no way of determining the actual prevalence of this type of substance abuse and the frequency with which it may contribute to medical problems (Re-Solv, 2011).

Grant *et al*. compiled a large reference database for acute inhalation in 2007, estimating acute inhalation NOAELs and acute lethality data for 97 chemicals. Their conclusion for 1,4-dichlorobenzene was GHS 4C acute inhalation toxicity (corresponding to Acute toxicity category 4 according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS)). Their estimated values for 1,4-dichlorobenzene are presented in Table B11:

Table B11: Comparison of estimated air concentrations to published toxicity values

Source:	Toxicity value ($\mu g/m^3$)	Adjusted duration (original study duration)	GHS category	TOC 5th Percentile ($\mu g/m^3$)	TOC 10th percentile ($\mu g/m^3$)	N–L ratio 5th percentile ($\mu g/m^3$)	N–L ratio 10th percentile ($\mu g/m^3$)
MRL	12,000	Not specified; occupational exposures	4C	60	125	230	420

Sources: California Office of Environmental Health Hazard Assessment (OEHHA), Agency for Toxic Substances and Disease Registry (ATSDR) and National Research Council of the National Academies of Science
MRL: Minimum Risk Level;
TOC: (Toxicity) Threshold of Concern
N-L ratio: NOAEL to LC_{50} ratio
The fifth or tenth percentiles were divided by an UF = 100 and converted from mg/m^3 to $\mu g/m^3$ to calculate the composite TOC concentrations and 95% tolerance bounds for each separate category.

B.5.2.3 Conclusion

The acute toxicity of 1,4-dichlorobenzene is considered to be low, regardless of the route of exposure.

B.5.3 Irritation

B.5.3.1 Non-human information

EU RAR 2004

According to the EU RAR, an OECD rabbit study revealed slight skin irritation such as reversible erythemas at day 7 at an exposure of 500 mg for 4 h (Maertins, 1988, as cited in the EU RAR). No significant dermal irritation was observed in a 21 days dermal irritation study (GLP) at an exposure of 300 mg/kg/day of 1,4-dichlorobenzene (Arletta, 1989, as cited in the EU RAR). Slightly reversible eye irritation was observed in a 24 h OECD rabbit study at an exposure of 90 mg 1,4-dichlorbenzene. Only isolated damage to the conjunctiva and no iris or cornea irritations were observed (Maertins, 1988, as cited in the EU RAR).

The sensory irritant potential of 1,4-dichlorobenzene during inhalation exposure was investigated by measuring the decrease in respiratory rate (dose concentration causing a 50 % decrease in respiratory rate (RD_{50})). However, it was concluded in the EU RAR that the protocol of this study was not detailed (number of animals per dose tested unknown) and only 2 or 3 concentrations/sex/species were tested with only 10 min exposure; in the ASTDM protocol 8 mice /concentration, 8 concentrations and 1-hour exposure have to be used.

Inhalation exposure of 500 ppm during 6 h was associated with a severe decrease in the respiratory frequency in rats and mice with a 50 % decrease of the mean minute volume (Wilson, 1990, as cited in the EU RAR).

Based on the available data on rabbits, EU RAR concluded that 1,4-dichlorobenzene is a slight irritant on skin and in the eyes.

Additional information

No additional information was found.

B.5.3.2 Human information

EU RAR 2004

The human studies taken into consideration by the EU RAR revealed that prolonged and/or repeated cutaneous contact with 1,4-dichlorobenzene in liquid or vapour form (warm fumes) causes slight irritation (burning sensation without cracking). Irritation of the mucous membranes has also been described in workers exposed to 1,4-dichlorobenzene although exposure levels were not given (Waligren, 1953, as cited in the EU RAR).

Workers exposed to 1,4-dichlorobenzene via inhalation (58 workers, 8 h/day, 5 days/week, for 8 months to 25 years with an average of 4.75 years) were studied by Hollingsworth *et al*. (1956, as cited in the EU RAR). It was concluded that irritation complaints (nasal and eye irritation) were evident at a vapour concentration between 50 and 80 ppm; irritation became severe at concentration greater than approximately 160 ppm and was accompanied by signs of pulmonary irritation. Certain individuals developed acquired tolerance after repeated exposures. It was not specified if workers were exposed to other chemicals than 1,4-dichlorobenzene; moreover, concentration data were given as range concentrations with median values and peak exposure concentrations cannot be excluded. No clear correlation between concentrations and effects were found.

Other human studies with inhalation exposure to 1,4-dichlorobenzene are of limited interest because level of exposure or respiratory data were not reported.

In the EU RAR it was concluded that 1,4-dichlorobenzene is a slight skin irritant (burning sensation without cracking) upon repeated skin exposure. Ocular and nasal irritation symptoms were found above 50 ppm.

The classification Irritant R36 "irritating to eyes" was considered justified.

Additional information

In a case report (Kondo, 2007) a 41-year-old housewife reported nasal irritation during time spent at home. Serum level of 1,4-dichlorobenzene was found to be 25.4 ng/ml, corresponding to a level of 0.35 ppm in the indoor air. The main source of 1,4-dichlorobenzene was assumed to be the mothballs placed in the bedroom.

B.5.3.3 Conclusions

Based on animal studies, 1,4-dichlorobenzene is a slight irritant for skin and eyes. The limited human data available are not conclusive but indicate a certain irritation potential to skin, eyes and the respiratory system.

The substance was classified as R 36 – irritating to eyes (and subsequently H319), on the basis of the available data on rabbits and humans.

Because of the lack of information about the determination of the RD_{50} in the study by Wilson 1990, it was concluded in the EU RAR that it was difficult to take this information into consideration and that the data seemed not to be valid for the endpoint in question (sensory irritation).

B.5.4 Corrosivity

It was concluded in the EU RAR 2004 that 1,4-dichlorobenzene is not corrosive. No additional data have been found.

B.5.5 Sensitisation

B.5.5.1 Non-human information

EU RAR 2004

The EU RAR reported on a Magnusson/Kligman test on guinea pigs (EEC method, 24 controls, 24 test animals, induction concentrations of 0.1 % intradermally, 25 % topically and challenge concentrations of 25 % in petrolatum, positive controls used) demonstrating a rather weak potential for sensitisation. At 0.1 % intradermally in a pre-test, slight irritation was observed in the animals. The maximum non-irritating concentration was greater than 25 % as no irritation was observed in a pre-test at 25 % in petrolatum. Minimal signs of irritation (1/24) were observed after induction. Over all, no treated animals were sensitised after 24 h; 21 % were sensitised with scores of 2 and 3 after 48 h (also one of the control animals was considered sensitised with a score of 2). No histological examination was conducted (Bornatowicz, 1995, as cited in the EU RAR).

An open epicutaneous test (Klecak) on guinea pigs did not reveal any sign of sensitisation on days 32 and 46. Signs of irritation were observed at induction (Schmidt, 1985, as cited in the EU RAR).

Other sensitisation tests, including a passive cutaneous anaphylaxis test carried out with detection of antibodies against 1,4-dichlorobenzene in the serum of guinea pigs treated *in vivo* with 1,4-dichlorobenzene, and a microtubule disassembly *in vitro* assay on mouse and human foreskin fibroblasts showed negative results. These tests had not been validated for the detection of sensitisation potential (Suzuki, 1991; Leung, 1990, as cited in the EU RAR).

Based on the animal data reviewed, the EU RAR concluded that 1,4-dichlorobenzene showed a weak sensitisation potential. Some animal skin sensitisation studies (*in vitro* study, open epicutaneous test) gave negative results. The interpretation of the maximisation study was difficult due to limitations in its conduct. The data was not considered sufficient to classify 1,4-dichlorobenzene as a sensitiser or to further request further animal testing.

Additional information

No additional data was found.

B.5.5.2 Human information

EU RAR 2004

The EU RAR reported on one isolated case of acute petechial purpura appearing between 24 to 48 h after skin contact with an armchair treated on the same day with 1,4-dichlorobenzene. A basophilic degranulation test with 1,4-dichlorobenzene was positive after 5 months in this subject. (Nalbandian, 1965, as cited in the EU RAR). The allergenic potential of 1,4-dichlorobenzene in this reaction was found to be questionable according to the EU RAR.

It was concluded in the EU RAR that a single, questionable human case report was not sufficient to justify the classification of 1,4-dichlorobenzene as a sensitiser taking the widespread use of 1,4-dichlorobenzene for many years in occupational and consumer settings, giving substantial possibilities of direct contact both in the occupational setting and for consumers.

Additional information

The ATSDR 2006 summarized the limited human and animal data available on the sensitising potential of 1,4-dichlorobenzene, suggesting that in the case of a 19-year-old black woman who ingested 4-5 moth pellets of 1,4-dichlorobenzene daily for a two and a half-year period (Frank and Cohen, 1961, as cited in the ATSDR), the immune system might have been affected. This and other additional data referred to in the ATSDR (2006) mainly report symptoms occurring in situations which are not relevant for the present report, like daily ingestion (misuse).

New information related to asthma and other respiratory alterations

For additional details see Table B12 below.

Delfino et al. (2003)

In a 3 months study on 21 children (10-16 years of age) which looked at the association between prevalence of asthma and exposure to eight quantifiable volatile organic compounds (VOCs) in breath samples (benzene, methylene chloride, styrene, tetrachloroethylene, toluene, m,p-xylene, o-xylene and 1,4-dichlorobenzene), no significant correlation between allergenic symptoms and atmospheric levels of 1,4-dichlorobenzene could be established. However, there was a positive association between asthma symptoms and breath concentrations of benzene, as well as, associations with symptoms and ambient petroleum-related VOCs measured (toluene, m,p-xylene, o-xylene and benzene). Exposures were determined from outdoor air samples collected in the area of the subjects' homes. There were limitations with this study such as the small sample size and the fact that ambient exposure only was measured which is difficult to correlate to true personal exposure.

Rumchev et al. (2004)

An Australian population-based case-control study reported on the association of domestic exposure to ten VOCs (benzene, toluene, m-xylene, o,p-xylene, ethylbenzene, styrene, chlorobenzene, 1,2-dichlorobenzene, 1,3-dichlorobenzene and 1,4-dichlorobenzene) in children aged between 6 months and 3 years who were diagnosed to be asthmatic (Rumchev *et al*., 2004). The domestic levels of 1,4-dichlorobenzene for these children were compared to a control group of children of the same age range but who had never been diagnosed as asthmatic. The levels of 1,4-dichlorobenzene showed a slight extension of the exposure range for asthma cases (0.01 median; 0.01-123.9 µg/m^3) compared with controls (0.01 median; 0.01-34.7 µg/m^3). This change was, however, not statistically significant. Adjusted Odds Ratios (OR) calculated for dichlorobenzene (no further specification given) indicated a small but statistically significant increase in asthma prevalence with increasing exposure. Unfortunately, although 1,2-, 1,3- and 1,4-dichlorobenzene were measured in this study, the results did not specify which dichlorobenzene substance was found to have an effect on the incidence of asthma. Domestic levels of benzene, toluene and dichlorobenzene appeared to have significant independent effects on asthma. The highest odds ratios (ORs) were calculated for benzene, toluene and ethylbenzene. For every 10 unit increase in the concentration of toluene and benzene, the risk of having asthma increased by almost 2 and 3 times respectively. As measurements were taken in the home, results may not fully reflect individual exposure.

Elliot et al. (2006)

Associations between blood concentrations of eleven VOCs (1,4-dichlorobenzene, benzene, toluene, styrene, m,p-xylene, o-xylene, ethylbenzene, acetone, 2-butanone, tetrachloroethene and 1,1,1-TCE) and pulmonary function were evaluated in 953 adult participants in the Third National Health and Nutrition Examination Survey (NHANES III) (1988–1994) of the general population who had both blood VOC and pulmonary function measurements (Elliot *et al.* 2006). The mean age of the subjects was 36.6 years (range 20–59), 43.1% were female, and 26.3% were current smokers. Pulmonary function measures included forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), and maximum mid-expiratory flow rate (MMEFR). Least squares regression models were used to evaluate the association between each VOC and each pulmonary function outcome.

The models used natural log transformations of VOC concentrations, and were adjusted for race/ethnicity, age, standing height, body mass index, sex, smoking, and emphysema to account for differences in pulmonary function based on these characteristics. In the models unadjusted for smoking variables, reductions in at least one pulmonary function outcome were statistically significant for 1,4-dichlorobenzene, benzene, ethylbenzene, styrene, and toluene. When the models were adjusted for smoking variables, 1,4-dichlorobenzene was the only VOC that was statistically significantly associated with reduced pulmonary function.

Amongst all participants with a measured blood concentration of 1,4-dichlorobenzene (n=846), there was a statistically significant ($p<0.05$) inverse relationship between 1,4-dichlorobenzene blood concentration levels and FEV_1 and MMEFR. The linear regression coefficient (β) was -96 mL (95% CI -182 to -11) for FEV_1 and -198 mL/sec (95% CI -388 to -8) for MMEFR. The β coefficient estimates the expected change in lung function as the concentration of 1,4-dichlorobenzene increases from the 10th to 90th percentile (3.76 µg/L) on the natural log scale.

Analysis by race and sex showed statistically significant results for FEV_1 in non-Hispanic white females [β=-266 mL (95% CI -488 to -43)] and African-American males [β=-282 mL (95% CI -497 to -66)]. Analyses conducted in 534 subjects using urinary concentrations of 1,4-dichlorobenzene and its major metabolite, 2,5-dichlorophenol, showed statistically significant β coefficients for FEV_1 for both 1,4-dichlorobenzene (-96 mL, 95% CI not reported) and 2,5-dichlorophenol (-134 mL, 95% CI not reported).

Analyses were also performed using non-logarithmically transformed blood concentrations of 1,4-dichlorobenzene that were categorized into deciles. Tests for linear trend across deciles were statistically significant for FEV_1 and MMEFR. Compared with subjects in the lowest decile of 1,4-dichlorobenzene concentration (0.10 ppb), subjects in the highest decile (>4.40 ppb) had FEV_1 decrements of -153 mL (95% CI -297 to -8) and MMEFR decrements of -346 mL/sec (95% CI -667 to -24). However, there was no dose response relationship evident between increasing blood concentrations of 1,4-dichlorobenzene in participants and reduction in lung functions.

The authors concluded that the findings of this study suggest that exposure to 1,4-dichlorobenzene at levels found in the general population may result in decreases in lung function.

The authors reservations in concluding on a link between exposure to 1,4-dichlorobenzene and decreased lung function were published in the paper. They stated that it was not possible to determine if 1,4-dichlorobenzene exposure preceded pulmonary function decline due to the cross-sectional nature of the study and also, that the inverse association between 1,4-dichlorobenzene concentration and pulmonary function may have been affected by unmeasured confounders. They stated that they had no data to address the possibility that those who are exposed to toilet bowl, air fresheners or other room deodorisers may also be exposed to cleaning products that impair pulmonary function. They concluded that larger and longitudinal studies (measuring exposure and function at various time points) would be necessary to properly evaluate the effects on respiratory symptoms and disease.

Arif and Shah (2007)

A 2007 study (Arif and Shah, 2007) as part of the National Health and Nutrition Examination Survey (NHANES) 1999–2000, collected passive personal exposure data for ten VOCs (benzene, toluene, m,p-xylene, o-xylene, ethylbenzene, tetrachloroethene, trichloroethene, chloroform, 1,4-dichlorobenzene and MTBE) from a total of 550 subjects (non-Hispanic whites, Mexican-Americans, non-Hispanic blacks). Levels were analysed against physician-diagnosed asthma and presence of wheezing in the previous 12 months amongst those without physician-diagnosed asthma. Exploratory factor analysis was used to generate factor scores to group VOCs, which were included as indicator variables in the analyses and the associations between exposure to VOCs, physician-diagnosed asthma, and wheezing in the previous 12 months were evaluated using multiple logistic regression analyses. In addition interaction terms between individual VOCs, race/ethnicity, and smoking were included in the model and distribution of potential confounders was compared between those with and without physician-diagnosed asthma using chi-square statistics.

1,4-dichlorobenzene exposure was significantly associated with physician diagnosed asthma with an adjusted OR of 1.16 (95% CI 1.03-1.30). No association was seen between exposure to 1,4-dichlorobenzene and wheezing in the previous 12 months (adjusted OR for 3 or more attacks 1.43 (95% CI 0.83-2.46).

Toluene showed the highest exposure concentrations and was associated with 21% increased odds for asthma. Similarly benzene, ethylbenzene, o-xylene and m,p-xylene were all significantly associated with both asthma and wheezing.

The study included personal exposure measurements for VOCs however only for a short duration which may not be a true reflection of lifetime exposure. There were other limitations in that the temporal relationship between VOC exposure and asthma/wheezing cannot be established with certainty due to the cross-sectional nature of the study.

The indoor exposures to 1,4-dichlorobenzene were highest among Mexican-Americans and non-Hispanic blacks as compared to non-Hispanic whites, possibly due to its presence in household products such as air fresheners, mothballs and toilet bowl deodorizer blocks. It was concluded by the authors that as 1,4-dichlorobenzene is considered a potential respiratory irritant but no previous study have linked exposure to asthma, more studies are needed to further investigate this association. The authors seem not to have been aware of the study by Elliot *et al.* (2006) as cited above before publishing of this paper.

Billionnet et al. (2011)

A quantitative assessment of respiratory health problems associated with indoor air pollution was conducted in a national cross-sectional representative survey by Billionnet (2011). A population-based sample of 567 dwellings from Mainland France with 1612 individuals (15-89 years old) was included in the study (Oct. 2003-Dec. 2005). 20 VOCs were measured for 1 week in the parents' bedroom of the reference persons of the households and VOC exposure was related to the prevalence of asthma and rhinitis. Other variables included health status, gender, age, sex, smoking status, relative humidity, time of survey, time spent at home, presence of pets, mould, educational level and other pollution sources over 500 m radius.

Exposure to 1,4-dichlorobenzene was not statistically significantly associated with asthma or rhinitis. Concentrations of 1,4-dichlorobenzene were: median: 4.1; 3rd quartile: 12.46; and maximum: 4809.8 (all in $\mu g/m^3$). After adjustment for possible confounders, the assessment showed ORs for the relationships between rhinitis/asthma and the exposure to 1,4-dichlorobenzene of 1.31 for rhinitis, respectively 1.13 for asthma. Asthma (8.6%) was, however, significantly associated with N-undecane & 1,2,4-trimethylbenzene exposure and exposure to ethylbenzene, trichloroethylene, m/p- and o-xylene was associated with rhinitis (38.3%). Specific VOC scores for aromatic hydrocarbons (which include benzene and toluene) and aliphatic hydrocarbons were associated with a significant risk of asthma. Specific scores

for halogenated hydrocarbons (which included 1,4-dichlorobenzene) were significantly associated with rhinitis.

Limitations in this study included lack of personal exposure measurement and self-assessment of asthma symptoms. Also other VOCs, for example benzene and toluene, which have been reported to increase the prevalence of asthma in other studies, did not show individual statistically significant associations with asthma in this study.

Discussion of possible effects of VOCs on the human respiratory system

The relationships between VOCs and asthma have been highlighted in several studies (Billionnet *et al*., 2011; Rumchev *et al*., 2004), although there are contradictory results (Ezratty *et al*., 2007). VOCs have also been related to rhinitis and upper airway disorders and with inflammation in the airways (Viegi *et al*., 2004). Experimental studies have shown that even moderate concentrations of VOCs may cause inflammation and obstructive reactions in the airways (Koren *et al*., 1992, as cited in the Billionet et al. 2011), decline of forced expiratory volume in 1 s (FEV_1) among asthmatics (Harving *et al*., 1991, as cited in the Billionet et al. 2011) and inflammatory response in the nose (Koren *et al*., 1992, as cited in the Billionet et al. 2011). A potential mechanism of action could be the irritation properties of VOCs.

To explain the effects of VOCs on the respiratory system in humans, it has been suggested that VOCs may facilitate penetration of allergens in the target organs by irritating of the respiratory mucosa and impaired mucociliary clearance (D'Amato *et al*., 2005). It has also been suggested that exposure to VOC affects airway reactivity, thus lowering the dose of antigen exposition needed to provoke bronchial or nasal constriction (Leikauf, 2002; Roux *et al.*, 1999). Yet another mechanism that may explain the effects of VOCs on inflammation in the airways, is oxidative stress (Baeza and Marano, 2007; Bonay and Aubier, 2007), in which VOCs have been suggested to play a key role (Baulig *et al*., 2003, as cited in the Billionet et al. 2011).

While there may be a correlation between exposure to 1,4-dichlorobenzene and respiratory function, the evidence to link these two effects is not robust. There is a well-conducted two year inhalation study in F344 rats and BDF1 mice showing no evidence of respiratory effects in either species and no report of histological changes in the respiratory tract. There is no evidence in any study reported of changes in the tissue of the bronchial tract which would indicate a decrease in airway resistance.

For respiratory irritant effects, the key study is Hollingsworth (1956) where respiratory irritation was reported from 160 ppm in exposed workers. However, there are limitations of this study in that it was not clear whether there was exposure to other chemicals at the time of monitoring and peak exposure concentrations could be a cause of the high exposure levels. The lack of irritating properties of the substance add to the weight of evidence that exposure to 1,4-dichlorobenzene may not be the cause of the reduced lung function.

There have been five epidemiological studies located which have addressed respiratory effects following exposure to 1,4-dichlorobenzene. These studies have used different methodologies, in particular with regard to the exposure assessment, and the results are therefore not fully comparable. Two of the studies (Elliot *et al*., 2006 and Arif and Shah 2007) show positive correlations to at least one endpoint while the remaining three show no or unclear correlations.

The study by Delfino *et al.* (2003) did not reveal any correlations between exposure to 1,4-dichlorobenzene and asthma. This is a small study with only 21 cases and health outcomes were related to low levels of ambient exposure to 1,4-dichlorobenzene. It is unclear how ambient levels of air pollutants relate to the true exposure of the individual.

The second study showing no significant correlation between exposure to 1,4-dichlorobenzene and asthma is the large and well-performed study by Billionnet *et al.* (2011) performed in

France. However, weaknesses of this study include the lack of personal exposure measurement and symptoms were self-assessed. The authors concluded that 75% of self-reported asthma is confirmed by physicians, but the possible incorrect diagnoses might have made it more difficult to identify correlations between symptoms and exposure. Some other individual VOCs which have been reported to increase the prevalence of asthma in other studies, for example benzene and toluene, did not show a statistically significant association with asthma in this study.

Unfortunately it is not possible to fully evaluate the study by Rumchev *et al.* (2004) due to lack of clarity regarding which of the dichlorobenzene substances were measured in the report.

The two studies showing the clearest correlation between respiratory effects and exposure to 1,4-dichlorobenzene both build on national health surveys in the US. The reasons for the positive findings are likely connected to the fact that they are both large and use very appropriate methodology, including individual exposure estimates – blood concentrations in the study by Elliot *et al*. (2006) and personal samplers in the case of Arif and Shah (2007). The use of doctor-diagnosed asthma (as opposed to self-diagnosed asthma) is also likely to improve the accuracy of correlations in the study by Arif and Shah, as is the objective measurement of lung functioning parameters by Elliot and co-workers.

In the Elliott study, analyses were conducted for 11 different VOCs and although the association between blood concentration and reduced lung function was statistically significant for 1,4 dichlorobenzene and not for other substances when adjustments were made for smoking variables, those other VOCs such as styrene, toluene, benzene and ethylbenzene were also present in the blood. As can be seen from other studies (Rumchev, Delfino and Arif & Shah), there is an often significant association between respiratory effects (such as asthma and wheezing) and exposure to these other VOCs e.g. toluene, benzene and ethylbenzene. Due to the presence of a number of VOCs in the blood of participants in the Elliott study, it cannot be established whether the reduction in lung function is solely as a result of 1,4-dichlorobenzene exposure. The cumulative effect of other VOCs present in the blood which have been reported to have significant effects on respiration needs to be also taken into account.

In addition, the inverse association between 1,4-dichlorobenzene concentration and reduced lung function may have been affected by unmeasured potential confounders which were not taken into consideration in the analyses in the Elliott study. As the paper itself concludes, the findings suggest that 1,4-dichlorobenzene exposure at levels found in US population may result in decreases in lung function. The authors aired uncertainties and reservations in their paper in concluding on the link between exposure to 1,4-dichlorobenzene and decreased lung function stating that it was not possible to determine if 1,4-dichlorobenzene exposure preceded pulmonary function decline due to the cross-sectional nature of the study and that they had no data to address the possibility that those who are exposed to toilet bowl, air fresheners or other room deodorisers may also be exposed to cleaning products that impair pulmonary function. They concluded that larger and longitudinal studies (measuring exposure and function at various time points) would be necessary to properly evaluate the effects on respiratory symptoms and disease.

The study by Elliott does not prove that 1,4-dichlorobenzene is the causative chemical for the respiratory effects observed. Overall, the weight of evidence for correlating exposure to respiratory effects is limited for 1,4-dichlorobenzene whereas there have been significant associations between exposure to other VOCs e.g. benzene and toluene and prevalence of asthma reported in a number of papers. Given the lack of a dose-response relationship between the concentration of 1,4-dichlorobenzene measured in the blood and the reduction in lung function (FEV_1), as well as the lack of irritating properties of the substance, the findings in Elliott are not robust enough to support the conclusion that exposure to 1,4-dichlorobenzene interferes with the human respiratory system.

Table B12: Overview of asthma studies

Focus of study	Geogra-phical area	Study population	Methodology	Exposure	Results	Comments	Reference
Asthma symptoms in children in relation to ambient exposures to air pollutants	Los Angeles, USA	21 Hispanic children (10-16 years old) physician-diagnosed with asthma.	Regression models were used to investigate correlation between respiratory infection variables and levels of pollutants. Interquartile range increases used to establish OR.	Air sampling at outdoor sites in the area of subjects' homes. Concentrations of 1,4-DCB: Min 0.05 ppb Max 0.5 ppb (3 µg/m^3)	No relationship between 1,4-DCB exposure and asthma symptoms were found.	Small study with narrow exposure range. Unclear how relevant ambient levels are to individual exposure.	Delfino *et al.* 2003
Association of domestic exposure to volatile organic compounds with asthma in young children	Perth, Austra-lia	Children (6 months-3 years) with physician-diagnosed asthma. 88 cases; 108 controls.	Case-control study. Exposure to VOC including 1,4-dichlorobenzene were compared between cases and controls. Crude and adjusted ORs for asthma with 10 µg/m^3 increase of exposure were calculated.	Sampling in subjects' living rooms. Concentrations of 1,4-DCB (µg/m^3): <u>Cases</u> 25th percentile: 0.01; 75th percentile: 1.2;	Estimation of independent effect on asthma showed that <u>dichlorobenzene</u> had marginally significant effect on asthma (all significant VOCs included as independent factors). OR: 1.04 (95% CI (1.02-1.06).	It is not clear from the publication by Rumchev *et al.* which of the diclorobenzenes the calculated OR refers to (or if it refers to a pooled analysis for all three diclorobenzenes included in the study). The power of	Rumchev *et al.* 2004

				90th percentile: 6.7; Median: 0.01 (0.01-123.9) <u>Controls</u> 25th percentile: 0.01 75th percentile: 0.01 90th percentile: 5.0; Median: 0.01 (0.01-34.7)		the study (90 %) was set at detecting a true OR of 2.0.	
Association between blood levels of Volatile Organic Compounds (VOC) and pulmonary function	89 locations in the US	953 non-institutionalized adults (20-59 years) (NHANES II, 1988-1994).	Correlations of blood concentrations and pulmonary function measurements (FEV_1=forced expiratory volume at 1 sec (ml); FVC=forced vital capacity (ml); PEFR=peak expiratory flow rate (ml/s); MMEFR=	Blood concentrations of 1,4-dichlorobenzene (µg/L): <u>Males</u> Median: 0.33 10th percentile: 0.11	1,4-dichlorobenzene was the only VOC associated with reduced pulmonary function after adjustment for smoking. Results were consistent across subgroups, and exposure was inversely related to all 4 lung function measurements although only statistically significant	As NHANES II is a cross-sectional study, it is not possible to conclude if 1,4-diclorobenzene exposure preceded lung function decline. Inverse association between 1,4-dichloroben-	Elliot *et al.* 2006

			maximum mid-expiratory flow rate (ml/s)) for 11 VOCs, including 1,4-dichlorobenzene, were examined.	90th percentile: 3.89 Max: 51.89 <u>Females</u> Median: 0.30 10th percentile: 0.10 90th percentile: 4.83 Max: 46.46 NB: A blood level of 1 µg/L corresponds approximately to an inhalation exposure of 10 µg/m^3.	for FEV_1 and MMER. Its urinary metabolite, 2,5-DCP, revealed similar associations with FEV_1 which were of statistical significance.	zene concentration and pulmonary function may have been affected by unmeasured confounders. No data provided regarding exposure to toilet bowl air fresheners, deodorisers or cleaning products which could impair pulmonary function.	
Association between personal exposure to volatile organic compounds	US	550 non-institutionalized adults from NHANES (1999-2000), 20-59 years old.	Prevalence of doctor-diagnosed asthma and wheezing attacks the last 12 months were assessed by questionnaire. Geometric means	Passive personal exposure data on 10 VOCs measured with organic vapour monitors for 48-72h after medical examination of	1,4-dichlorobenzene exposure was significantly associated with asthma with an adjusted OR of 1.16 (95% CI 1.03-1.30) for physician	Participation rate for the NHANES subgroup examined in this study was 78.6%.	Arif and Shah, 2007

and asthma			values of VOCs were computed and compared across independent variables. Associations between personal exposure to each VOC variable, measured on a continuous scale, asthma diagnosis, and wheezing attacks was evaluated using unconditional multiple binary logistic regression and multinomial logistic regression analyses reporting adjusted odds ratios (expressed as 1-U increase in level of exposure), along with their corresponding 95% confidence	subjects. Concentrations of 1,4-dichlorobenzene ($\mu g/m^3$) Mexican-Americans (mean: 3.73; 95% CI=1.63-8.51) non-Hispanic Blacks (mean=2.64; 1.03-6.74) non-Hispanic whites (mean=0.68 $\mu g/m^3$; 0.35-1.30).	diagnosed asthma. No association was noted between exposure to 1,4-dichlorobenzene and wheezing in the previous 12 months (adjusted OR for 3 or more attacks 1.43 (95% CI 0.83-2.46).	Short duration may not be a true reflection of lifetime exposure.	

			intervals.				
Assessment of indoor air pollution in relation to respiratory health	France	1612 individuals (15-89 years old) from 567 households.	Prevalence of self-diagnosed asthma and rhinitis were assessed by questionnaire. ORs were calculated using the third quartile exposure concentrations as a cut off.	20 VOCs, including 1,4-DCB, measured for 1 week in the parents' bedroom of the reference persons of the households. Concentrations of 1,4-DCB (µg/m^3): Median: 4.1; 3rd quartile: 12.46; Max: 4809.8	Overall prevalence of asthma was 8.6% (significantly assoc. with exposure to N-undecane and 1,2,4-trimethylbenzene) and for rhinitis 38.3% (sign. assoc. with exposure to ethylbenzene, trichloroethylene, m/p- and o-xylene). 1,4-dichlorobenzene: OR for asthma: 1.13 (CI approx 0.6-2.0); for rhinitis: 1.31 (CI approx. 0.9-1.9). None of the outcomes were statistically significant. NB: Confidence intervals (95%) were not given by the authors but estimated from figures in the publication.	The authors concluded that 75% of self-reported asthma is confirmed by physicians. Participation rate in the study was 19.5% but participants seemed to have representative exposures and prevalence of health outcomes.	Billionnet *et al*., 2011

B.5.5.3 Conclusions

Based on animal studies, 1,4-dichlorobenzene has been concluded to have weak sensitizing properties, but the available data did not provide sufficient evidence to classify 1,4-dichlorobenzene as a sensitiser at the time of the EU RAR. This conclusion remains valid.

The limited human data available do not allow any firm conclusions to be drawn regarding 1,4-dihlorobenzenes' sensitising properties.

B 5.6 Repeated dosed toxicity

B.5.6.6 Non-human information

EU RAR 2004

The EU RAR reviewed two 2-year studies in the rat and mouse: one oral study (NTP, 1987) and one inhalation study (JBRC, 1995, as cited in the EU RAR; Aiso *et al*., 2005b). It also reviewed one oral 1-year study in the dog (Naylor, 1996, as cited in the EU RAR and ATSDR, 2006). In addition a number of studies of shorter duration (oral and inhalation exposure) in the rat, mouse, rabbit guinea pig and monkey were assessed. All studies are summarized in Annex 2. The most important studies for the present report, i.e. the inhalation studies (of which some are also addressed in the section on carcinogenicity) are described below as summarized in the EU RAR.

Oral studies

In a one-year oral feeding study (GLP) in Beagle dogs, 1,4-dichlorobenzene was administered via capsule at doses of 10, 50 and 150 mg/kg/day (5 animals/sex/dose) and a control group of 5 animals/sex. Due to the severe toxicity at the highest dose (lethality observed at 150 mg/kg/day after 12 days), the initial dose of 150 mg/kg/day was adjusted to 100 mg/kg/day during the third week and 75 mg/kg/day at the beginning of the sixth week for both sexes. Both high dose males and females were untreated during weeks 4 and 5 to allow for recovery. Two males and one female at 150 mg/kg/day died during the study (1 male at D12 and 1 at D25 and 1 female at D24); one control dog died at D83 due to jejunal displacement; two treated animals (one male and one female) died from inflammatory lung lesions, associated in one female with pulmonary hemorrhages: the possibility that death was treatment related could not be ruled out as the cause of the death of the third animal was not clearly determined. All animals that died (2 males, 1 female) during treatment, had congestion or hemorrhage in different tissues [congestion (2 males) and hemorrhage (1 male) of intestine, hemorrhage of lung (1 male,1 female) and hemorrhage of lymph node (1 female). As pulmonary inflammation was observed in dogs and can be caused by nematodes parasites (filariasis, oxocaris), such parasites were researched in the lung mesenteric lymph node but not detected. At the highest dose tested (150, 100 and then 75 mg/kg/day) hypoactivity, emesis, dehydration and emaciation were observed in the animals who died during the study.Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia reversible at one year was observed in both sexes at 6 months at the highest dose and the platelet count was increased in high dose female (3 out of 4 female were affected with mean: 413.25 ± 108 ($p < 0.05$), control: 267.00 ± 68). A marrow erythroid hyperplasia in one high dose female and a splenic excessive hematopoiese in high dose animals (2 females, 1 male) were observed.

In the liver, absolute and relative liver weights were significantly increased in both sexes at 50 and 75 mg/kg/day (except for absolute liver weight in 50 mg/kg/day males). A statistically significant dose dependent increase of liver enzymes was noted: serum alkaline phosphatase (AP) in males at 50 mg/kg/day (5/5), and females at 50 (5/5) and 75 mg/kg/day (4/4), at months 6 and 12 (serum AP levels were not statistically significantly increased in the 75

mg/kg/day males (2/3) at months 6 or 12, but to note that only 3 animals were evaluated in this dose group); alanine aminotransferase (ALT) in females at 75 mg/kg/day at month 12 (3/4), and gamma-glutamyltransferases (GGT) in females at 75 mg/kg/day (3/4) at months 6 and 12. Serum albumin was significantly decreased in males at ≥50 mg/kg/day (months 6 and 12) and females at 75 mg/kg/day (month 6). Hepatic lesions included hepatocellular hypertrophy in all males and females at 50 and 75 mg/kg/day (as well as one female at 10 mg/kg/day), hepatocellular pigment deposition at 50 and 75 mg/kg/day (two males and one female at each level), bile duct/ductule hyperplasia at 75 mg/kg/day (one male and one female), and hepatic portal inflammation at 50 and 75 mg/kg/day (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day).

Kidney effects included increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day as well as collecting duct epithelial vacuolization in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). A statistically significant increased relative adrenal weight in high dose female and thyroid weight in mild dose female were noted.

No significant neoplastic findings were reported.

A NOAEL of 10 mg/kg/d is selected for long-term oral systemic liver effects in the dog based on elevated serum AP levels noted at the mid and high doses in a number of male and females.

Inhalation exposure

A study (brief report, no GLP, imprecise data, rat and mouse strains unknown) where different species (rats, guinea pigs, mice, rabbits, monkeys) were exposed to 1,4-dichlorobenzene vapour at concentrations of 0, 96, 158, 173, 341 and 798 ppm, 7 hours per day, 5 days per week for five or seven months, showed no significant toxic effect at the lowest dose of 96 ppm. Slight hepatic (hepatocellular degeneration, statistically significant increased liver weight) and kidney (statistically significant increased weight) abnormalities were observed beginning from 158 ppm in rats and guinea pigs. These were followed by signs of focal liver cell necrosis at 341 ppm. Pulmonary abnormalities (oedema, congestion) were observed in rats, rabbits and guinea pigs starting from 173 ppm; at higher concentrations (798 ppm), severe signs of intoxication (pulmonary irritation, marked tremor, weakness, unconsciousness and even death, histological hepatic, renal and pulmonary damage) were observed.

The NOAEC was found to be 96 ppm for rats and guinea pigs, 158 ppm for rabbits and monkeys, and higher than 158 ppm for mice. No clear dose response on incidence or severity has been shown (Hollingsworth, 1956).

In another study (detailed protocol, GLP) carried out on Wistar rats over 76 weeks (5 hours/day, 5 days/week, vapour), the following effects were noted at 500 ppm: a statistically significant slight increase in liver weight in both sexes (not dose dependent) with hepatocyte hyperplasia in females after 26-week recovery and renal abnormalities (increased kidney weight with urinary coproporphyrins but no hyaline droplet nephropathy) in males. At 75 ppm in females, slightly increased liver weight (statistically significant) at 26 weeks but not at 76 weeks and some hepatocyte hyperplasia (6 out of 79 animals) at recovery but not at 76 weeks were seen. No treatment-related effects on haematology or blood chemistry nor irritative symptoms were noted. The NOAEC was estimated at 75 ppm in both sexes (Riley, 1980a).

A 56-week study (vapour) on Swiss mice showed that these animals suffered respiratory abnormalities, but the interpretation of these results was limited by the presence of intercurrent infections. No treatment-related toxic effects on blood chemistry, haematology or histopathology (studied in female mice only) were noted. It was not possible to estimate a value for the NOAEC (Riley, 1980b).

A two-year inhalation carcinogenicity study (GLP) was carried out on F344 rats (50 animals per sex) at 0, 20, 75 and 300 ppm (vapour), 6 h/day, 5 days/week, for a total of 104 weeks. The only significant abnormalities observed were lesions in the kidney (mineralisation of the papilla collecting tube and urothelial hyperplasia – both graded as slight) at 300 ppm in males associated with increased kidney weight. Increased liver weight in both sexes at 300 ppm was noted. Centrilobular hepatocellular hypertrophy was noted at the high dose in male rats (5/50), however, this was not accompanied by any other effects indicating hepatocellular injury. Respiratory metaplasia in the nasal cavity gland and eosinophilic changes in respiratory epithelium were observed at the highest dose of 300 ppm in female rats. Eosinophilic changes in the olfactory epithelium were observed in a majority of control and treated rats of both sexes, but the grade was higher in treated animals at 300 ppm in both sexes and 75 ppm in females than controls [sacrified animals: (control sacrified: 38/38 in females, 24/33 in males) and (dose treated sacrified at 300 ppm: 12/18 in males, 36/36 in females; at 75 ppm: 17/29 in males, 36/38 in females)]; the same tendency was observed in dead animals [(control dead: 11/12 in females, 9/17 in males; dose treated dead at 300 ppm: 13/32 in males, 14/14 in females; at 75 ppm: 4/21 in males, 10/12 in females)]. The NOAEC was estimated at 75 ppm for kidney effects (JBRC, 1995, as cited in the EU RAR).

The two-year inhalation carcinogenicity study (GLP) was also carried out on BDF1 mice (50 animals per sex), at 0, 20, 75 and 300 ppm, 6 h/day, 5 days/week, vapour, for a total of 104 weeks. At 300 ppm, central hepatocellular hypertrophy in 34/49 males were observed, however, this was not accompanied by any other effects indicating hepatocellular injury. Liver weight was increased in both sexes at the highest dose. In the EU RAR, it is stated that liver effects in the mouse included increased liver enzymes in both sexes (AST, ALT, LDH, alkaline phosphatases) and slight local necrosis in both sexes, however, this is not reported in the Aiso paper (2005a) on the study nor in any other reviewed reports. (It is noted that liver necrosis and increase in liver enzymes were noted in both sexes of BDF1 mice in a 13 inhalation week study carried out by JBRC and again reported by Aiso). As a full copy of the JBRC study is not available and Aiso states in his paper that there was no histopathological change indicating hepatocellular injury in any of the exposed mouse groups of either sex, these effects have not been included for risk assessment. Increased kidney weight was noted at 300 ppm in both sexes.

Conclusions

It was concluded in the EU RAR that studies on oral administration of 1,4-dichlorobenzene to F344 or unknown species of rats (4 weeks to 13 weeks) show that there is an appreciable difference between males and females as hyaline droplet nephropathy was only observed in male rats (at concentrations beginning at 75 mg/kg/day and becoming significant at level of 150 mg/kg/day). This hyaline droplet nephropathy was specific to the male rats.

Above these concentrations (usually at 300 mg/kg/day), hepatic abnormalities (increased liver weight, hepatocellular hypertrophy) and renal abnormalities (increased kidney weight, nephropathy) were observed in both sexes. A NOAEL for renal effects of 150 mg/kg/day in female rats was considered. For male rats, the LOAEL for renal effects was set at 75 mg/kg/day.

In other species (NMRI and B6C3F1 mice and rabbits), the LOAEL was found to be greater or equal to 300 mg/kg/day with hepatic (increased liver weight, hepatocellular hypertrophy and degeneration) and kidney (nephropathy) abnormalities observed from this concentration except in Beagle dogs where the NOAEL was estimated at 10 mg/kg/day from the one-year study, with liver effects observed from the mid-dose. This NOAEL was considered relevant for the risk assessment as dogs are an appropriate model for humans.

By the inhalation route, a NOAEC for non-carcinogenic effects was estimated at 75 ppm in two chronic toxicity studies: one in Wistar rats exposed to 1,4-dichlorobenzene over a period of 76 weeks and one in BDF1 mice and F344 rats exposed to 1,4-dichlorobenzene over a period of 104 weeks (JRBC, 1995). This NOAEC was found to be in agreement with the results of an old

inhalation exposure study (Hollingsworth, 1956, as cited in the EU RAR; see also Annex I) on different species (rats, guinea pigs, mice, rabbits and monkeys, strain unknown) over periods of 5 to 7 months which gave a NOAEC of 96 ppm for rats based on increased liver and kidney weights together with hepatic oedema and minimal hepatocellular degeneration.

Additional information

Although no new relevant animal studies have been reported after the EU RAR assessment where repeated dose toxicity has been addressed, the chronic inhalation toxicity study by the Japan Bioassay Research Centre (JBRC, 1995, as cited in the EU RAR) described above was published by Aiso *et al*. (2005a). This study is described below due to its importance for this report and the detailed presentation of the changes in the olfactory epithelium described in the publication by Aiso *et al*. (2005a). The summary is from ATSDR (2006) and contains a statistical re-analysis performed by ATSDR addressing the relation between exposure to 1,4-dichlorobenzene and changes in the olfactory epithelium of moderate or greater severity in rat.

In the chronic study (JBRC, 1995, as cited in the EU RAR; Aiso *et al*., 2005a), groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF1 mice were exposed to 1,4-dichlorobenzene in target concentrations of 0, 20, 75, or 300 ppm for 6 h/day, 5 days/week for 104 weeks. Study end points included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), and hematology, blood biochemistry, and urinalysis indices (evaluated at end of study).

Selected organ weight measurements (liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, and ovary) and comprehensive gross pathology and histology evaluations were performed on all animals at the end of the study or at the time of unscheduled death. No interim pathology examinations were performed. As summarized below, this study identifies a NOAEC of 75 ppm for effects in the respiratory metaplasia in the nasal gland and eosinophilic changes in respiratory epithelium in female rats.

For the rats, the actual mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study (JBRC, 1995, as cited in the EU RAR; Aiso *et al*., 2005a). The number of rats surviving to scheduled termination was significantly ($p<0.05$) reduced at 300 ppm in males. Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and overall survival at 0, 20, 75, and 300 ppm was 66 % (33/50), 68 % (34/50), 58 % (29/50), and 36 % (18/50), respectively. The significant decrease in the survival rate in males exposed to 300 ppm was attributed to an increased number of leukemia and chronic progressive nephropathy deaths.

There were no exposure-related decreases in survival in the female rats, or effects on growth or food consumption in either sex. Changes in various hematological and blood biochemical indices (mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, and calcium in males; total protein, total bilirubin, blood urea nitrogen, and potassium in females) occurred at 300 ppm, but a lack of numerical data and statistical analysis precludes interpretations of significance for these end points. Absolute and relative liver weights in both sexes and kidney weights in males were significantly increased at 300 ppm. Additional findings included histopathological changes in the kidneys and nasal epithelia. The kidney lesions occurred only in male rats at 300 ppm and included significant increased incidences of mineralization of the renal papilla and in hyperplasia of the urothelium (both of slight grade).

The nasal lesions mainly included incidences of eosinophilic changes (globules) in the olfactory epithelium of rats in all animals, both control and treated (slight to severe in grade in controls and all dose groups), with increases in severity of the grade in males at 300 ppm (moderate) and in the olfactory epithelium of females at ≥75 ppm (severe). The lesions were graded for severity (1+, 2+ 3+). Incidences of this lesion at 0, 20, 75, and 300 ppm were 33/50, 22/50, 21/50, and 26/50 in males, and 49/50, 46/50, 46/50, and 50/50 in females. The increases were statistically significant ($p\leq0.01$, Chi SquareTest performed by Aiso, 2005a) at ≥75 ppm in females. The increased incidences of eosinophilic globules were closely associated with a

marked decrease in the number of olfactory cells in the olfactory epithelium of 300 ppm-exposed females.

Other nasal lesions that were significantly increased at 300 ppm were eosinophilic globules in the respiratory epithelium (38/50 compared to 11/50, 10/50, 14/50 at 0, 20 and 75 ppm, respectively) and respiratory metaplasia in the nasal gland (33/50) in females at 300 ppm (compared to 5/50, 4/50, 4/50 at 0, 20 and 75 ppm, respectively). The eosinophilic globules were abundantly present in both the supporting cells of the olfactory epithelium and in the ciliated and non-ciliated cells of the respiratory epithelium.

Kidney lesions were increased only in male rats at 300 ppm and included significantly increased incidences of slight grade mineralization of the renal papilla (0/50, 1/50, 0/50, 41/50) and of slight grade hyperplasia of the urothelium (7/50, 8/50, 13/50, 32/50).

For the mice, the actual mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm over the duration of the study. Survival was significantly reduced in male mice at 300 ppm (due to an increase in liver tumor deaths), but comparable to controls in the females. Terminal body weight was significantly reduced at 300 ppm in males (11.5 % less than controls, beginning at study week 80). Changes in various hematological and blood biochemical indices (total cholesterol, serum glutamic oxaloacetic transaminase [SGOT], serum glutamic pyruvic transaminase [SGPT], lactic dehydrogenase [LDH], and alkaline phosphatase [AP] in both sexes; platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, and calcium in females) occurred at 300 ppm (JBRC, 1995), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these endpoints.

Absolute and relative liver and kidney weights in both sexes were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal cavity, liver and testes. The nasal lesions included significantly increased incidences of respiratory metaplasia in the nasal gland in males at 75 ppm with an increase in the severity of the grade (increase in no. of animals with moderate grade) but not at 300 ppm. Incidences of respiratory metaplasia in the olfactory epithelium were also significantly increased in males at 75 ppm (38/50) (compared to 23/49, 30/49 and, 24/49 at 0, 20 and 300 ppm, respectively) and in females at 300 ppm (20/50) (compared to 7/50, 6/50, 2/49 at 0, 20 and 75 ppm, respectively); the effects in the males were not dose-related (i.e. incidences were increased at 75 ppm but not at 300 ppm).

The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 300 ppm (0/49, 0/49, 0/50, 34/49). Incidences of liver tumors were also increased at 300 ppm; these included hepatocellular carcinomas in males (12/49, 17/49, 16/50, 38/49) and females (2/50, 4/50, 2/49, 41/50), hepatocellular adenomas in females (2/50, 10/50, 6/49, 20/50), hepatoblastomas in males (0/49, 2/49, 0/50, 8/49) and females (0/50, 0/50, 0/49, 6/50), and histiocytic sarcomas in males (0/49, 3/49, 1/50, 6/49).

Testicular mineralization was significantly increased in males at ≥75 ppm (27/49, 35/49, 42/50, 41/49) (JBRC, 1995). The testicular mineralization was not considered to be a toxicologically significant effect (Aiso, 2005a) because (1) no signs of testicular toxicity were observed in mice exposed for 13 weeks (Aiso, 2005b), and (2) it was confined to the testicular capsules and testicular blood vessels and not observed in the testicular parenchyma, indicating that it is a finding commonly observed in aged mice independent of exposure to 1,4-dichlorobenzene (Aiso, 2005b).

Nasal lesions observed following inhalation exposure were characterised by respiratory metaplasia and eosinophilic changes. Respiratory metaplasia in the nasal gland is not of concern for either male rats or mice or for female mice. Female rats however did show a statistically significant increase in incidence at the highest dose, however, the grade was slight only. Incidence of respiratory metaplasia of the olfactory epithelium was statistically significant in female mice only at the highest dose with the grade slight. Eosinophilic changes occurred only in the rat with grade of changes in the olfactory epithelium in females more severe at the

mid and high doses but the number of animals affected was similar across a control and exposed groups. There was a statistically significant increase in the incidence in eosinophilic changes in respiratory epithelium in female rats at the high dose but graded as slight only. As there was no dose response associated with these effects, a NOAEC of 75ppm is selected based on the findings (respiratory metaplasia in the nasal gland and eosinophilic changes in respiratory epithelium in female rats).

B.5.6.2 Human information

EU RAR 2004

It was concluded in the EU RAR that no epidemiological study in humans was available. A number of case studies were reviewed, but these were found to be of poor quality. Symptoms described include neurological symptoms, hepatic or hematological changes (including anaemia and decreased numbers of white blood cells). It was not possible to establish a cause-effect relationship in terms of 1,4-dichlorobenzene exposure. Because data came from mixed occupational exposures to several substances, the level and duration of the exposure was rarely known. Regarding cases reported after domestic exposure the exposure was often intentional. Taken together, these data were not found suitable for risk assessment purposes.

Additional information

Some additional information is available on the long-term toxicity of inhaled 1,4-dichlorobenzene in humans.

A case of pulmonary granulomatosis was reported to have occurred in a 53-yearold woman, who, for 12–15 years, had been inhaling 1,4-dichlorobenzene crystals which were scattered on a weekly basis on the carpets and furniture of her home. A lung biopsy revealed the presence of 1,4-dichlorobenzene crystals with the surrounding lung parenchyma being distorted by fibrosis, thickening of the alveolar walls, and marked infiltrates of lymphocytes and mononuclear phagocytes. Also, there was some thickening of the muscular walls of small arteries and focal fibrous thickening of the pleura (Weller and Crellin 1953 as cited in the ATSDR 2006).

The effects were most likely related to the physical interaction of 1,4-dichlorobenzene crystals (or any crystals when inhaled) with lung tissue, rather than to chemical toxicity. This conclusion by the authors of the study was based on exposure history of the patient, radiography, and histological examination of the lung tissue which showed the presence of birefringent crystals and a clear granulatomous reaction.

Periodic occupational health examinations of workers who were exposed to 1,4-dichlorobenzene for an average of 4.75 years (range, 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth *et al*. 1956, as cited in the EU RAR).

The US third National Health and Nutrition Examination Survey carried out on a population of 1,338 adult Americans (NHANES III; Elliott *et al*. 2006) concluded that the findings of the study suggest that exposure to 1,4-dichlorobenzene at levels found in the general population may result in decreases in lung function. The authors noted the evidence of considerable exposure to this substance in US homes and estimated a mean blood level of 38 µg/L for the population included in this study.

Hsiao *et al*. (2009) reported on a small cross-sectional study (46 exposed and 29 non-exposed) workers at insect repellent factories in Taiwan in which they found elevated serum alanine amino transferase (ALT) activities and raised blood white cell counts in exposed workers; these effects were significantly ($p<0.05$) correlated with urinary level of the main metabolite 2,5-dichlorophenol (105.4 µg/L in exposed group). Blood urea nitrogen (BUN) was

also raised in exposed workers suggesting that, as well as affecting liver function, kidney function may be affected by high occupational exposure to 1,4-dichlorobenzene.

Wu *et al*. (2006) analyzed data from a national sample to examine the relationships between blood concentrations of selected volatile organic compounds (VOCs) and the assessment scores of neurobehavioral evaluation tests. They calculated summary statistics to describe blood concentrations of 30 VOCs. The 95th percentile for 1,4-dichlorobenzene was 11.081 µg/l. For this substance a blood level higher than the 95th percentile was associated with a poorer neurobehavioral assessment score than was a blood level up to the 95th percentile.

This finding suggests that exposure to 1,4-dichlorobenzene may result in decreased neurobehavioral performance. According to the authors the study was exploratory and precludes a conclusive statement with further investigation warranted.

Cheong *et al*. (2006) reported the development of signs of neurotoxicity (encephalopathy associated with cognitive, pyramidal, extrapyramidal and cerebellar effects) following rapid withdrawal from chronic ingestion of moth balls containing 1,4-dichlorobenzene.

B.5.6.3 Conclusions

Although no new long-term studies in animals have been performed, the re-publishing of the two-year study by the Japanese Bioassay Research Institute (originally published in 1995) by Aiso *et al*. (2005a) provides new information about local lesions of the nasal epithelium in rats, for which a NOAEC of 75 ppm can be established. A NOAEC for kidney toxicity of 75 ppm in rats after exposure by inhalation has also been established.

The ATSDR (2006) provides more detailed information on the results of the sub-chronic oral study in dogs. A NOAEL of 10 mg/kg/d for liver toxicity in dogs is selected for DNEL derivation.

It was concluded in the ATSDR (2006) that the respiratory tract is a target of inhaled 1,4-DCB as shown by histopathological changes in the lungs of acutely exposed rats and guinea pigs and nasal olfactory epithelium of chronically exposed rats and mice. Pulmonary effects (interstitial oedema, congestion, and alveolar haemorrhage) were also observed in rats and guinea pigs following intermittent exposure to 175 ppm of 1,4-dichlorobenzene for 16 days. The experimental design and report of this old study by Hollingsworth *et al*. (1956) have however a number of deficiencies, such that the observations provide only qualitative evidence of exposure-related acute respiratory effects.

An increased incidence of histological changes of the nasal olfactory epithelium occurred in female rats exposed to 75 or 300 ppm, and female mice exposed to 300 ppm. These nasal lesions were observed in one study only and were not accompanied by clinical signs or histological effects in the lung. The lesions were mild, characterised by eosinophilic changes which are typically found in ageing rodents and which were not accompanied by degenerative changes and were concluded as being age-related (not degenerative) and accelerated by treatment and there is no correlation between their occurrence and effects with lung function. Also the dose-response was only apparent if the severity of the lesions were graded and compared.

Because nasal lesions were not found in a 13-week inhalation study (Aiso, 2005b), it appears that the lesions are late-developing effects of chronic exposure. Nasal lesions were not reported in any other inhalation study.

As stated above there were no no clinical signs indicating effects on lung function or effects in lung at necropsy were noted following daily observations for clinical signs and complete necropsy in the 2 year inhalation study (JBRC, 1995, Aiso, 2005a). No histological changes in the respiratory tract were reported in F344 rats and BDF1 mice following inhalation exposure for 13 weeks (Aiso study (2005b)). Nor were there any treatment-related histological

alterations observed in larynx, trachea, or lungs in rats exposed to air concentrations of 1,4-dichlorobenzene for 76 weeks (Riley *et al*. (1980a)).

In the epidemiological studies reported (further described in section B.5.2.1), while there were signs of nasal irritation in the Hollingsworth study (1956) on workers, the uncertainties regarding exposure to other chemicals and the fact that the concentration data are range concentrations with median values, in which peak exposure concentrations cannot be excluded, make the findings in this study unreliable. There was no significant correlation between asthma/rhinitis and exposure to 1,4-dichlorobenzene in indoor air (Billionnet, 2011) whereas there were associations between respiratory effects and exposure to the other individual VOCs measured in that study (N-undecane and 1,2,4-trimethylbenzene, ethylbenzene, trichloroethylene, m,p-xylene and o-xylene). The finding by Elliot *et al*. (2006) regarding a relationship between exposure to 1,4-dichlorobenzene and decreased lung volume, as well as those by Arif and Shah (2007) indicating a risk for asthma, are in accordance with findings for other VOCs with irritating properties. The Elliott study does not establish a correlation between exposure to the substance and decreased lung function. It can only establish that lung function was decreased in participants who had concentrations of 1,4 dichlorobenzene in their blood samples.

There is a lack of evidence that 1,4-dichlorobenzene is a respiratory irritant.

There is also a very limited weight of evidence for linking nasal lesions and effects in pulmonary function based on the data available. Overall, the weight of evidence for correlating exposure to 1,4-dichlorobenzene and respiratory effects is limited whereas there have been significant associations between exposure to other VOCs e.g. benzene and toluene, and prevalence of asthma.

The findings by Hsiao *et al.* regarding liver and kidney function appear to be consistent with effects seen in animal studies. It thus seems that liver and kidney are target organs for 1,4-dichlorobenzene both in animals and humans.

The findings in the human studies are not suitable for (quantitative) human hazard assessment for 1,4-dichlorobenzene but are further discussed in section F in relation to the health impact assessment.

B.5.7 Mutagenicity

EU RAR 2004

It was concluded in the EU RAR that even if 1,4-dichlorobenzene had been investigated in a large number of *in vitro* and *in vivo* tests, data did not provide consistent evidence for the genotoxicity of the substance. Standard tests for genotoxicity did not generally suggest that 1,4-dichlorobenzene had genotoxic potential, and the evidence pointing in the direction of genotoxicity came from non-standard tests that may not be fully recognised by regulatory authorities. The overall weight of evidence from the most reliable studies indicated that 1,4-diclorobenzene does not have any significant genotoxic potential. According to the EU criteria for classification and labelling of dangerous substances and following the CMR meeting of TC C&L in May 2003, 1,4- dichlorobenzene was not found to qualify for classification in Category 3 mutagen (R68) and it was not considered as a genotoxic agent.

Additional information

No relevant new studies have been found. However, Butterworth *et al.* (2007) reviewed the mutagenicity of 1,4-dichlorobenzene and concluded that the general pattern of data indicate that 1,4-dichlorobenzene is negative *in vitro* and *in vivo* in a battery of standard, proven genotoxicity assays. The authors referred to other evaluations of the genotoxic properties of

1,4-dichlorobenzene, including the EU RAR 2004, and stated that they had all reached the same conclusion.

The U.S. EPA IRIS (US EPA, 2006) reviewed the genotoxicity tests performed with 1,4-dichlorobenzene and concluded that negative results were reported in the vast majority of a variety of assays, including gene mutation in *Salmonella typhimurium* and mouse lymphoma cells *in vitro*; DNA damage in rat and human hepatocytes *in vitro*; unscheduled DNA synthesis in mouse hepatocytes and rat kidney cells *in vivo*, sister chromatid exchange(SCE) in Chinese hamster ovary (CHO) cells *in vitro*; mouse bone marrow cells and erythrocytes *in vivo*; chromosomal aberrations in rat bone marrow cells *in vivo;* and dominant lethal mutations in mice. They further concluded that the exceptions to the negative responses generally fell into the categories of (1) results that were not reproducible; (2) tests that were more unconventional and less well validated such as the micronucleus test in rat kidney (validation means that test performance has been evaluated with a large set of known mutagens and known non-mutagens); and (3) assays that were prone to false positives due to toxicity, such as the alkaline elution assay, the comet assay, and the SCE assay.

Conclusions

Although no new studies have been found that further clarify the issue of the genotoxic potential of 1,4-dichlorobenzene, recent evaluations (as outlined below in B.5.8.3) provide further support for the conclusion on non-genotoxicity as drawn in the EU RAR.

B.5.8 Carcinogenicity

B.5.8.1 Non-human information

EU RAR 2004

The EU RAR reviewed a 2-year oral study in rat and mouse (NTP, 1987, as cited in the EU RAR) and one 2-year inhalation study in rat and mouse (JBRC, 1995, as cited in the EU RAR). In addition two older inhalation studies of shorter duration (76 weeks in rat and 57 weeks in mouse) were reviewed. Annex 2 provides an overview of these studies. Summaries of the two 2-year studies (as given in the EU RAR) are given below due to their importance for the discussion of carcinogenic properties of 1,4-dichlorobenzene.

Oral exposure

An oral study (GLP) was carried out on F344/N rats and B6C3F1 mice (50 animals/sex/dose) for two years (NTP, 1987 as cited in the EU RAR).

F344/N rats were dosed for 103 weeks at 0, 150 and 300 mg/kg/day by gavage for male rats, and 0, 300 and 600 mg/kg/day for female rats. The results revealed general toxicity beginning at 300 mg/kg/day in male rats, and at 600 mg/kg/day in female rats.

A dose-dependent increase in the frequency of nephropathy was observed in the female rats (21/49, 32/50, 41/49) from 300 mg/kg/day and in males from 150 mg/kg/day. This increase was accompanied by renal histological lesions (epithelial hyperplasia of the renal pelvis, mineralisation of the collecting tubules). A dose-dependent increase in the incidence of tubular cell adenocarcinomas (statistically significant at 300 mg/kg/day) was observed in male rats (1/50, 3/50, 7/50). The historical control incidence of the laboratory was 0.4 %. No liver tumours were observed but slight hepatotoxicity was observed (transient proliferation and liver enlargement) at 600 mg/kg/day. A parathyroid gland hyperplasia was also found in male rats: this was probably a consequence of renal damage. A marginally increased level of mononuclear cell leukaemia (5/50, 7/50, 11/50) was observed in male rats (this number falls within interval of laboratory control group and was not statistically significant): its toxicological significance was regarded as limited in the EU RAR.

No increase in the number of malignant tumours was observed in females.

In B6C3F1 mice at dose levels of 0, 300 and 600 mg/kg/day by gavage (for 103 weeks), it was shown that there was an increase, for both sexes, in the number of non-neoplastic liver lesions (hyperplasia, degeneration and individual hepatocellular necrosis), and in the number of renal lesions (nephropathy, regeneration of renal tubules) from 300 mg/kg/day.

At 600 mg/kg/day, the incidence of hepatocellular carcinomas (statistically significant $p<0.001$) was higher in males (14/50, 11/49, 32/50) and in females (5/50, 5/48, 19/50). The incidence of malignant liver tumours in female control mice in this study (10 %) was higher than in historical controls (3 %).

Hepatic adenomas observed in males (5/50, 13/49, 16/50) and females (10/50, 6/48, 21/50) were statistically significant at 600 mg/kg/day. Hepatoblastomas (not statistically significant) were observed in male mice suffering from hepatocarcinomas at 600 mg/kg/day (4/50 total number of male mice, that is 4/32 male mice with hepatocarcinomas), tumours which occur only exceptionally in mice (1/2080). Adrenal gland pheochromocytomas (0/47, 2/48, 4/49), not statistically significant, appeared in male mice, one of which at 300 mg/kg/day was malignant (figure within the historical interval for control groups of the laboratory: 2.2 ± 3.1 %); they were associated with adrenal gland and thyroid hyperplasia.

Inhalation exposure

An inhalation study (GLP) was carried out on F344 rats and BDF1 mice (50 animals/sex/dose), at 0, 20, 75 and 300 ppm, vapour, 6 h/day, 5 days/week, for a total of 104 weeks (JBRC, 1995 as cited in the EU RAR; Aiso, 2005a).

In rats, the mortality was the same in treated and control females but was above controls in males at 300 ppm (64 %) and 75 ppm (42 %). The only significant abnormalities observed were non-neoplastic lesions in the kidney (at 300 ppm in males) and in the nasal cavity (slight eosinophilic changes in respiratory epithelium, respiratory metaplasia in nasal cavity gland) at 300 ppm in females. Eosinophilic changes in the olfactory epithelium were observed in treated but also in control animals but the grade was higher in treated females at 75 ppm and 300 ppm than in control animals. With the exception of mononuclear leukaemia, which was not dose-related and with no statistically significant increase (9/50, 14/50, 10/50, 13/50), there were no incidences of neoplasms in male or female F344 rats.

In BDF1 mice, an increased incidence of hepatocellular carcinomas, statistically significant at 300 ppm ($p<0.01$), was observed in males (12/49, 17/49, 16/50, 38/49) and in females (2/50, 4/50, 2/49, 41/50); historical control data in JBRC for this strain of mice and for liver tumours are 2 - 36 % in males and 0 - 4 % in females (Katagiri, 1998, as cited in the EU RAR). Hepatocellular adenomas in females, statistically significant ($p < 0.01$) at 300 ppm (2/50, 10/50, 6/49, 20/50) were observed: historical control data for female's 2 - 10 %. Liver histiocytosarcomas statistically significant ($p<0.05$) at 300 ppm in males (0/49, 3/49, 1/50, 6/49) were noted only in males with hepatocellular carcinomas: historical control data for males between 0 and 6 % (Katagiri 1998, as cited in the EU RAR).

Hepatoblastoma-like features (subtype of hepatocellular carcinomas, within a portion of hepatocellular carcinomas with continuity between hepatocellular carcinomas and hepatoblastoma-like features) statistically significant at 300 ppm were observed in females (6 out of 41 females with hepatocarcinomas at 300 ppm) and in males (0/12, 2/17, 1/16, 8/38 males with hepatocarcinomas): historical control in BDF1 untreated mice: 6 % in males, 0% in females (Yamate 1990, as cited in EU RAR).

Bronchiolar-alveolar carcinomas, statistically significant ($p<0.05$), appeared in females at 300 ppm (4/50), figures at the least upper bound of the historical control data of the laboratory (0-8 %).

It was concluded in the EU RAR that the carcinogenic potential of 1,4-dichlorobenzene for the liver had been clearly demonstrated in B6C3F1 and BDF1 mice from 600 mg/kg/day and from 300 ppm, with 3 types of tumours: hepatocarcinomas, hepatoblastomas and histiocytosarcomas; the two previous ones being very rare tumours in mice.

A NOAEL for carcinogenic liver effects of 300 mg/kg/day via the oral route in B6C3F1 mice, a NOAEC of 75 ppm via inhalation route in BDF1 mice were suggested in the EU RAR.

A LOAEL of 300mg/kg/d is selected for long-term oral systemic hepatocellular effects based on the degenerative changes (cellular swelling with clearing or vacuolation of the cytoplasm) in hepatocytes in male and female B6C3F1 mice at low and high dose, the cell size alteration (cytomagaly and karyomegaly) in low dose males and high dose males and females and focal necrosis (individual cell necrosis) in low dose males and high dose males and females.

A LOAEL of 150mg/kg/d was suggested in the EU RAR for tubular cell adenocarcinoma noted at the highest dose in the male F344 rat kidney, however, these tumours are not of relevance to man due to the mechanism of action (αlpha 2μ-globulin nephropathy and tumour formation).

The effects seen in the male rat kidney, nephropathy, mineralisation of the tubules and hyperplasia are likely to be related to the formation of the tumours. Therefore, a LOAEL of 300mg/kg/d is taken for long-term oral systemic effects in the kidney based on nephropathy (consisting of degeneration of the cortical tubular epithelium, thickening of the tubular and glomerular basement membranes) at 300mg/kg/d in kidney in male B6C3F1 mice.

Additional information

No additional information has been found.

B.5.8.2 Human information

EU RAR 2004

Two cases of leukemia were reviewed in the EU RAR, one after exposure to a mixture of dichlorobenzenes and the other after domestic exposure (Girard, 1969 as cited in EU RAR). It was concluded that these cases did not show any clear cause-effect relationship with exposure to 1,4-dichlorobenzene.

Additional information

No additional information has been found.

B.5.8.3 Mode of action of the carcinogenic effects

EU RAR 2004

It was concluded in the EU RAR that although 1,4-dichlorobenzene has been shown to induce kidney tumours in rats and liver tumours in mice it is probably not a genotoxic carcinogen as mutagenicity studies are in general negative.

Regarding the kidney tumours in rats (US NTP, 1987 as cited in the EU-RAR) it was concluded that these tumours appear to be male specific and are most likely related to accumulation of complex between 1,4-dichlorobenzene and alpha-2μ-globulin. For this reason, no NOAEL was proposed based on renal tumours in male rats.

The mechanisms behind the hepatic tumours reported in mice (hepatocellular carcinomas, histiocytosarcomas and hepatoblastomas) were seen as less clear. While hepatocellular carcinomas are common tumours in mice, especially in males, histiocytosarcomas and the hepatoblastomas are rare. The liver tumours were observed at doses of 600 mg/kg/day or 300

ppm. At these doses the frequency of hepatocellular carcinomas did not exceed the historical control of the laboratory (BDF1 mice: 2-36 % of males, 0-4 % of females; B6C3F1: 14-29 % of males, 1-5 % of females); but liver carcinomas were observed at a higher rate at the next dose (highest dose tested) of 300 ppm and 600 mg/kg/day (BDF1 mice inhalation: 78 % of males, 82 % of females; B6C3F1 oral route: 64 % of males, 38 % of females). Hepatotoxicity was seen at doses causing an increase of liver tumours in B6C3F1 mice in the oral study, however, there was no evidence of hepatocellular injury accompanying liver tumours following inhalation exposure in BDF1 mice (only centrilobular hypertrophy noted at the highest dose).

Only slight hepatotoxicity was observed in rats (transient increased liver weight, mild centrilobular hypertrophy) at 600 mg/kg/day and 75ppm (highest dose tested) in the two-year studies without liver tumours (NTP, 1987 as cited in the EU RAR).

Possible reasons for the difference in tumour induction by 1,4-dichlorobenzene between species were discussed in the EU RAR, including differences in metabolism. *In vivo*, there are some species differences in metabolism between rats and mice, with 2,5-dichlorohydroquinone found in F344 and SD rats, but not in Wistar rats nor in mice. *In vitro*, the major metabolites in rat, mouse and human liver microsomes are dichlorophenols (50%), hydroquinone metabolites (10 to 27%) and to a less extent glutathione-epoxide and glutathione-quinone conjugates. Differences in the hepatic microsomal metabolism between rat and mouse (and human) have also been shown: conversion of 1,4-dichlorobenzene is much higher in B6C3F1 mouse microsomes than in F344, Wistar or SD rat or human microsomes, while mice, F344 and human liver microsomes produce more hydroquinones metabolites than Wistar and SD rats.

In vitro, covalent binding to protein is higher in mouse than rat or human liver microsomes.

The EU RAR considered that the redox active nature of chloro(hydro)quinones and their glutathione conjugates could be implicated in carcinogenesis with formation of reactive oxygen species (inducing oxidative DNA damage) when oxidation of hydroquinones metabolites takes place: *in vitro*, the induction of single and double strand breaks in DNA and DNA base alterations was demonstrated when native DNA was incubated in the presence of 2,5-dichlorohydroquinone and the enhancement in DNA damage was observed in the presence of the intracellular reductant nicotinamide adenine dinucleotide (NADH); the damaging effects on DNA were completely eliminated when catalase, a scavenger of hydrogen peroxide, was present (Oikawa, 1996a, as cited in the EU RAR).

The hypothesis of the role of the oxidation products of hydroquinone (benzoquinone) in the development of liver tumours had not been clearly demonstrated by experiments in view of the same percentage of hydroquinones metabolites formed *in vitro* in human and mouse, even if covalent binding to protein was greatly inhibited in mice (but also to a small extent in human) by the addition of ascorbic acid with a concomitant increase in the formation of hydroquinones metabolites (in mouse but also in human), indicating that benzoquinone species (derived from oxidation of hydroquinone metabolites) are involved in the covalent binding. It was however concluded in the EU RAR that these differences in hepatic metabolism could not at that moment completely explain the results of the carcinogenicity studies.

It was further concluded that the carcinogenic effect on the mouse liver was probably not the result of a peroxisomal proliferation in view of the negative result of a study on peroxisomal proliferation in CF1 mice liver (Bomhard, 1996, as cited in the EU RAR). However, cellular proliferation produced by 1,4-dichlorobenzene was observed in rats and mice after single (up to 1,800 mg/kg) or repeated oral administrations (up to 600 mg/kg/day) in the absence of elevated liver enzymes or hepatic necrosis, as result of a mitogenic stimulation (Umemura *et al*., 1996; Eldridge *et al*., 1992; as cited in the EU RAR). Cellular proliferation was observed in the liver of F344 rats and B6C3F1 mice treated with 1,4-dichlorobenzene at the same dose as in the carcinogenicity study but rats did not develop any cancer of the liver; a threshold effect for cellular proliferation (from 75 mg/kg/day in rats (transient) and 150 mg/kg/day in mice (prolonged)), below which no proliferative response was observed, was suggested based on

the study of Umemura *et al*. Even if a prolonged response was considered to be predictive of carcinogenesis, measurements of hepatocellular proliferation alone were not considered sufficient to elucidate the mechanisms of liver tumour development or to predict liver carcinogenesis.

Another possibility addressed in the EU RAR was that the liver carcinogenic effects could be related to tumour promotion. However 1,4-dichlorobenzene did not promote hepatic foci formation in a two stage model of carcinogenesis in rats (Gustafson *et al*., 1998).

It was finally concluded in the EU RAR that the mechanism of induction of the liver tumours in mice was not completely elucidated. However, a threshold approach was considered appropriate and NOAEC and NOAEL were determined for the liver carcinogenic effect (at 75 ppm and 300 mg/kg/day).

Additional information

A number of studies of the mechanisms by which 1,4-dichlorobenzene induces tumours were identified and summarized by RPA in their preliminary literature search (RPA, 2010). No additional relevant studies have been reported. The summaries of RPA are given below.

Further publications by Gustafson *et al*. in 2000 were built on work already considered in the EU RAR. The 2000 paper showed that there was no promotional effect of 1,4-dichlorobenzene on the development of glutathione-S-transferase (GSTP1-1) positive preneoplastic hepatic foci following diethylnitrosamine initiation of rats; this was unlike the response seen with a number of other chlorobenzene compounds known to be positive carcinogens in rat. This lack of effect was also shown to correlate with the absence of induction of CYP1A2 and CYP2B1/2 in these animals, which led the authors to conclude that the extent to which a chlorobenzene induces CYP1A2 or CYP2B1/2 may be a marker of carcinogenic promotional ability, at least in the rat.

In a study published in 2003, Ou *et al*. reported on the influence of a single dose (at 0.1 mol/kg) of each of a number of chlorobenzenes (including 1,4 dichlorobenzene) on the occurrence and subsequent progression of preneoplastic liver foci in F344 rats that were pre-induced by a single initiating dose of the carcinogen diethylnitrosamine. As such the study design was based on the 'medium-term' bioassay developed by Ito *et al.* (1989, as cited by RPA 2010). Under this method, cell proliferation was promoted by partial hepatectomy one week after dosing with the chlorobenzenes and the numbers of glutathione-S-transferase positive foci (an indicator of pre-neoplastic status) assessed between 23 and 56 days after initiation. Two clonal cell populations were identified as existing within the foci of which cells referred to as B-cells showed a selective growth advantage over either the type A-cells or normal hepatocytes. Furthermore, the growth rate of B cells was closely associated with the measured volume of foci at the end of the study period. This suggests that the B-cells are probably of particular importance for ultimate tumour progression. Although time-dependent changes in foci were found to be very similar in the diethylnitrosamine initiated control and the diethylnitrosamine and 1,4-dichlorobenzene treated group, the other chlorobenzenes tested showed higher rates of foci growth (i.e. clear promotional activity).

Chou and Bushel (2009) reported on a gene expression data analysis based on the Agilent Rat Oligonucleotide Microarray and fluorescent intensity measurement using a microarray scanner of liver samples from F344 rats exposed to substances with varying degrees of hepatotoxicity. Examination of response patterns for the genes examined suggested 1,4-dichlorobenzene treatment was not associated with any changes suggestive of DNA damage. Therefore, the authors concluded that the hepatic response to 1,4-dichlorobenzene in the rat did not involve a genotoxic mechanism.

Muller (2002) in a review suggested that, in the mouse, the formation of hepatic adenoma and carcinoma may be attributed to the formation of substituted hydroquinone metabolites.

Kokel *et al*. (2006) reported on the effects of 1,4-dichlorobenzene on the regulation of the genes involved in control of apoptosis in a genomically-characterised model species, the nematode *Caenorhabditis elegans*; these genes are well conserved between the nematode and humans. It was found that 1,4-dichlorobenzene would suppress apoptosis in both wild-type and mutant nematodes, though the magnitude of effect was greatest in mutants (for which apoptotic mechanisms are already compromised). It also influenced apoptosis rates at several developmental stages and for multiple cell types. Other effects noted with exposure at the levels that caused apoptosis included slow development, reduced brood size and some deaths but survivors appeared anatomically normal and showed no behavioral changes. The authors concluded that inhibition of apoptosis by 1,4-dichlorobenzene was by non-genotoxic mechanisms in *C. elegans,* and suggested that the tumourogenic effects seen in animals may represent non-genotoxic suppression of the apoptosis of latent cancer cells, thereby acting to promote their survival and proliferation.

Evaluation by Butterworth *et al*. (2007)

The cancer mechanisms of 1,4-dichlorobenzene, in particular related to its mitogenic/promotional mode of action of 1,4-dichlorobenzene were evaluated by Butterworth *et al*. (2007). The authors concluded that stimulation of liver growth and a sustained increase in liver weight, so long as the chemical is continually administered on a daily basis, is one effect common to all of the mitogenic liver carcinogens. Mitogenic activity in the mouse liver was clearly seen early and late in both the gavage and inhalation bioassays with 1,4-dichlorobenzene (NTP, 1987, as cited in the EU RAR; Aiso *et al*., 2005a (originally reported by JBRC, 1995); Eldridge *et al*., 1992, as cited in the EU RAR).

There was no regenerative cell proliferation in the inhalation study or early in the gavage study because no liver cell death or necrosis was occurring. In the case of induced mitogenic activity, the cell turnover rate may actually return to normal levels, but the livers remain enlarged so long as the 1,4-dichlorobenzene is continually administered. However, in the gavage bioassay, doses were so high that liver necrosis and cytolethality (and very likely regenerative cell proliferation) were also seen at the final sacrifice (NTP, 1987, as cited in the EU RAR).

Key experimental results that indicate that 1,4-dichlorobenzene is driving tumor induction via a mitogenic mode of action were summarized by Butterworth *et al*.:

1. A 90 day gavage study was conducted in male and female B6C3F1 mice under conditions of the cancer bioassay (Eldridge *et al*., 1992, as cited in the EU RAR). In that study, 1,4-dichlorobenzene given daily induced an increase in liver weight in the male and female B6C3F1 mice. When the compound was withdrawn, the livers returned to normal size, as is typical for mitogenic agents.

2. In the Eldridge *et al.* (1992, as cited in the EU RAR) study, a dramatic increase in the percentage of cells in S-phase (labeling index) was observed, indicating that the liver cells were not just increasing in size, but that the actual number of liver cells was increasing.

3. In the Eldridge *et al*. (1992, as cited in the EU RAR) study, histopathological evaluation revealed no evidence of hepatocellular necrosis and no elevations in liver-associated plasma enzymes were seen. Thus, in that study the cell proliferation was mitogenic in nature rather than regenerative.

4. The dose dependent increase in liver weights in the Eldridge *et al*. (1992, as cited in the EU RAR) study was similar to the dose dependent increase in liver weights described in the gavage cancer bioassay (NTP, 1987, as cited in the EU RAR). As expected, this parameter was seen in parallel to liver tumor induction.

5. Similarly, increases in liver/body weight ratios were seen in the Aiso *et al*. (2005a) inhalation bioassay that were directly proportional to the incidence of liver tumors in the male and female BDF1 mice.

6. The dramatic nonlinearity and correlation between increased liver weight and eventual tumor formation are clearly evident in the inhalation study (Aiso *et al.,* 2005a). In that study, liver tumors were induced only at the highest airborne concentration of 300 ppm that also produced dramatic increases in liver size. The next lower concentration of 75 ppm represented a no observed adverse effect level (NOAEL) for the induction of increased liver weight, the induction of altered cell foci, as well as the induction of liver tumors.

7. In no case with 1,4-dichlorobenzene have liver tumors been induced without preceding large increases in liver/body weight ratios. All of the above observations constitute a cohesive and classical pattern of activity observed for chemicals that have been characterized as acting via a nongenotoxic-mitogenic/promotional mode of action (Schulte-Hermann *et al.,* 1983 as cited in Butterworth *et al*. 2007).

The authors furthermore concluded that a lack of rat liver tumors is not evidence against a mitogenic mode of action as substantial species-to-species, strain-to-strain, and organ-to-organ differences in susceptibility are common for any given carcinogen. Furthermore, rats are less prone to induced or spontaneous liver tumors than mice.

Regarding the lack of effects of 1,4-chlorobenzene on the development of preneoplastic foci seen in some studies (for example by Gustafson *et al.,* 1998), Butterworth *et al.* considered this finding to be in line with the threshold identified for the nongenotoxic-mitogenic/promotional mode of action. No preneoplastic foci or tumor induction would be expected by the doses used in the negative studies, even with an abundance of initiated hepatocytes foci were produced. The inability of lower doses of 1,4-dichlorobenzene to promote the development of tumors from liver cells, even in the extreme case of initiation by dimethylnitrosamine, was thus considered consistent with the threshold nature of the promoting potential of 1,4-dichlorobenzene.

B.5.8.3 Conclusions

No new long-term carcinogenicity studies have been reported after the finalization of the EU RAR. New data focus mainly on mechanistic issues related to the carcinogenic properties of 1,4-dichlorobenzene. These data, together with recent reviews of the carcinogenic potential of the substance (ATSDR, 2006; Butterworth *et al.,* 2007) provide further support on the non-genotoxic, threshold approach as proposed in the EU RAR. The NOAEL/NOAECs proposed for carcinogenicity in the EU RAR are still the most appropriate.

As regards the mechanism of 1,4-dichlorobenzene's carcinogenic properties the non-genotoxic/mitogenic/promotional mode of action, possibly mediated by substituted hydroquinone metabolites, has received further support since the finalization of the EU RAR. A possible role for altered (suppressed) apoptosis has also been suggested. Taken together, the existing evidence supports a non-genotoxic mechanism, and the evidence is stronger today than at the time of the previous EU-wide assessment.

IARC classified 1,4-dichlorobenzene in November 1998 in Group 2B (the agent is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans). No reclassification has so far been undertaken.

It is noted that regulatory bodies in other jurisdictions (NICNAS, Australia (2000) and the Health Effect Division (HED) Cancer Assessment Review Committee (CARC) US EPA (2008)) have not classified 1,4-dichlorobenzene as a carcinogen based on the fact that there was no evidence of liver tumours of any type from the rat studies, formation of tumours at doses above or close to the maximum tolerated dose, a high spontaneous incidence of hepatocellular

adenoma and carcinoma in strains of mice used and on the substantial differences in the hepatic metabolism of the substance by mice in comparison to rats and humans as well as the fact that it exerts its carcinogenicity by a non-mutagenic mode of action involving mitogenesis.

B.5.9 Toxicity for reproduction

B.5.9.1 Non-human information

EU RAR 2004

The EU RAR reviewed two two-generation reproductive toxicity studies, one dominant lethal assay and five prenatal developmental toxicity studies for reproductive toxicity (Neeper-Bradley, 1989; Tyl, 1989; Anderson, 1976b, Hodge, 1977, Hayes, 1982; 1985; Giavini, 1986 and Ruddick, 1983, as cited in the EU RAR; Bornatowicz, 1994). Effects following administration via inhalation and oral routes have been investigated.

Effects on fertility

A two-generation study (GLP) on Sprague Dawley rats (28 rats/sex/dose) by inhalation exposure (vapour) at 0, 66, 211, and 538 ppm (6 hours/day, 7 days/week) over the course of 10 weeks before mating, during mating, gestation and lactation (except from 19 gestation day through Day 5 post-partum) revealed no adverse effects on reproduction (Neeper-Bradley, 1989; Tyl, 1989, as cited in the EU RAR). At the highest concentration of 538 ppm, parental toxicity including 10% reduction in body weight gain, mucosal irritation, tremors and salivation were observed in both genders and generations (F0 and F1 adults) and also during lactation (F1 adults). In addition to the clinical signs, the liver weight and histopathology (hepatocellular hypertrophy) were affected at 538 ppm in both genders with a NOAEC of 211 ppm. However, for males, kidney toxicity (increased kidney weight and hyaline droplet nephropathy) was seen at lower concentrations leading to a LOAEC of 66 ppm for males. Perinatal mortality was significantly increased at the highest concentration level of 538 ppm as indicated by reduced litter size and reduction in number of live foetuses per litter. In addition, a significant weight loss of offspring was observed at 538 ppm. No developmental effects were reported and there was no indication of histopathological effects in ovaries of testes or macroscopic anomalies in organs of offspring. The NOAEC for offspring toxicity was 211 ppm based on the increased perinatal mortality and reduced body weight of pups observed at the highest dose of 538 ppm

The calculated P/D ratio (parental NOAEC/descendant NOAEC) indicates no excessive reproductive risk using the adult female toxicity data (NOAEC of 211 ppm) and offspring toxicity data (NOAEC of 211 ppm). It is not possible to estimate P/D ratio based on male toxicity due to effects the lowest concentration level examined. The overall NOAEC of 211 ppm was established based on the study.

In a two-generation oral gavage study (OECD TG 416; GLP) in Spraque Dawley rats (24 rats/dose/sex) at 0, 30, 90, 270 mg/kg/day, 7 days/week, parental toxicity was observed at the highest dose level examined (270 mg/kg bw/day) without any effect on fertility (Bornatowicz, 1994). No significant clinical signs were observed in either generation. In F1 males and females, body weight was slightly reduced (less that 10%) at the highest dose. Liver, kidney and spleen weights were increased in F0 and F1 males with associated nephrotoxicity at 270 mg/kg bw/day; relative liver weights were increased only at 90 mg/kg bw/day in males. Histological examination was not systemically done in control and high dose group animals. Food consumption was reduced in dams of both generations (P and F1) at the highest dose between days 1-14 of lactation. This was assumed to be linked to the increased pup mortality and, thus, reduced nutritional and energy requirements in dams.

Offspring perinatal mortality was increased in both generations as indicated by reduced number of live pups at birth, decreased number of pups per litter during early and late lactation and increase in total number of stillborn pups a the highest dose level of 270 mg/kg be/day. In addition, mean body weight of pups was reduced during the whole lactation and there were alterations of skin. Pup mortality was increased between postnatal days 1-4 in F1 pups at the highest dose (1.5, 2.0, 2.6 and 32.3%) and at and above 90 mg/kg bw/day in F2 pups (1.0, 1.4, 5.4 and 13.7%) at 0, 30, 90 and 270 mg/kg bw/day, respectively)(Bornatowicz, 1994). Individual litter data was not reported in the paper by Bornatowicz, therefore, it is not possible to determine whether pup mortality was similar among all litters.

Body weights of F1 pups were reduced at birth at and above 90 mg/kg bw/day. However from postnatal day 4 onwards pups showed no significant body weight reduction. Body weights of F1 and F2 pups at the highest dose (270 mg/kg/day) were significantly reduced at birth and onwards.

Development of pups was retarded at the highest dose level of 270 mg/kg bw/day; the day of eye opening was delayed in pups of both generation as well as the day of erection of ears in the second generation (F2 pups). Percentage of pups per litter with positive draw up test was also reduced in both generations at 270 mg/kg bw/day and in the second generation at 90 mg/kg bw/day.

Malformations were noted in both control and treated animals e.g. anasarca, heart defects. Other more rare isolated incidences of malformations in treated pups of both generations, such as ectopic kidneys, did not reach statistical significance due to the low incidences and sampling method used. It was not possible to get reliable information on the potential teratogenic effect of the substance.

The NOAEL for fertility was 270 mg/kg bw/day, the highest dose examined. The parental NOAEL was 90 mg/kg bw/day for both generations based on slightly reduced body weight, increased liver, kidney and spleen weights and nephrotoxicity at 270 mg/kg bw/day.

A NOAEL of 30 mg/kg bw/day is selected for toxic effects noted in the offspring based on increased early postnatal mortality in F1 pups at the highest dose and F2 pups at and above 90 mg/kg/day, reduced birth weight at birth in F1 pups at and above 90 mg/kg/day and associated slight behavioural changes at 90 mg/kg bw/day with more pronounced findings at 270 mg/kg bw/day.

A Dominant lethal assay (Anderson, 1976b, as cited in the EU RAR) via inhalation route was negative.

Developmental toxicity

Inhalation exposure of pregnant rats during gestation days of 6-15 at vapour concentrations up to 508 ppm reduced the gestation period in 5% of the dams (Hodge, 1977, as cited in the EU RAR). There was no other sign of toxicity in dams or any dose-related sings of embryotoxicity or skeletal or soft tissue anomalies. The NOAEC for maternal and developmental toxicity (teratogenicity) was 508 ppm.

In the developmental toxicity study in rabbits, dams were exposed to the vapour of 1,4-dichlorobenzene during gestation days 6-18 (Hayes, 1982; 1985, as cited in the EU RAR). The highest concentration of 800 ppm reduced the body weight gain of dams without signs of embryotoxicity. Increased number of resorptions at 300 ppm was considered as a sign of embryolethality. Minor abnormalities, not considered as malformations, were observed at the highest exposure concentration included retro-oesophageal subclavian artery (5% (6/119) vs 2 % in the laboratory control group), deformation of paws on flexion (5% vs 0% in the control group). The total number of major malformations and skeletal and visceral defects were not

significantly different in treated and control groups. The NOAEC for maternal and developmental toxicity (teratogenicity) is 300 ppm.

After oral exposure up to 1000 mg/kg bw/day during organogenesis (gestation days 6-15), minimal decrease in mean foetal body weight was observed at the highest dose level whereas maternal body weight was reduced with a LOAEL of 500 mg/kg bw/day in a developmental toxicity study in rats (Giavini, 1986, as cited in the EU RAR). Skeletal variations, including a dose-dependent increase in the frequency of extra ribs at and above 500 mg/kg bw/day, were considered to be linked to maternal toxicity. The incidence of major skeletal and visceral abnormalities or embryotoxicity was not increased due to administration of the substance. The results of the study were only briefly reported. The NOAEL for maternal and developmental toxicity (teratogenicity) is 250 mg/kg bw/day.

In a very brief report of a developmental toxicity study by Ruddic (1983, as cited in the EU RAR), there was no maternal or developmental toxicity (teratogenicity) up to the highest tested dose of 200 mg/kg bw/day.

The two-generation reproductive toxicity studies and prenatal developmental toxicity studies provided do not justify classification for reproductive toxicity as concluded in the EU RAR.

Additional information

The effects of dietary exposure to 1,4-dichlorobenzene alone and in combination with 1,1-dichloro-2,2-bis(p-chlorophenyl)-ethylene (p, p'-DDE) were examined in adult rats after exposure *in utero* and during lactation periods (from gestation day 1 to postnatal day 21)(Makita, 2008). Dietary concentration of 25 ppm of 1,4-dichlorobenzene (approximately 0.8 and 2 mg/kg bw/day during pregnancy and lactation, respectively) did not cause maternal or developmental effects, including no effects in anogenital distance measurements, eye opening, vaginal opening or oestrous cycle. Animals exposed *in utero* and postnatally were killed in pre-oestrous stage at the age of 16 weeks. There was no change in serum levels of measured hormones (luteinising hormone, follicle-stimulating hormone, 17ß-oestradiol and testosterone), body weight or organ weights of liver, kidney, spleen, uterus and thymus. However, the ovary weight decreased significantly (by 20%) after combined exposure to 25 ppm of 1,4-dichlorobenzene and 125 ppm of p,p'-DDE. There were no histopathological findings in any of the organs examined including the ovaries. The authors reason that because p,p'-DDE is a potent inducer of cytochrome P450 enzymes, and the organ toxicity by 1,4-dichlorobenzene is associated with the formation of reactive metabolites, the combined exposure may increase the formation of reactive metabolites of 1,4-dichlorobenzene. Decreased ovary weight may be attributed to the accelerated apoptosis but quantitative follicle staging and counting or examination of apoptosis was not conducted.

B.5.9.2 Human information

EU RAR 2004

The EU RAR reported a case of a pregnant woman who ingested 5 to 10 g of 1,4-dichlorobenzene daily throughout her pregnancy. No abnormalities were reported in the infant, whereas the mother showed reversible signs of toxicity after cessation of exposure in the form of haemolytic anaemia (Campbell, 1970, as cited in the EU RAR).

These available human data were not considered relevant for the human risk assessment in the EU RAR.

Additional information

No additional data were found.

B.5.9.3 Conclusions

The overall NOAEC of 211 ppm was established based on increased perinatal mortality and weight loss of pups at parentally toxic concentration of 538 ppm in the two-generation reproductive toxicity study via the inhalation route. After oral administration of 1,4-dichlorobenzene through two generations, an offspring NOAEL of 30 mg/kg bw/day was derived based on increased postnatal mortality, reduced birth weight and slight behavioural changes at and above the parental NOAEL of 90 mg/kg bw/day.

Based on results from developmental toxicity studies via inhalation route, a NOAEC for maternal and developmental toxicity was 508 ppm for rats and 300 ppm for rabbits. The oral NOAEL for maternal and developmental toxicity was 250 mg/kg bw/day in rats.

There is limited information on ovarian toxicity after combined exposure with agents likely via increasing formation of reactive metabolites from 1,4-dichlorobenzene.

The EU RAR did not propose classification for reproductive toxicity and the additional new information on *in utero* exposure does not change that conclusion.

B.5.10 Other effects

B.5.10.1 Non-human information

EU RAR 2004

There is no information on other effects of 1,4-dichlorobenzene described in the EU RAR.

Additional information

Changes in endocrine functions

Only a few studies indicating limited oestrogenic potential of 1,4-dichlorobenzene have been found after the publication of the EU RAR (which was based on literature published up to 2002).

Versonnen *et al.* (2003) evaluated the estrogenicity of o-, m-, and p-dichlorobenzene with a yeast estrogen screen (YES) and zebrafish (Danio rerio) vitellogenin (VTG) assays. With the YES, 1,4-dichlorobenzene (*p*-isomer) was found to be estrogenic in a concentration responsive manner. Blood samples showed elevated VTG levels and decreased female gonadosomatic indices (GSIs) after exposure to 1,4-dichlorobenzene. Low GSIs coincided with high levels of VTG in the blood of female zebrafish. An indirect effect of VTG on the GSI was suggested rather than a direct toxic effect of 1,4-dichlorobenzenes on the gonads. The results suggested that the investigated compounds have estrogenic potency, both *in vitro* and *in vivo*, although only at extremely high exposure concentrations, which do not occur in the environment. Additionally, the position of chlorine substitution is important; the p-substituted compound (1,4-dichlorobenzene) having the highest estrogenic potency. Although VTG is a necessary component of egg development, it was suggested that high levels of VTG may have a direct or indirect negative influence on female gonadal development and egg maturation in zebrafish and thus jeopardize reproductive success.

In a study performed in China on crucian carps (Carassius auratus) by Qian *et al*. (2004) the serum testosterone and 17b-estradiol concentrations were detected using radioimmunology assay and the activities of two hepatic microsome enzymes, glutathione S-transferase and

UDP-glucuronosyltransferase were measured after the administration of 1,4-dichlorobenzene by peritoneal injections in the laboratory for 30 days. The results showed that 1,4-dichlorobenzene caused significant increases in serum testosterone concentration in the crucian carps compared to the controls, but it caused no significant effect on 17b-estradiol level. It was also observed a change in hepatic glutathione S-transferaze activity in crucian carps, with significant increases in enzyme activity. The changes in hepatic microsome enzyme activities may have resulted in the alterations of serum sex steroids levels in the crucian carps. The results indicated that 1,4-dichlorobenzene may change the endocrine functions and may also affect the reproductive function of crucian carp and other species. The mechanism of the alteration of serum sex steroids resulting from exposure of fish to the environmental toxicant is not clear. The plasma concentrations of sex steroids are dependent upon the synthesis of the steroids by the endocrine organ, the storage of the steroids in the plasma by binding proteins, and the degradation of the steroids by hepatic cells. Since sex steroids are degraded by hepatocytes, an alteration in the activities of the enzymes responsible for the degradation could dramatically change the circulating sex steroid concentrations. Biotransformation phase enzymes such as cytochrome P450-dependent monooxygenases, glutathione S-transferase, and UDP-glucuronosyltransferase are important enzymes responsible for the hepatic degradation of sex steroids. The authors concluded that changes in the activities of these hepatic enzymes may have profound effects on serum sex steroid levels in fish.

Takahashi *et al*. (2007) examined the estrogenic/antiestrogenic effect of 1,4-dichlorobenzene in the uterotrophic assay using immature mice and rats.

A significant increase/decrease in uterine and ovarian weights was occasionally seen in immature mice and rats subcutaneously administered 1,4-dichlorobenzene at doses of 22–67 mg/kg/day, with no reproducible results. A dose of 800 mg/kg/day 1,4-dichlorobenzene reduced the uterine and ovarian weights. The intraperitoneal administration of 1,4-dichlorobenzene at doses more than 400 mg/kg/day significantly inhibited the uterotrophic effect of β-estradiol in CD-1 (ICR) mice. β-estradiol-induced uterotrophy was dose-dependently prevented by 204–400 mg 1,4-dichlorobenzene/kg/day in C57BL/6N (Ah responsive) mice but not DBA/2N (Ah non-responsive) mice. While 1,4-dichlorobenzene did not bind to α-estrogen receptor up to a concentration of 10^{-3} M, the hepatic ethoxyresorufin- O-deethylase in adult female C57BL/6N mice was induced by intraperitoneal administration of 1,4-dichlorobenzene. These results compared to results obtained for 2,3,7,8-tetrachlorodibenzo-p-dioxin suggested that 1,4-dichlorobenzene is a weak antiestrogenic/antiuterotrophic compound possibly due to estrogen-receptor modulation through arylhydrocarbon receptor. Considering a NOAEL for antiuterotrophic activity of subcutaneous administration of 1,4-dichlorobenzene of 100–200 mg/kg/day and for inhalation a NOAEC of 250 ppm (1,500 mg/m^3), the authors recommended the avoidance of high concentrations of 1,4-dichlorobenzene, especially for women.

In their 2009 review on non-genotoxic carcinogens' mechanisms, Hernandez *et al*. cites 1,4-dichlorobenzene as one of the many human non-genotoxic carcinogens which are endocrine modifiers by binding to receptors such as the aryl hydrocarbon receptor.

Neurologic effects

Yan *et al.* performed in 2008 an *in vitro* study on 1,4 dichlorobenzene effects on the changes of cytosolic calcium concentration following nicotinic acetylcholine receptor (AChR) stimulation with epibatidine and a muscarinic AChR stimulation with methacholine in human neuroblastoma SH-SY5Y cells. The authors based their study on the relevant for the inhalation route of exposure, the physiological phenomena occurring in the nasal cavity, which contains an olfactory neuron, linked with an interneuron to relay information to the brain. Therefore the neuronal signal transduction is considered important. The neuronal receptors' airway such as nicotinic acetylcholine receptor nAChR) and muscarinic acetylcholine receptor (mAChR) were used in the study and the effects of 1,4-dichlorobenzene were investigated on the changes in cytosolic calcium concentration following the nicotinic AChR stimulation with epibatidine and the muscarinic AChR stimulation with methalcholine in human neuroblastoma SH-SY5Y cells,

as being recognized to have various characteristics of sympathetic ganglion cells and various subtypes of nAChR and mAChR.

The study revealed several novel characteristics of 1,4-dichlorobenzene, like the modulation of neuronal $[Ca^{2+}]_c$ homeostasis. The substance induced first a cytosolic free Ca^{2+} ($[Ca^{2+}]_c$) elevation of the source of Ca^{2+} including extracellular Ca^{2+} influx and intracellular Ca^{2+} release. The addition of 1,4-dichlorobenzene in a buffer with or without Ca^{2+} content resulted in an observed $[Ca^{2+}]_c$ increase. Secondly, 1,4-dichlorobenzene inhibited the Ca^{2+} signalling coupled with the stimulation of AChRs including nAChRs and mAChRs, as evidenced by the inhibition of 1,4-dichlorobenzene in the $[Ca^{2+}]_c$ increase induced by carbachol, epibatidine, and methacholine. The inhibition of 1,4-dichlorobenzene on the activities of nAChR was also demonstrated by the electrophysiological measurements, when the influx current coupled with nAChR was blocked by 1,4-dichlorobenzene. Thirdly, 1,4-dichlorobenzene inhibited the Ca^{2+} signalling coupled with the K^+-mediated activation of voltage-operated Ca^{2+} channel (VOCC).

The authors interpreted their findings as a consequence of the estrogenic-like activities (Versonnen *et al.,* 2003), the estrogen being able to alter the neuronal excitability by augmenting or inhibiting neurotransmitter-activated responses mediated via receptor gated channels and by hydrophobic interaction at the low-affinity binding site. The membrane-mediated non-genomic estrogenic characteristics can also increase the inhibition functional activities of nAChR channels and VOCCs compared to the mAChR signalling. The authors also proposed that 1,4-dichlorobenzene could deplete the Ca^{2+} stored in the endoplasmic reticulum. They concluded that 1,4-dichlorobenzene interference with Ca^{2+} homeostasis is conceivable *in vitro* and *in vivo*, but that further study of its neuronal activities in animal models is required to directly link human exposure to the substance with its interference on Ca^{2+} homeostasis.

B.5.10.2 Human information

EU RAR 2004

There is no information on other effects of 1,4-dichlorobenzene described in the EU RAR.

Additional information

No new information was found.

B.5.10.3 Conclusions

New information related to endocrine activity of 1,4-dichlorobenzene indicates that the substance may be a weak antiestrogenic/antiuterotrophic compound in mice and rats. An inhalation NOAEL for this effect was suggested at 250 ppm. One new *in vitro* study on neurological effects of 1,4-dichlorobenzene has been identified but is not considered sufficient to conclude on.

B 5.11 Derivation of DNEL(s)/DMEL(s)

EU RAR (2004)

No DNELs were established at the point in time when the EU RAR was being produced. Instead, the Margins of Safety approach (MOS) was applied in the EU RAR. Several endpoints were addressed, including systemic toxicity (liver and kidney) after long-term oral or inhalation exposure, and carcinogenicity. Consideration was afforded to all animal studies available and DNELs were derived for all relevant endpoints (see Tables B13 and B14 below). Although a somewhat lower DNEL was calculated for the liver effects observed in the one year oral study in dogs (Naylor *et al*. 1996), carcinogenicity is the endpoint of higher relevance for the human

health assessment of 1,4-dichlorobenzene and, therefore, the DNELs derived for carcinogenicity for both consumers and workers were brought forward for risk characterisation.

The studies used in the risk characterization were the same as those used in the present report.

DNEL setting in the present report

DNEL for oral exposure in the dog

A NOAEL of 10 mg/kg/d is selected for oral systemic liver effects in the dog based on elevated serum AP levels noted at the mid- and high dose in males and females (Naylor *et al.,* 1996).

Even if exposure by the oral route is seen as less relevant than exposure by inhalation for the human risk assessment of 1,4-dichlorobenzene-containing toilet blocks and air fresheners, the dog is a relevant model for humans and therefore the NOAEL is seen as relevant for DNEL derivation.

DNELs for long-term oral systemic exposure

A LOAEL of 300 mg/kg/d was selected for long-term oral systemic hepatocellular effects based on the degenerative changes (cellular swelling with clearing or vacuolation of the cytoplasm) in hepatocytes in male and female B6C3F1 mice at low and high dose, the cell size alteration (cytomagaly and karyomegaly) in low dose males and high dose males and females and focal necrosis (individual cell necrosis) in low dose males and high dose males and females (NTP, 1987).

A LOAEL of 150 mg/kg/d was suggested in the EU RAR for tubular cell adenocarcinoma noted at the highest dose in the male F344 rat kidney, however, these tumours are not of relevance to man due to the mechanism of action (α2μ-globulin nephropathy and tumour formation). The effects seen in the male rat kidney, nephropathy, mineralisation of the tubules and hyperplasia are likely to be related to the formation of the tumours. Therefore, a LOAEL of 300 mg/kg/d was taken for long-term oral systemic effects in the kidney based on nephropathy (consisting of degeneration of the cortical tubular epithelium, thickening of the tubular and glomerular basement membranes) at 300mg/kg/d in kidney in male B6C3F1 mice (NTP, 1987).

DNEL for long-term inhalation exposure – systemic effects

A NOAEC of 75 ppm was selected for long term inhalation systemic kidney effects in male F344 rats based on mineralisation of the papilla and hyperplasia of the pelvic urothelium observed at the highest dose (JBRC, 1995; Aiso *et al.*, 2005a).

Liver tumours were noted only in BDF1 mice with statistical significance at the highest dose. Hepatocellular carcinomas were observed in both sexes. Hepatoblastomas were seen in males and females with hepatocellular carcinomas and a similarly histiocytosarcomas were noted only in those males with hepatocellular carcinomas. The incidence of hepatic adenomas was statistically significant in females only. Based on these findings, a NOAEC of 75 ppm is selected based on hepatic carcinogenicity in male and female BDF1 mice following inhalation exposure (JBRC, 1995; Aiso *et al.*, 2005a).

DNEL for long-term inhalation exposure – local effects

A NOAEL of 75 ppm was selected for DNEL derivation based on the statistically significant increase in the incidence of slight respiratory metaplasia in the nasal gland and eosinophilic changes in respiratory epithelium in female rats at the highest dose (JBRC, 1995; Aiso *et al.*, 2005a).

DNEL for oral exposure – reproductive effects

From the two-generation oral reproduction toxicity study (Bornatowicz, 1994), a NOAEL of 30 mg/kg/day was selected for toxic effects noted in the offspring based on early postnatal mortality in F1 pups at the highest dose and in F2 pups at and above 90 mg/kg/day, reduced birth weight at birth in F1 pups at and above 90 mg/kg/day and associated slight behavioural changes at 90 mg/kg bw/day with more pronounced findings at 270 mg/kg bw/day.

DNEL for inhalation exposure – reproductive effects

From the two-generation oral reproduction toxicity study (Neeper-Bradley, 1989), a NOAEC for offspring toxicity of 211 ppm was selected for DNEL derivation based on the observed increase in perinatal mortality and reduced body weight of pups at the highest dose of 538 ppm.

Calculations used in DNEL derivation

For some calculations, a species specific allometric scaling factor was used (7 for mice; 1.4 for dog and 4 for rat) in accordance with the REACH Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (2010a; in the following referred to as the R.8 guidance). In further calculations, corrections for differences in absorption between routes (absorption oral animal/ absorption inhalation human) and for exposure duration were performed. For rodents oral absorption was assumed to be 62% (as per EU RAR) and oral absorption for the dog was assumed to be 100%. For consumers, assessment factors of 2.5 for interspecies variation and 10 for intra-species variations were applied. For workers, assessment factors of 2.5 for interspecies variation and 5 for intraspecies variations were applied.

Where required, an assessment factor of 3 was used in order to make a correction for starting point (to convert LOAEL to NOAEL). In order to compensate for differences in duration of exposure to (sub-chronic to chronic) an assessment factor of 2 was used while calculating DNELs.

The differences in exposure conditions were also taken into consideration including an adjustment made from 6 hours a day, 5 days a week (inhalation study exposure period) to 24 hours 7 days a week for consumer exposure. For workers, the adjustment was made from 6 hours, 5 days a week to 8 hours exposure for 5 days. An additional adjustment for respiratory volume was made for workers from 6.7m^3/8h (rest) to 10m^3/8h (light work).

When calculating the DNEL for local effects it was assumed that during exposure via inhalation, irritation in the nose is only superficial, i.e. there is no absorption. Thus there was no need to correct for absorption and differences in bioavailability were not accounted for in the calculations.

The oral NOAEL in dogs (10 mg/kg bw/day for liver toxicity) was converted into an inhalation NOAEL for consumers and workers using formulas shown below:

corrected $NOAEL_{consumers}$ = ($NOAEL_{oral}$ / allometric scaling) * (70 kg bw person/ 20 m^3/person);

corrected $NOAEL_{workers}$ = ($NOAEL_{oral}$ / allometric scaling) * (70 kg bw person/ 10 m^3/person).

When calculating the DNEL for carcinogenicity, the weight of evidence points to a low potency, non-genotoxic carcinogen which exerts its tumourogenic response via a mitogenic mode of action in mice only. However, a steep dose-response was observed, especially in female mice in the inhalation study, and, in addition, rare tumours (hepatoblastomas, histiocytosarcomas) were induced. Based on this evidence, an assessment factor (AF) of 3 for dose response relationship is used in the calculation of the DNEL. In choosing this AF, consideration was afforded to uncertainties in the dose descriptor, taking into account the steep-dose response observed, as well as, to the severity of the carcinogenic effect and the uncertainties associated with quantifying the risk from a low potency Category 2 carcinogen as detailed below:

- 1,4-dichlorobenzene is a category 2 carcinogen, which was classified due to the formation of liver tumours in only one species (mouse). Liver tumours were not observed in F344 rats in either a 2-year oral study or a 2-year inhalation study.

- The hepatoblastomas and histiocytosarcomas, as observed in conjunction with hepatocellular carcinomas, are rare tumours in mice.

- The liver tumours in the two strains of mouse (B6C3F1 mice following oral exposure and BDF1 mice following inhalation exposure) were evident at the highest dose tested only, however, a steep dose-response was observed.

- The EU RAR concluded that the overall weight of evidence from the most reliable genotoxicity studies indicates that 1,4-dichlorobenzene does not have any significant genotoxic potential. Since the publication of that report, further evidence supports a non-genotoxic/mitogenic mode of action. This conclusion is also supported by the lack of apparent liver toxicity in the inhalation study at the dose inducing tumours (increased liver weight and centrilobular hypertrophy was noted at the highest dose).

A conversion factor of 6.013 was used to convert ppm to mg/m^3.

Table B13 and Table B14 summarize all DNELs and calculations made.

Table B13: DNELs for consumers

DNEL (endpoint)	NOAEC ppm (mg/m³) (spec.)	NOAEL mg/kg bw	Corrected $NOAEL_{consumers}$; mg/m³	Compen-sation for differences in exposure conditions	Com-pen-sation for diff. in abs.	Assess-ment factors[1]	Resul-ting DNEL mg/m³	Resul-ting DNEL mg/kg/day	Reference
1 yr. oral study in dogs; based on bile duct hyperplasia & hepatic portal inflammation	-	10 (dog)	25	From 5 days a week to 7; (0.71) -	1 (oral 100 % dogs, inhalation 100 % humans)	2*2.5 * 10	0.36	0.12	Naylor *et al*., 1996, as cited in the EU RAR
2 yr. oral study in mice; hepatotoxicity; Degeneration, cell size alteration, focal necrosis hepatocytes in male mice)	-	300mg/kg/d (LOAEL) (mouse)	150 (corrected LOAEL)	From 5 days a week to 7; (0.71)	0.62 (oral 62% rodent according to EU RAR, inhalation 100% human)	3*2.5*10	0.3	0.89	As per EU RAR

2 yr. oral study; nephrotoxicity; Nephropathy in male mice		300mg/kg/d (LOAEL) (mouse)	150 (corrected LOAEL)	From 5 days a week to 7; (0.71)	0.62 (oral 62% rodent according to EU RAR, inhalation 100% human)	3*2.5*10	0.3	0.89	As per EU RAR
Long-term, Systemic (2 yr. inhala-tion study; carcinogenicity; Liver tumours in male and female mice)	75 (451) (mouse)	-	-	From 5 days a week to 7 days; from 6 h a day to 24 h (0.179)	0,6 (inhalation 60% mouse, 100% human)	3*2.5*10	0.64	0.21	JBRC, 1995, as cited in the EU RAR
Long-term, Systemic (2 yr. inhala-tion study; nephrotoxicity; Pelvic urothelial hyperplasia and mineralisation in male rats)	75 (451) (rat)	-	-	From 5 days a week to 7; from 6 h a day to 24 (0.179)	0,3 (inhalation 30% rat, 100% human)	2.5*10	0.97	0.32[2]	JBRC, 1995, as cited in the EU RAR
Long-term, Local (2 yr. inhala-tion	75	-	-	From 5 days a week to 7; from 6 h a	-	2.5*10	3.22	1.07[2]	JBRC,1995, as cited in

study; nasal lesions; Respiratory metaplasia in female rats & mice; eosinophilic changes in respiratory epithelium in female rats)	(451) (rat)			day to 24 (0.179)					the EU RAR Aiso, 2005a
Toxicity for reproduction (2-generation oral study with rats; perinatal mortality, reduced body weight)	-	30 (NOAEL)(rat)	52.5	0.62 (oral 62% rodent according to EU RAR, 100% human)	0.62 (oral 62% rodent according to EU RAR, inhalation 100% human)	1*2.5*10	0.65	0.22	Bornatowicz, 1994
Toxicity for reproduction (2 generation inhalation study with rats; perinatal mortality, reduced body	211 (1269) (rat)	-	-	From 7 days a week to 7; from 6 h a day to 24 (0.25)	0,3 (inhalation 30% rat, 100% human)	1*2.5*10	3.81	1.27	Neeper-Bradley, 1989; Tyl, 1989

weight)									

[1]The following assessment factors were used: 1.4 (dog), 7 (mouse) for allometric scaling; 2.5 for 'remaining inter-species differences; 3 for severity of effect (cancer); 10 for intra-species differences.
[2] Assuming a body weight of 60 kg and a respiratory volume of 20 m^3/24 h.

Table B14: DNELs for workers

DNEL (endpoint)	**NOAEC ppm (mg/m^3) (spec.)**	**NOAEL mg/kg bw**	**Corrected $NOAEL_{workers}$; mg/m^3**	**Compen-sation for differences in exposure conditions**	**Com-pen-sation for diff. in abs.**	**Assess-ment factors[1]**	**Resul-ting DNEL mg/m^3**	**Resul-ting DNEL mg/kg/day**	**Reference**
1 yr. oral study in dogs; based on bile duct hyperplasia & hepatic portal inflammation	-	10 (dog)	50	-	1 (oral 100 % dogs, inhalation 100 % humans)	2*2.5*5	2.0	0.29	Naylor *et al.*, 1996, as cited in the EU RAR
2 yr. oral study in		300mg/kg/d	300	-	0.62	3*2.5*5	4.96	0.71	As per EU

mice; hepatotoxicity; Degeneration, cell size alteration, focal necrosis hepatocytes in male mice)		(LOAEL) (mouse)	(corrected LOAEL)		(oral 62% rodent according to EU RAR, inhalation 100% human)				RAR
2 yr. oral study; nephrotoxicity; Nephropathy in male mice		300mg/kg/d (LOAEL) (mouse)	300 (corrected LOAEL)	-	0.62 (oral 62% rodent according to EU RAR, inhalation 100% human)	3*2.5*5	4.96	0.71	As per EU RAR
Long-term, Systemic (2 yr. inhalation study; carcinogenicity; Liver tumours in male and female mice)	75 (451) (mouse)	-	-	From 6 h a day to 8, from rest to light work[3]	0,6 (inhalation 60% mouse, 100% human)	3*2.5*5	3.62	0.51	JBRC, 1995, as cited in the EU RAR
Long-term, Systemic (2 yr. inhalation study;	75 (451)	-	-	From 6 h a day to 8, from rest to	0,3 (inhalation 30% rat,	2.5*5	5.44	0.78[2]	JBRC, 1995, as cited in the EU RAR

nephrotoxicity; Pelvic urothelial hyperplasia and mineralisation in male rats)	(rat)			light work[3]	100% human)				
Long-term, Local (2 yr. inhala-tion study; nasal lesions; Respiratory metaplasia in female rats & mice; eosinophilic changes in respiratory epithelium in female rats)	75 (451) (rat)	-	-	From 6 h a day to 8, from rest to light work[3]	-	2.5*5	18.13	2.59[2]	JBRC,1995, as cited in the EU RAR Aiso, *et al*. 2005a
Toxicity for reproduction (2-generation oral study with rats; perinatal mortality, reduced body weight)	-	30 (NOAEL)(rat)	26.25	From 7 day to, 5 days a week;	0.62 (oral 62% rodent according to EU RAR, 100% human)	1*2.5*5	3.65	0.52	Bornatowicz, 1994

Toxicity for reproduction (2 generation inhalation study with rats; perinatal mortality, reduced body weight)	211 (1269) (rat)	-	-	From 7 day to, 5 days a week; from 6 h a day to 8; from rest to light work[3]	0,3 (inhalation 30% rat, 100% human)	1*2.5*5	21.42	3.06	Neeper-Bradley, 1989; Tyl, 1989

[1] The following assessment factors were used: 1.4 (dog), 7 (mouse) for allometric scaling; 2.5 for 'remaining inter-species differences; 3 for severity of effect (cancer); 5 for intra-species differences.
[2] Assuming a body weight of 70 kg and a respiratory volume of 10 m^3/8 h, 5 days per week.
[3] Assuming a respiratory volume 8 h at rest of 6.7 m^3/8 h; at light work 10 m^3/8 h.

Limits proposed by national authorities

ATSDR (2006)

In their review of 1,4-dichlorobenzene ATSDR established Minimal Risk levels (MRL) for a number of endpoints, of which the chronic oral and chronic inhalation MRLs are the most relevant for the present risk assessment.

The MRL for chronic oral exposure was based on liver lesion in the dog study by Naylor *et al.* (1996; in the ATSDR report referred to as Naylor and Stout, 1996, unpublished). ATSDR determined a BMDL[9] of 12.32 mg/kg/day based on changes in serum alkaline phosphatise and relative liver weights in female dogs, which was rounded to 10 mg/kg/day and adjusted from an experimental exposure of 5 days per week to 7 days per week (7 mg/kg/day). An uncertainty factor (UF) of 100 was applied to arrive at a MRL of *0.07 mg/kg/day*. The UF consisted of a factor 10 for intra-species variability and a factor 10 for intra-species variability.

A MRL of 0.01 ppm (0.06 mg/m^3) was derived for chronic-duration (≥365 days) inhalation exposure to 1,4-dichlorobenzene. Benchmark dose modelling was conducted on the eosinophilic changes to the olfactory epithelium in female rats in the chronic inhalation study by JRBC (1995, as cited in the EU RAR). After adjusting data to continuous exposure the BMCL associated with a 10% increase in olfactory effects ($BMCL_{10}$) was selected as the point of departure for the MRL. The $BMCL_{HEC}$ was calculated using the rules for a category 1 gas with effects in the extra-thoracic region as described by U.S. EPA (1994) and determined to 0.27 ppm (1.65 mg/m^3). An UF of 30 was applied, consisting of a factor 3 to account for the interspecies variability in extrapolating from rats to humans. As the interspecies extrapolation factor encompasses two areas of uncertainty: pharmacokinetics and pharmacodynamics, and the pharmacokinetic component had been addressed by the dosimetry adjustments (i.e., calculation of the Human Equivalent Concentration (HEC) for time and concentration). Accordingly, only the pharmacodynamic area of uncertainty remained as a partial factor for interspecies uncertainty ($10^{0.5}$ or approximately 3). A 10-fold UF was used to account for variation in sensitivity within human populations. This resulted in a MRL of *0.06 mg/m^3*. The calculations are described in detail Annex 3.

EPA (2006)

EPA published a toxicological review of 1,4-dichlorobenzene in 2006. Reference doses (RfD) were established for chronic oral and inhalation exposure, and cancer risk estimates were calculated.

The RfD for chronic oral exposure was based on liver lesion in a dog study published by the Monsanto Company in 1996. This study is the one referred to as Naylor *et al.* (1996) in the EU RAR. EPA determined a $BMDL_{10}$ of 9.1 mg/kg/day and applied an Uncertainty Factor (UF) of 300 to arrive at a RFD of 0.03 mg/kg/day. The UF consisted of a factor 10 for intra-species variability, a factor 10 for intra-species variability, and a factor 3 was used to account for database deficiencies.

Benchmark dose modeling was conducted on the eosinophilic changes to the olfactory epithelium in female rats in the chronic inhalation study by JRBC (1995, as cited in the EU RAR). After adjusting data to continuous exposure the BMCL associated with a 10% increase in olfactory effects (BMCL10) was selected as the point of departure for the RfC. The BMCLHEC was calculated using the rules for a category 1 gas with effects in the extrathoracic region as described by U.S. EPA (1994) and determined to 2.52 mg/m^3. An UF of 30 was applied, consisting of a factor 3 to account for the interspecies variability in extrapolating from rats to humans. As the interspecies extrapolation factor encompasses two areas of uncertainty: pharmacokinetics and pharmacodynamics, and the pharmacokinetic component had been

[9] Benc Mark Dose Limit derived from the first standard deviation of the dose-response curve.

addressed by the dosimetry adjustments (i.e. calculation of the Human Equivalent Concentration (HEC) for time and concentration). Accordingly, only the pharmacodynamic area of uncertainty remained as a partial factor for interspecies uncertainty (100.5 or approximately 3). A 10-fold UF was used to account for variation in sensitivity within human populations. This resulted in a RfD of 0.08 mg/m^3. The slight deviation from the corresponding value established by ATSDR (above) seems to stem from different models used in the BMD extrapolations.

For carcinogenicity, EPA based their derivation of an inhalation unit risk on the hepatocellular carcinoma in male mice and the hepatocellular adenomas and carcinomas combined in female mice from the two-year bioassay (JBCR, 1995, as cited in the EU RAR). A multistage model with linear extrapolation from the point of departure was used to derive a unit risk of 4×10^{-3} $(mg/m^3)^{-1}$. In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March 2007), the CARC classified 1,4-dichlorobenzene as "Not Likely to be Carcinogenic to Humans" based on evidence that a non-mutagenic mode of action (MOA) involving mitogenesis was established for 1,4-dichlorobenzene induced liver tumours in mice and that the carcinogenic effects are not likely below a defined dose that does not perturb normal liver homeostasis (e.g., increased liver cell proliferation).

Committee on Sick House Syndrome, Japan

The Committee reported in their 4th report on a guideline value for indoor air concentration of 240 µg/m^3 (0.04 ppm) based on liver and kidney effects in beagles dogs exposed orally (Committee on Sick House Syndrome 2002). The details of the setting of the value seem only to be available in Japanese.

In a later report (Kondo, 2007) a reference concentration was determined to be 800 µg/m^3 based on a NOAEL of 80 mg/m^3 and divided by an uncertainty factor (100). The NOAEL was determined from a chronic (2-year) inhalation exposure study in mice, with the endpoint of non-neoplastic hepatic changes. It is presumed the study referred to is the study by JBCR (1993). However, the details of the setting of the value seem only to be available in Japanese.

In addition Occupational Exposure Limits have been set, which are further described in section B.9.1.1 presenting Occupational safety and health - related legislation.

Limit proposed by research group

Butterworth *et al.* (2007), applying benchmark dose analysis techniques to the combined data set for the inhalation and oral dose carcinogenicity studies considered in the EU RAR (with adjustment for route-specific absorption), established the atmospheric exposure level and oral dose that would associate with a 1% extra risk. Applying an uncertainty factor of 300 to the point of departure thus established, suggested that an atmospheric level of 0.1 ppm (approx. 0.6 mg/m^3) would equate with a level at which there was unlikely to be any increased lifetime risk of cancer.

Discussion

DNELs of 0.64 mg/m^3 for consumers and 3.62 mg/m^3 for workers have been derived in the present report based on carcinogenicity in the mouse following inhalation exposure.

Adjustment/assessment factors and other adjustments

In general, adjustment factors used in the MOS calculations in the ER RAR (2004) were similar to the assessment factors in the present report. For interspecies differences a factor of 3 was used in the RAR while the present REACH guidance (R8) recommends 2.5. For intra-species differences the EU RAR used 3 for workers while we have used 5. For intra-species differences between consumers it is not apparent which factor that was used in the EU RAR, but it can be assumed that 10 was used, which is in accordance with the present report. For allometric

scaling from dogs to humans the EU RAR used a factor of 2 while we have used 1.4 in accordance with the R.8.

The EU RAR applied the same absorption factors for experimental animals as those used in the present report, but assumed 75% in humans. No explanations for the assumptions were made in the EU RAR. In the present report absorption following inhalation exposure was set at 60% in mouse. For oral exposure 100% absorption was also used for deriving a DNEL from a dog feeding study. For humans a default factor of 100% absorption from the respiratory system and the gastrointestinal tract was made as very little data is available that could justify a lower assumption. The latter assumption is slightly more conservative than that in the EU RAR.

In the EU RAR no adjustments were done to extrapolate between experimental conditions (exposure 6 h 5 days a week at rest) and realistic working conditions (8 hours 5 days a week at light work). Such adjustments were done in the present study according to the R8 guidance and resulted in a slight decrease of the DNEL.

Assessment of carcinogenicity

All assessment factors described above which were used in the DNEL derivation could be regarded as default factors. However, for deriving the DNEL for carcinogenicity based on the inhalation study in mice (JRBC 1995) the factor of 3 was chosen for dose-response relationship (severity of effects).

Butterworth *et al*. (2007) also applied an uncertainty factor of 3 to compensate for uncertainties in the data, which resulted in a 'level of no concern' at approx. 0.6 mg/m^3. EPA (2006) took a considerably more conservative approach and used linear modeling to derive a unit risk for carcinogenicity of 4 x 10^{-3} (mg/m^3)$^{-1}$.

The EU RAR applied a factor of 5 for and concluded that a MOS of 95 for consumers was not sufficient concerning the severity of the effect (carcinogenicity). Additional information regarding the mechanisms of 1,4-dichlorobenzene-induced carcinogenicity has become available since the preparation of the EU RAR, giving better support for a threshold approach and that mitogenic properties of the substance or its metabolites seems to be involved.

However, the uncertainties associated with quantifying the risk from a low potency (category 2) carcinogen were not considered in an assessment factor (AF) of 5 as used in the EU RAR. Those uncertainties are as follows:

- 1,4-dichlorobenzene is a category 2 carcinogen, which was classified due to the formation of liver tumours in only one species (mouse). Liver tumours were not observed in F344 rats in either a 2-year oral study or a 2-year inhalation study.

- The hepatoblastomas and histiocytosarcomas, as observed in conjunction with hepatocellular carcinomas, are rare tumours in mice.

- The liver tumours in the two strains of mouse (B6C3F1 mice following oral exposure and BDF1 mice following inhalation exposure) were evident at the highest dose tested only, however, a steep dose-response was observed.

- The EU RAR concluded that the overall weight of evidence from the most reliable genotoxicity studies indicates that 1,4-dichlorobenzene does not have any significant genotoxic potential. Since the publication of that report, further evidence supports a non-genotoxic/mitogenic mode of action. This conclusion is also supported by the lack of apparent liver toxicity in the inhalation study at the dose inducing tumours (increased liver weight and centrilobular hypertrophy was noted at the highest dose).

Applying an AF higher than 3 would result in an overly conservative DNEL for a substance which is a low potency, non-genotoxic carcinogen. As a consequence, the assessment factor of

3, which takes into account the steep dose-response in liver tumours in female mice following inhalation exposure, is seen to be most appropriate in calculating the DNEL for 1,4-dichlorobenzene.

Assessment based on other endpoints

The consumers' DNEL derived in this report corresponds to a daily intake of 0.21 mg/kg bw (assuming a respiratory volume of 20 m^3 per 24 h and a body weight of 60 kg). The values obtained are higher than values used in other studies. The limit value of 0.078 mg/kg bw is used in Canada and the respiratory limit of 0.04 ppm (0.25 mg/m^3; 0.069 mg/kg bw and day) is used by the Japanese Committee for Sick Building Syndrome. Although the proposed DNEL for local effects is based on the same study and endpoint as the MRL established by ATSDR 2006, the latter is lower (0.01 ppm or approximately 0.06 mg/m^3) due to more conservative assumptions in the extrapolation between rat and man and by using a $BMD10_L$ as the point of departure when deriving the MRL.

Appropriate DNEL for risk characterisation

Section 1.1.4 of Annex I to the REACH Regulation mentions the following: *"[…] If there are several studies addressing the same effect, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs […] If the study or studies giving rise to the highest concern are not used, then this shall be fully justified and included as part of the technical dossier. […]".*

Chapter R.8 of the ECHA Guidance on information requirements and chemical safety assessment, in this respect remarks: "*If there are several studies addressing the same effects from which different NOAELs could be derived, normally the lowest relevant value should be used in DNEL derivation.*"

For the risk characterization of 1,4-dichlorobenzene it might be argued that the NOAEL taken from the sub-chronic oral study in dogs should be taken forward for risk characterization. The adverse findings in this study manifest at the mid-dose as increased serum AP levels, hepatic portal inflammation (periportal accumulation of neutrophils) noted in one male as well as hepatocellular pigment deposition in some males and females, however, the significance of this latter effect is not apparent in the summary provided. Similar effects are noted at the highest dose with the additional effect of bile duct hyperplasia in one male and one female and elevated GGT in females only. The effects observed are possible early markers of hepatobilary injury as indicated by the elevation of the choleostatic enzymes (AP and GGT), periportal inflammation in males and bile duct hyperplasia in 1 male and 1 female at the highest dose.

These findings are taken from an sub-chronic feeding study using small group size with a low number of animals affected. Route-to-route extrapolation is required for deriving the DNEL increasing uncertainty. While these findings cannot be dismissed in this assessment, their significance for risk characterisation in the case of 1,4-dichlorobenzene is not warranted as the severity of the tumour effects from the long-term inhalation study in mice is considered of higher relevance for human health assessment.

It is worth noting that the DNEL derived for carcinogenicity is protective of the effects noted in the 2-generation oral study in rats as well as the kidney effects noted in rats in the 2-year inhalation study.

Based on the above, the DNEL for carcinogenicity as taken from the long-term inhalation study is considered the leading health effect and of higher relevance for the human health assessment.

<u>Conclusion</u>

Long-term systemic DNELs of 0.64 mg/m^3 for consumers and 3.62 mg/m^3 for workers based on a long-term inhalation study in mice with liver tumours as the critical effect were selected for risk characterization of exposure to 1,4-dichlorobenzene in humans in this report (section B.10).

B.6 Human health hazard assessment of physico-chemical properties

B.6.1 Explosivity

No explosivity is expected as a result of its chemical structure.

B.6.2 Flammability

1,4-dichlorobenzene is a moderate flammable substance with a flash point of 65-66 °C. Auto-flammability arises at more than 500 °C and the vapors can form explosive mixtures with air within the range of 1.7 to 5.9 % by volume according to EU RAR. It is also mentioned that the test conducted according the method A10 from the Council Regulation No 440/2008 is negative.

B.6.3 Oxidising potential

No oxidizing properties are expected as a result of the chemical structure of 1,4-dichlorobenzene.

B.7 Environmental hazard assessment

Not relevant.

B.8 PBT and vPvB assessment

Not relevant.

B.9 Exposure assessment

The uses relevant for the present report are summarized in Table B15.

Table B15: Uses for exposure assessment

Use	End user	Exposed group considered
Use of 1,4-Dichlorobenzene in toilet blocks/air fresheners	Professional worker	Toilet cleaners/attendants
Use of 1,4-Dichlorobenzene in toilet blocks/air fresheners	Consumer	Adult consumers

B.9.1 General discussion on releases and exposure

B.9.1.1 Summary of the existing legal requirements

Professional workers safety legislation

Professional workers employed in public toilets as toilet attendants, cleaners or doing maintenance work could be exposed to 1,4-dichlorobenzene at their place of work. The

following paragraph presents an overview of EU legislation that currently applies to workers in relation to their exposure to chemical substances.

Occupational safety and health - related legislation

a) The Framework Directive (Directive 89/391 on the introduction of measures to encourage improvements in the safety and health of workers at work) defines the general obligation of the employer in relation to health and safety of workers.

   On the basis of this Directive, the risk assessment has to be conducted on the place of work for all activities including use of or exposure to 1,4-dichlorobenzene along with work place environmental conditions such as temperature and ventilation. Appropriate risk management measures would have to be provided, according to the hierarchy of control principles. The risk assessments would have to be documented and periodically reviewed. Workers have to be provided with information and training in relation to use of the substance to and safe work practices.

b) The provisions of the Framework Directive in relation to exposure to chemical substances are reinforced by the Directive 98/24/EC (Chemical Agents Directive - CAD). It 'lays down minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents.' In the directive, 'hazardous chemical agents' are defined as "*any chemical agent which meets the criteria for classification as a dangerous substance according to the criteria in Annex VI to Directive 67/548/EEC, whether or not that substance is classified under that Directive, other than those substances which only meet the criteria for classification as dangerous for the environment; (ii) any chemical agent which meets the criteria for classification as a dangerous preparation within the meaning of Directive 88/379/EEC, whether or not that preparation is classified under that Directive, other than those preparations which only meet the criteria for classification as dangerous for the environment; iii) any chemical agent which, whilst not meeting the criteria for classification as dangerous in accordance with (i) and (ii), may, because of its physico-chemical, chemical or toxicological properties and the way it is used or is present in the workplace, present a risk to the safety and health of workers, including any chemical agent assigned an occupational exposure limit value under Article 3.*"

   1,4-dichlorobenzene fulfils the classification criteria and therefore any risk to the safety and health arising from its presence must be assessed. The employer must conduct and document an assessment of the risk, in accordance with Article 9 of the Framework Directive. Substitution is the preferred method of controlling the risk. This assessment must be regularly reviewed and updated, particularly if there have been changes to work practices or if the results of health surveillance show it to be necessary.

c) As 1,4-dichlorobenzene is classified as a Carcinogen Category 3, the provisions of the Directive 2004/37/EC of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work do not apply.

d) Directives 91/322/EEC, 2000/39/EC, 2006/15/EC and 2009/161/EU list indicative occupational limit values (OELs). They serve as benchmarks in evaluating workers' exposure to chemical substances. Indicative OEL values are health-based and non-binding. On their basis, the Member States must establish national occupational exposure limit values for the chemical agents listed. They must take into account the Community values, but may determine their national value in accordance with national legislation and practice.

   The employer must regularly measure exposure to chemical agents which may present a risk to workers' health and must immediately take steps to remedy the situation if the occupational exposure limit values are exceeded.

1,4-dichlorobenzene is included in the list of OELs in the Directive 2000/39/EC with the eight hour exposure limit set at 122 mg/m^3 (20 ppm) and the short-term exposure limit value at 306 mg/m^3 (50 ppm).

According to the Exploratory survey of Occupational Exposure Limits (OELs) for Carcinogens, Mutagens and Reprotoxic substances (CMRs) at EU Member States level (2009) conducted by EU OSHA on behalf of the European Commission in 2007 among 21 EU member states (MS), 1,4-dichlorobenzene was recognised as a carcinogenic substance in two EU MSs, namely Austria and Estonia. The exposure levels set in these two countries are: for 8 h – 122 mg/m^3 and 450 mg/m^3, and for short term exposure – 306 mg/m^3 and 700 mg/m^3, respectively.

The protection provided by the legislation currently in force is closely linked to the established in 2000 OEL.

The current OEL is based on the recommendation of the Scientific Expert Group on Occupational Exposure Limits (SCOEL) prepared in 1994 and is not based on carcinogenicity. The 8-hour TWA is based on the study of Hollingsworth *et al*. (1956), indicating a NOAEL of 95 ppm (580 mg/m^3) for liver and kidney toxicity, is supported by the unpublished study of Riley *et al*., (1980a). In view of the lack of data on long term effects in humans, an uncertainty factor of 5 was considered appropriate. The recommended 8-hour TWA is 20 ppm (122 mg/m^3). The short-term exposure limit – STEL – of 50 ppm (306 mg/m^3) is based on the observations of irritation in workers (Hollingsworth *et al*., 1956). The values of OEL are currently under review by SCOEL.

Within EU, the OELs introduced on the national level vary. In some countries the TWA values are higher than proposed by the Directive, for example in Greece, is TWA is 450 mg/m^3, in UK 153 mg/m^3, and in the Netherlands 150 mg/m^3. There are also counties where TWA is lower: Belgium, Czech Republic, Denmark, Poland, Portugal and Sweden. The lowest values are in Germany – 6 mg/m^3 , and France – 4.5 mg/m^3 (RPA, 2010).

Accordingly, the employers are expected to ensure that the 8-hours exposure of workers, including toilet attendants and cleaners, is below the level of OEL. However, the DNEL used as a benchmark to evaluate the exposure is significantly lower than the OEL. Currently used work practices – operational conditions and risk management measures presented in this report – lead to exposures significantly lower than the OEL.

A protective Occupational Exposure Limit, set taking into account a suitable DNEL, is discussed as a separate risk management option in section E.1.3.

Directive 98/24/EC establishes binding occupational exposure limit values and binding biological limit values are drawn up at Community level taking into account also feasibility factors. There are no binding limit values for 1,4-dichlorobenzene.

Relevant Consumer safety related legislation

1,4-dichlorobenzene is present in high concentration in consumer products, such as toilet blocks and air fresheners. The legislative provisions applicable to consumer use of products that may present a risk are presented below.

a) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Annex XVII of REACH does not contain any restrictions on the manufacture, placing on the market and use of 1, 4 dichlorobenzene.

   The substance is classified under CLP legislation and is required to be labeled accordingly in order to inform the consumer of the hazards associated with the substance. The current classification – Carcinogen Cat. 2 under Regulation 1272/2008 –

allows the substance to be used by consumers, as it is not included in the entry 28 of the REACH Annex XVII.

b) The General Product Safety Directive (2001/95/EC) (GSPD) requires that the producers must place only safe products on the market, and must inform consumers of the risks associated with the products they supply.

In general, the provisions of GPSD complement the provisions of REACH and CLP.

c) According to the Art. 3 of the GPS Directive *"A product shall be deemed safe, (…) when, in the absence of specific Community provisions governing the safety of the product in question, it conforms to the specific rules of national law of the Member State in whose territory the product is marketed (…)*

A product shall be presumed safe as far as the risks and risk categories covered by relevant national standards are concerned when it conforms to voluntary national standards transposing European standards, the references of which have been published by the Commission in the Official Journal of the European Communities in accordance with Article 4. The Member States shall publish the references of such national standards."

d) The Art 13 of the GPSD Directive indicates that the Commission does have an option to adopt a decision to take action in relation to the risk subject to certain conditions. However, such decisions are not permanent and have to be reviewed every year.

Currently, the only Member state where the use is prohibited is Sweden (see Table G54). There is no Community-wide action in relation to air fresheners and toilet blocks containing 1,4-dichlorobenzene used by consumers.

e) Decision 2004/129/EC (Non-inclusion of Pesticide Active Substances Decision) - according to the EU Pesticides database, 1,4-dichlorobenzene has been used as a rodenticide and insecticide. Insect repellent and fungicide uses (outside the EU) have been identified in the literature. The substance is not authorised for use in the EU. The Maximum Residue Level for the substance is the default level of 0.01 mg/kg according to Article 18(1) (b) of Regulation (EEC) No 396/2005.

The above mentioned Decision does not apply to the use of 1,4-dichlorobenzene in toilet blocks and air freshener.

Decision 2007/565/EC concerning the non-inclusion in Annex I, IA or IB to Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market of certain substances is to be examined under the 10-year work programme referred to in Article 16(2) thereof. According to the Decision, 1,4-dichlorobenzene is not to be included in Annexes I, IA and IB to Directive 98/8/EC for product types 18 (Insecticides, acaricides and products to control other arthropods) and 19 (Repellents and attractants)[10].

The above mentioned decision targeted the following two product types in relation to 1,4-dichlorobenzene:

[10] There was no dossier submitted by industry under the Biocidal Products Directive (RPA, 2010). Consequently there was no assessment report elaborated to allow the inclusion of the substance in the annexes of the above mentioned Directive. See available reports for other substances included in Annex I or IA to Directive 98/8/EC :
https://circabc.europa.eu/faces/jsp/extension/wai/navigation/container.jsp

- Product-type 18: Insecticides, acaricides and products to control other arthropods (e.g. insects, arachnids and crustaceans).

- Product-type 19: Repellents and attractants. Products used to control harmful organisms (invertebrates such as fleas, vertebrates such as birds), by repelling or attracting, including those that are used for human or veterinary hygiene either directly or indirectly.

The product types above are not related to the uses targeted by this Restriction proposal. 1,4-dichlorobenzene air fresheners and toilet blocks mask unwanted odours (mainly in toilets). Such products, marketed as deodorizers and not e.g. as insect repellents would not be in breach of the EU legislation on biocides.

Legislation applicable to both consumers and workers' safety –

a) 1,4-dichlorobenzene was included in the Annex 1 to the Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labeling of dangerous substances. It was classified, in relation to human health, as Xi irritant, (R36 – Irritant to eyes) and in 2004 the classification was updated to include Carcinogen Cat. 3 (R40 – Limited evidence of a carcinogenic effect).

b) According to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, replacing the Directive 67/548/EEC, the related Hazard statement codes are: H351 – Suspected of causing cancer, H319 – Causes serious eye irritation. The following information has to be included on the label: pictogram GHS08, indicating carcinogenicity, hazard category 2 and the hazard statements: H351 – Suspected of causing cancer, H319 – Causes serious eye irritation. There are no safety statements (see Table B10).

The label under Regulation (EC) No 1272/2008 does not specify that the risk relates to exposure via inhalation. A safety data sheet should be available to workers and the risks associated with exposure via inhalation should be indicated in the exposure scenario.

B.9.1.2 Summary of the relevant operational conditions (OCs) and risk management measures (RMMs)

'Guidance on information requirements and chemical safety assessment - Chapter R.13: Risk management measures and operational conditions' (2008) outlines the information related to the uses of the substance that is required to assess exposure. The operational conditions (OCs) and risk management measures (RMMs) for the professional workers' and consumers' use of toilet blocks and air fresheners are presented below in accordance with the guidance' recommendations.

B.9.1.2.1 Consumers

The operational conditions affecting the exposure of consumers are as follows:

- **Duration and frequency of exposure**. In relation to consumer uses, the exposure is calculated as a 24 hours average. Within this period, there is an actual time of exposure, in this case – the time spent in the toilet/bathroom. The literature presenting measured (Djohan, 2007) and modelling (Aronson, 2007) data indicates that there is some air exchange between the toilet/bathroom and other areas of the house. Therefore, the total exposure also includes exposure in other parts of the house.

- **Applied amount of chemical**. The same type of toilet block/air freshener is used both in the private and public toilets. The size of the toilet blocks vary between 25 and 115

g. The concentration of the active substance differs between 70 % and >95 %. The blocks are supposed to be replaced every 14, 21 or 30 days at 20 °C. (RPA, 2010).

- **Temperature.** There is a significant temperature variation in the EU due to geographical location and seasons usually ambient temperature is expected. The guidance R13 and R15 recommend the use of 20 °C for exposure estimation. However, in some geographical regions the ambient air temperature may be higher. Exposure estimations were based on daily exposure and RAC considered that in some homes the average temperature could be higher than 20°C especially where the consumer is infirmed. **Containment of the process**. The toilet blocks/air fresheners are usually placed in plastic casing/baskets, where there is no restriction to airflow. The purpose of the use of the substance is to deodorise the space they are provided for, therefore there could be no containment.

- **Capacity of surroundings and ventilation rate**. The toilet blocks are typically used indoors. According to ConsExpo, the general ventilation rate for the toilets in a private dwelling is considered to be 2 air exchanges per hour. There is a significant variation in the size of the bathroom/toilet facilities. The ECHA guidance chapter R15 and the ConsExpo model suggest the volume of a toilet to be 2.5 m^3 which is equivalent to a toilet cubicle. The 10m^3 referred to in ConsExpo equates to a bathroom where a shower/bath washing facilities would also be available. Therefore, RAC considered the 2 air exchanges per hour is relevant for such a bathroom size. It is expected that for a cubicle of 2.5 m^3 the air exchanges per hour would be higher as the action of opening and closing of a cubicle door would lead to one air exchange. However, to take account of very poorly ventilated bathrooms RAC also considered exposure in a bathroom where the air concentration was 0.2 air exchanges per hour.

Risk management measures

For the consumers, the range of risk management measures that could be used is very limited. The options include:

- Product-integrated RMMs under control of the supplier such as type of formulation (e.g. for liquids – high viscosity, for solids - granules rather than fine powder) packaging (limit of concentration, volume, dispensing options). Toilets blocks and air fresheners based on 1,4-dichlorobenzene are solid blocks. The active substance is released continuously, through sublimation. The purpose of use limits the options for managing the exposure as the substance is supposed to be released into the air. The air-tight packaging of blocks limits the number of sources of exposure to the block that is (intentionally) unwrapped.

- Consumer instruction/communication on safe use. The labelling provides information on safe use and includes 'warning' symbols, if appropriate. Instruction given on the number of blocks to be used at a time may be used to limit the exposure.

RMMs and OCs taken into consideration for modelling of exposure of consumers

Size of toilet block: There is a range of sizes of the toilet blocks available on the market, depending on the manufacturer. The size of the air freshener / toilet block selected for the modelling is 80g, expected to last 21 days. The parameters were chosen on the basis of the information on the product presented in the RPA. This size and longevity were also used by the RPA to develop the example of the cost calculation (table p. 95 (TC41). 80g is also the size of the air freshener block close to the one used in the Globol Werke study - 77.4g. The higher vapour pressure at increased temperature leads to higher sublimation rate and more frequent necessity to replace the blocks. There is no indication that the manufacturer may recommend the use of more that one block at a time for domestic premises.

Exposure duration: In this report, as a reasonable worst case scenario, 24 hours will be considered as exposure duration. This exposure duration may be applicable to persons who remain all day at home, such as elderly or with affected mobility. Within this period, there is an actual duration of exposure close to the source, in this case – the time spent in the toilet/bathroom. According to Djohan (2007), the average time spent in the toilet is 30 minutes per day. RIVM fact sheet presenting the exposure model for use of toilet rim blocks indicates that on average a person spends in the toilet/bathroom 50 min per day. As a reasonable worst case scenario 1 hour exposure will be used for the exposure estimation in a bathroom. However, the exposure estimation will also be presented for Djohan's estimation (30 min in a toilet cubicle, 23,5 hours in other areas of the house). For consumer exposure worst case scenarios exposure has been calculated using a bathroom with different ventilation rates.

Concentration in the home outside the bathroom: The literature presenting measured data indicates that there is some air exchange between toilet/bathroom and other areas of the house. It is assumed, as a worst case scenario (based on Djohan (2007) and Aronson (2007)), that in the living areas the concentration of the substance in the air is 3 times lower than in toilet/bathroom (the concentration of the substance in other areas of the house is variable – it depends, among others, on the rate of air exchange between the toilet and the other areas, size of the house and ventilation of the house). This exposure has also been included in the calculations. A respiration rate of 20 m^3/day was considered, as recommended by Guidance Chapter R15 for whole day assessment.

Exposure temperature: 24 hour exposure in an average temperature of 20 °C was considered, as recommended in the Guidance Chapter R.15. An average temperature of 30 °C was also considered to represent the variability of conditions in a day, within Europe and for consumers who may be infirm. For comparison however it is acknowledged that it is unlikely that 30 °C would be the average temperature over a 24 hour period. In such high average temperature circumstances it is more likely that greater ventilation would be employed by the consumer i.e. air conditioning or opening of windows to allow air to circulate in the home resulting in lower exposure.

Ventilation rate: Following the ConsExpo recommendation, 2 air exchanges per hour was used as the ventilation rate for the bathroom (10m^3) However, exposure modelling was also undertaken for the recommended by the Guidance R15 air exchange rate of 0.2 per hour for a bathroom (10m^3).

Note: The Exposure Scenario submitted by the registrant, presenting the use of the substance as an air-care product by consumers recommends 'sufficient ventilation' as the only RMM. The explanation of what ventilation rate is considered to be 'sufficient' is not provided.

B.9.1.2.2 Professional workers

The operational conditions affecting the exposure of workers include the following:

- **Duration and frequency of exposure**. There is a significant variability in the duration of exposure of the professional workers to the 1,4-dichlorobenzene. The group of workers with longest exposure are toilet attendants, who work at public toilets. Their duties include collecting fees for use of amenities and (some) cleaning. Even though part of their time would be spent in the anteroom, their exposure is expected to be significant due to the frequent opening of the door leading to the amenities. The second group are cleaning workers. For some of them, cleaning toilets would be a part of the daily duties. The exposure time would depend on the number and size of the toilets they have to clean. In addition, there may be an occasional need for repairs, for example by a plumber. The exposure duration to 1, 4 dichlorobenzene for this group would be less than the 8 hr (exposure of toilet attendants).

- **Applied amount of chemical**. According to the information available from RPA (2010) and other literature, the size of the toilet blocks varies between 25 and 115 g. The concentration of the active substance also differs from 70 % to more than 95 %. At 20 °C, the blocks are supposed to be replaced every 14, 21 or 30 days. The number of products uses will also have an impact on the exposure.

- **Temperature.** While air conditioning may be employed usually ambient temperature is expected. There is a significant temperature variation due to geographical location and seasons, even though the substance is used mainly in indoor facilities. The exposure in temperatures of 20 °C and 25 °C was considered as the average temperature for 8 hour period to represent the variability of conditions in a day and within Europe.

- **Containment of the process.** The toilet blocks/air fresheners are usually placed in plastic casing/baskets, where there is no restriction to airflow. The purpose of the use of the substance is to deodorise the space they are provided for, therefore there is no containment.

- **Capacity of surroundings**. The toilet blocks and air fresheners are typically used in indoor facilities. There is a significant variation in the size of the toilet facilities – from relatively small to quite large. The size of the facility is usually correlated with the number of toilet blocks used.

- **Ventilation**. There is expected to be significant variability in ventilation rates in public toilets as no harmonised Building Regulations for ventilation rates across the the 27 member states. However, there are a number of ventilation guides and codes in place which include ventilation rates for public toilet.

Risk management measures

For occupational exposure, the principles of the legislation applicable to the workers protection, especially in relation to exposure to chemical substances presented in the Chemical Agents Directive 98/24/EC have to be followed.

The availability of the risk management measures available for use to the professional workers – toilet attendants or cleaners - is limited.

- Elimination of the risk. While there are other products on the market, the 1,4-dichlorobenzene is still used particularly in public toilets where usage is high and cleaning is infrequent . Anecdotal evidence indicates that in some countries, there is no change in use pattern, while in other countries the use is decreasing (RPA, 2010).

- Reduction of the risk through limiting concentration of the substance, change of the physical form, use in closed process or effective local extraction ventilation. The product (toilet block/air freshener) may contain almost 100 % of 1,4-dichlorobenzene. There is no information in relation to possible change in the composition or size of the toilet blocks over the years. The physical state of the substance – solid – is linked to the function. While increasing the size of the block may reduce the frequency of replacing the blocks, handling of them is not the main risk factor as dermal protection in the form of gloves is available and skin exposure is thus not considered to be a major route of exposure. Due to the purpose for which the substance is used – deodorising – use in enclosed process is not appropriate. Similarly, local extraction ventilation is not always an option available to reduce the concentration of the substance in the air in public toilets.

- General ventilation. Usually, general ventilation is provided in public toilet facilities. The rate of ventilation, presented as a number of air exchanges per hour, depends on the location of the facility. The effectiveness and rate of the ventilation in public toilets is regulated by the national and/or municipal building codes. One study available (Globol

Werke GmbH, 1986) indicates that the ventilation was dependent on the users. There is no common, EU- wide default value for the public toilets. The CIBSE guidance B2 on ventilation rates (2009) provides for a minimum design of 3 air exchanges per hour in non-domestic toilets.

- Organisational measures, such as limiting the number of exposed persons by providing self flushing urinals/toilet could be considered for high use facilities where cleaning is infrequent. However, this would not address odours from spillages or poorly designed plumbing.

- Personal protective equipment. Dermal personal protection equipment such as gloves should be used during cleaning toilets. However, the analysis of the literature indicates that respiratory protective equipment is typically not used by toilet attendants or persons cleaning or conducting maintenance of toilet facilities. Taking into account the physical properties of the substance and the fact that RPE is typically not used the main exposure route is via inhalation.

RMMs and OCs taken into consideration for modelling of exposure for professional workers

For the purposes of the opinion, worst case scenario conditions have been analysed and recalculated based on the uncertainties in the modelling parameters. The duration of exposure of 8 hours with light cleaning activities was considered.

It is assumed that in public toilet facilities there is only one toilet attendant at a time. While job rotation may reduce the duration, and therefore the level of exposure, this administrative control may not be available in all situations, therefore it is not considered in the exposure estimations. As the duration of the exposure for other professional groups that may conduct some work in the public toilet (or in the toilet at private house) is significantly less than 8 hours, their exposure has been estimated only for the impact assessment.

There is a range of sizes of the toilet blocks available on the market, depending on the manufacturer. The size of the toilet block was taken as 80g, and they were assumed to be replaced every 21 days at 20 °C and every 10 days at 30 °C. On this basis, the longevity of 15.5 days was calculated for 25°C, assuming linear relationship between the temperature and sublimation rate. The differences in temperature affecting the volatility lead to different sublimation rates, necessitating more frequent replacement of the blocks (RPA, 2010). This size and longevity of the block were also used by the RPA to develop the example of the cost calculation (table p. 95 (TC41). 80g is also the size of the air freshener block close to the one used in the Globol Werke study - 77.4g.

There is no data available on cleaning industry work practices in relation to number of toilet blocks/air fresheners used in relation to the size/volume of the facility. There is only one publication presenting a set of measurement data from public toilets (Globol Werke GmbH, 1986, as cited in Aronson, 2007). In one facility six 41.3g blocks were used in approx. 40 m^3 (1 block per 6.6 m^3), in the second - three 41.3g blocks were used in 15.42 m^3 (1 block per 5.1 m^3), in the third – one 77.4g block was used in 15.42 m^3. The use of one 80g block per 5 m^3 will be used in developing the exposure estimation. The temperatures of 20 and 25 °C were considered to represent the average workplace temperatures over an 8 hour period and take into account the variability between the conditions in Member States.

The legislation and guidelines in relation to recommended ventilation rate are established on the national level. Use of natural ventilation is listed as a (preferred) option in the Global Guide for Practical Public Toilet Design published in 2011 by the International Code Council. It is also foreseen in the Greek guide "Communal toilets, Design and equipment".

If natural ventilation is not available, then mechanical ventilation is required. The required ventilation rates, in these cases, vary but usually 5-7 air exchanges per hour are required (e. g. Polska Norma PN-83/B-03430). For exposure estimations, in line with the only set of

measured data (Globol Werke GmbH, 1986), it will be assumed that the natural ventilation is available. The rate of ventilation provided in such conditions would vary depending on the direction of the wind, temperature gradient, location and number of the windows. There would be significant daily and seasonal variety. Therefore, to compensate for the variability the CIBSE guidance will be used. The CIBSE guidance B2 on ventilation rates (2009) provides for a minimum design of 3 air exchanges per hour in non-domestic toilets.

Considering that the substance is not used as a cleaning agent, and the presence of its odour is expected, no special precautions are used in relation to respiratory exposure by cleaning workers, including toilet attendants. Research of internet based sources dedicated to cleaning services and cleaning workers did not indicate any concerns related to toilet blocks or air fresheners used. EU-OSHA recently published a literature review – The occupational safety and health of cleaning workers, provides an overview of the occupational illnesses experienced by this group (2009). Respiratory ill health is mentioned, however the link between health outcome and use of toilet blocks or air fresheners is not mentioned.

Similarly, the report ´Preventing harm to cleaning workers´ (2009) lists respiratory disorders, including asthma as one of the work-related health problems found among cleaners. However, use of respiratory protective equipment is recommended only for biological risks, such as fungi, human excreta, blood and body fluids, bacteria, viruses, but not for chemical risks.

The Exposure Scenario submitted by the registrant, presenting the use of the substance as an air-care product by professional workers recommends 'sufficient ventilation' as the only RMM. The explanation of what ventilation rate is considered to be 'sufficient' is not provided.

Therefore, the use of respiratory protection is not taken into consideration in calculating estimated exposure levels for toilet attendants.

B.9.2 Manufacturing

The manufacturing stage of the toilet blocks has not been assessed as it is not within the scope of this report. The exposure of workers involved in the manufacturing processes was assessed in numerous reports, including the EU RAR (2004).

B.9.3 Use of 1,4-Dichlorobenzene in toilet blocks/air fresheners

The method of use of the block – as an air freshener or toilet block - may result in different exposures. For the air freshener use, all of the substance is a subject to sublimation[11] through the duration of use, whereas toilet blocks are becoming wet when the toilet is flushed. This may result in reduced sublimation rate, but also in a loss of some 1,4-dichlorobenzene into the water. EU RAR refers to a study by BUA (1994) indicating that 60% of the substance formulated into air fresheners and toilet blocks is used as air fresheners and 40% as toilet blocks. 20 – 30 % of the weight of the toilet block may be lost through the contact with water (flow: 60 ml/min). The change of the sublimation rate was not addressed. Considering that the same type of block is used for both purposes, the use as an air freshener will be considered for the estimation of exposure for the reasonable worst-case and realistic scenarios, for both workers and consumers.

More recent data, presenting uses in EU, indicate that the use as toilet block dominates – it accounts for approximately 77% of the use of the substance as toilet block / air freshener (RPA, 2010, AMEC, 2012) therefore the sole use of air fresheners in the exposure modelling is likely to lead to an overestimation of exposure levels.

B.9.3.1 General information

[11] Transition of a substance from the solid phase to the gas phase without passing through an intermediate liquid phase.

For the purposes of this report, only exposure of the end-user groups – professional workers, that is toilet attendants/ cleaners, and consumers was considered.

The professional workers may also be involved in the storage, transport and handling of the air fresheners and toilet blocks. Their exposure was not evaluated as there is a very significant number of uncertainties and variations in relation to their exposure.

Firstly, the properties of the substance – its ability to sublimate at room temperature - require air-tight packaging to prevent the loss of the substance during storage and transport of the product to the final user, but also during storage by the final user. It can be assumed that this risk management measure is implemented by the manufacturer. The air-tight packaging would eliminate / minimise the potential for exposure of those groups.

Secondly, the conditions of storage and transport vary – with differences in space volume, amount of product stored or transported at any one time, frequency of exposure depending on whether or not the product is stored or transported. These variations would make a meaningful modelling of exposure impossible. In the literature analysed there was no mention of potential exposure of these groups, so there is no sets of measured data that can be linked to these activities.

Thirdly, as it will be demonstrated in the following sections, the estimated levels of exposure of both consumers and professional users exceed the respective derived DNELs, leading to risk characterisation ratios above 1. The proposed RMO is restriction. As a result of this action, the potential exposure of storage and transport workers would also be eliminated.

B.9.3.2 Exposure estimation

B.9.3.2.1 Consumer exposure

An analysis of exposure of consumers to 1,4-dichlorobenzene in toilet blocks/air fresheners alone has not been included in the EU RAR (2004) – it is presented jointly with exposure to the substance resulting from use of mothballs. 'Guidance on information requirements and chemical safety assessment - Chapter R15: Consumer exposure estimation' (2010) presents the description of the methodology for developing exposure estimations for consumers.

Measured data

According to the Guidance Chapter R15, in general, the measured data are preferred to modelling in the evaluation of exposure. However, monitoring data has to be representative of the situation and fulfil certain quality criteria and the data needs to be representative and the methodology reliable.

In cases where there is no sufficient measured data to be used in an exposure scenario, some elements of the data available may be used. In the case of consumer exposure to 1,4-dichlorobenzene specifically in toilet blocks/air fresheners, measured data is limited to one study.

In a number of studies presented in detail in EU RAR (2004) and RPA (2010), as well as in the studies presented in IARC monograph volume 73 (IARC 1999a), in ATSDR (2006) and Australian NICNAS report (2000), household exposure to 1,4-dichlorobenzene is described. However, the sources of exposure presented in these studies are multiple – toilet blocks / space deodorants and moth repellents, or not specified. Only one study has been identified presenting the exposure to a single type of source in the form of toilet blocks (Djohan, 2007).

This study was undertaken in Australia. It presents a small sample size. There are uncertainties related to size of the toilet, ventilation rates, temperature variability, etc therefore it not considered as really representative for consumer exposure in EU, but only as a

random sample. While results of the Djohan's study are not representative for the purposes of this report, the migration rate of the substance from the bathroom to the other areas of the house has been derived from their study for use in the modelling input parameters.

Use of modelling tools

Guidance Chapter R15 presents a number of exposure modelling tools. Their features have been taken into consideration in the selection of the most appropriate tool for the type of substance under consideration.

ECETOC TRA Consumer is a Tier 1 tool. It takes into consideration the following parameters: fraction of the ingredient in the product, amount of product used per application, frequency of use, fraction released to air, room volume. Results are expressed as exposure air concentration (mg/m3). Product/article category and sub-category has to be provided.

However, the transfer of the substance into air is assumed to be instantaneous: a substance with vapour pressure >10 Pa is considered to be completely released into the air instantly. Ventilation rate is not taken into consideration. For these reasons, it was decided to continue the modelling of exposure with a higher tier tool.

THERdbASE, a tool used tor modelling of consumer exposure by Aronson *et al*. (2007) is no longer supported by EPA and is not available for downloading.

ConsExpo is an expert consumer exposure modelling tool that includes features of the higher tier models. It is used as one of the sources of algorithms for the GExFRAME tool. ConsExpo is also one of the models that is used to assess consumer exposure to biocides (Technical Notes for Guidance: Human Exposure to Biocidal Products – Guidance on Exposure Estimation (http://ecb.jrc.it)).

There are a number of facts sheets developed as guidance for use of the tool in specific exposure situations and for specified groups of products. Two of them have been used in the developing of the estimations of exposure of consumers to toilet blocks. The first, a RIVM report 320104002/2006 - General Fact Sheet – presents the general information necessary to calculate exposure of consumers to compounds in consumer products. Limits of conditions set as default in relation to ventilation, room size, body surface and weight are discussed.

Toilet blocks may be included in the Product Category 3, Air care products, as defined in the Guidance Chapter R12. This category has corresponding product types in ConsExpo. For consumers' use of cleaning products the factsheet 'RIVM report 320104003/2006' is relevant. In this factsheet, 36 product categories are described including, among sanitary products, toilet rim cleaners. For all products presented default exposure models and input parameters are suggested.

The input parameters include: frequency and duration of exposure, amount of the chemical used, rate at which it is released into air, room volume, ventilation of the room and inhalation rate. The possibility to describe the release mode is also included, with three models to choose from. One of these is constant rate, applicable to 1,4-dichlorobenzene, where the chemical is released with a constant rate in a specified time. The tool includes a set of default parameters for each product presented in the factsheet. It is possible to modify the parameters to suit specific exposure situations. Therefore, the ConsExpo 4.1 tool was used to develop exposure estimation for consumer use of toilet blocks.

The default parameters developed for the toilet rim cleaners in the factsheet were amended to better reflect the use, on the basis of information found in the guidance and literature, including EU RAR (2004) and RPA (2010).

Consumers' exposure to 1,4-dichlorobenzene

To develop the consumer exposure estimation for 1,4-dichlorobenzene the following parameters were used:

Table B16: Parameters used to develop exposure estimation for consumers

Parameter	Value	Source/Description
Body weight	60 kg	Guidance R.15 – female adult body weight (ECHA, 2010d)
	12.5 kg	ConsExpo - 2.5 year old child, default body weight (no value in R.15) (ECHA, 2010d)
Use frequency	365 d/y	Daily exposure
Exposure route - Inhalation		
Total Exposure duration	24 hours	Guidance R15 for the duration of total daily exposure
Product amount	80 g	Based on RPA (2010)
Weight fraction compound	1	Based on RPA (2010): concentration of the substance in the toilet block may be >95%
Room volume	Bathroom 10 m^3	ConsExpo
Ventilation rate	Scenario 1: 2 air exchanges per hour – bathroom	RIVM report 320104002/2006 (RIVM, 2006)
	Scenario 2: 0,2 air exchanges per hour - bathroom	Guidance R15 (ECHA, 2010d), conservative estimation
Concentration of the substance in other areas of the home	Concentration – 1/3 of the toilet	Based on Djohan (2007), Aronson (2007)
Emission duration	21 days at average 24 hour temperature of 20°C 10 days at average 24 hour temperature of 30°C	Based on RPA (2010)
Mode of release		

Constant rate		The chemical is released with a constant rate in a certain time, and it is simultaneously removed from the air by ventilation of the room. This scenario is recommended for use when details of evaporation are not exactly known, but the time period during which the compound evaporates can be estimated. It is used for calculating the steady air concentration.
Uptake		
Uptake fraction/absorption	100 %	Guidance R.8 (ECHA, 2010a)
Inhalation rate	20 m^3/day	Guidance R.15(ECHA, 2010d) - inhalation rate for adult for a whole day exposure

There are three options for the mode of release. In addition to the selected 'constant rate':

- Instantaneous release – all of the chemical is released into the room at once. It is recommended for a first tier approach, as will usually result in a relatively high exposure.

- Evaporation – describes the release of the compound from the surface of the product by evaporation. This model is to be used when details of evaporation are known.

For the modelling it was assumed that prior to use of the air freshener the concentration of the substance in the toilet / bathroom air was 0. The used 'constant rate' model is the most relevant.

However, the selection of a constant rate may lead to an overestimation of exposure. It is likely that there will be some variations in the air concentrations of the substance, and therefore exposure, as the air concentration may be affected by the surface area, declining with use. Once the products are replaced the cycle starts again. In addition it is also possible, that the block would not be replaced immediately – there may be some hours or even days when there is no air freshener in the facility. RAC took into account these uncertainities in there assessment of the magnitute of the RCR's in the risk characterisation.

It is possible to select a range of values for most of the parameters. However, "In performing the Monte Carlo simulations ConsExpo randomly draws values from all specified distributions without considering possible correlations between parameters. This may lead to unrealistic combinations of parameter values and thus to unrepresentative exposure levels." (ConsExpo 4.0 manual, p. 70)

In the generated exposure estimation, the reasonable worst–case scenario has been considered: a consumer staying at home, and therefore continuously exposed over the whole day. For this reason considering the exposure of consumers using public toilets is not necessary. The dose inhaled at a public facility would be off set against the duration of exposure-free time, spent outside of home and public amenity. Therefore, the cumulative daily exposure would be lower.

Algorithms presented in the workers exposure modelling section are also used for modelling of consumer exposure.

To calculate the air concentration of the substance reflecting combined exposure, including the exposure during time spent in the toilet and in other areas of the house, the following equation has been used:

$$\text{Exposure mg/m}^3 = [(\text{exp}_1 \times t_1) + (\text{exp}_2 \times t_2)] / 24$$

where:

- exp: the air concentration of the substance [mg/m^3]
- t: the duration of exposure; in this case - $t_1 + t_2 = 24$ [h]

The assumptions used were based on the data available from research and on the available guidance. The information presented in the research and other texts is not sufficient to develop an 'average model' for many of the variables listed above. Therefore, it is not possible to develop an estimation of 'average' consumer exposure to the 1,4-dichlorobenzene.

Using the parameters in table B21, the following estimations of exposures have been derived:

Table B17: Estimated exposure levels for consumers

Scenarios	**Variable Parameters**	**Exposure in mg/m^3** in an average 24 hr temp. environment	
		20°C	30°C
Reasonable Worst Case consumer	Based on a consumer spending 1 hour in a bathroom size of 10 m^3 with a ventilation rate of 0.2 air exchanges per hour where one air freshener of 80g size is used and a concentration in the rest of the home is 1/3 the concentration in the toilet for the remaining 23 hours	**2.68**	**5.63**
Changing the reasonable worst case scenario to 2 Air exchanges	Based on a consumer spending 1 hour in a bathroom size of 10 m^3 with a ventilation rate of 2 air exchanges per hour where one air freshener of 80 g size is used and the concentration in the rest of the home is 1/3 the concentration in the toilet for the remaining 23 hours	**1.62**	**3.41**
Realistic case consumer	Based on a consumer spending 1 hour in a bathroom size of 10 m^3 with a ventilation rate of 2 air exchanges per hour where one air freshener of 80 g size is used and the concentration in the rest of the home is 1/20 the concentration in the toilet for the remaining 15 hours	**0.33**	**0.69**

The calculated mean exposure values for consumers are 3.34 mg/m^3 for the reasonable worst case scenario and 0.51 mg/m^3 for the realistic scenario.

The main elements affecting the exposure level are the duration of exposure and the air exchange (ventilation) rate. Higher average ambient temperatures, necessitating more frequent replacement of the toilet blocks/air fresheners (due to higher sublimation rate), also results in increasing of the concentration of the substance in the air.

Consumer exposure to 1,4-dichlorobenzene depends on a large number of factors. They include: the size of the toilet/bathroom, the ventilation in this area, the general layout of the house/apartment and resulting air exchange between toilet/bathroom and the rest of the home and the temperature.

In addition behavioural elements, such as the duration of time a consumer spends in the toilet/bathroom, frequency of replacement air fresheners/toilet blocks as well as the time spent indoors also affect the level of exposure.

Consumers using public toilets

As stated above, the exposure of consumers to the 1,4-dichlorobenzene using public toilets is not significant and will not be greater than the realistic case scenario for consumers.

The resulting calculated exposure levels, averaged over 24 hours, with the assumption that the consumer would not be exposed to the 1,4-dichlorobenzene at home, are:

Table B18: Estimated exposure levels for consumers using public toilets

Activity	**Parameters**	**Exposure averaged over 24 hours in mg/m^3**
Consumer, room volume per block - 5 m^3, reasonable worst case scenario	Duration – 2 min, temperature – 20°C	0.00071
	Duration – 2 min, temperature – 30°C	0.00149
Consumer, room volume per block - 15 m^3, realistic scenario	Duration – 2 min, temperature – 20°C	0.000237
	Duration – 2 min, temperature – 30°C	0.000497

Source: ConsExpo 4.1 - exposure modelling results

The calculated mean exposure values for consumers using public toilets are 0.0011 mg/m^3 for the reasonable worst case scenario and 0.000367 mg/m^3 for the realistic scenario.

Exposure of housekeepers

While housekeepers are in principle workers, conditions of their exposure are more in line with the parameters of the exposure of consumers than workers, as they are likely to stay at home for extended period of time, combining the period of higher exposure in the toilet / bathroom, while cleaning (and using) the amenity, and the lower exposure in the other areas of the house. The exposure of housekeepers is likely to be lower than exposure of consumers spending 16 hours at home, if they do not use 1,4-dichlorobenzene air fresheners at their own homes, especially that it is likely that their work period is less than 16 hours and would also include outside duties. In fact, the exposures are likely to be in the range of calculated exposure of cleaners (worst case scenario). The exposure of housekeepers also needs to be compared against the DNEL developed for workers.

Literature review: Consumers' exposure to 1,4-dichlorobenzene – comparison with data presented in literature

Only one study presenting results of consumers' exposure to 1,4-dichlorobenzene released specifically form toilet block/air fresheners was found.

Djohan *et al*. (2007) presented the results of measurements of levels of 1,4-dichlorobenzene in three private residences. The source of exposure was identified as deodoriser blocks, containing 98,8 % 1,4-dichlorobenzene. The measured concentrations of the substance in the toilets were relatively low – with median values of 0.0467 (range of 0.026.5 – 0.871), 0.0128 (range of 0.005 – 0.0173) and 0.00005 (range of 0.00003 - 0.00015) mg/m^3. The concentrations of the substance in the other areas of the dwelling were also measured. Median concentration values in two houses were 30 and 7 times lower than in the toilet, and in the third house – 3 times higher than in the toilet. It is interesting to note that in the third house the owners did not use any products containing 1,4-dichlorobenzene.

The study presented information from a very small sample, all from the same urban area. Therefore, it cannot be considered as representative for the conditions of exposure in EU.

The information provided in relation to the conditions of measurements does not allow a comparison of the results with the developed exposure estimations either. The information on temperature, sizes of the bathrooms / toilets, ventilation rate, time spent in the bathroom / toilet and at home was not included in the study, therefore it is not possible to compare the measured concentrations with the presented estimated exposure values.

Aronson *et al*. (2007) presented a comparison of human health risk to consumers resulting from the use of toilet rim block products, one of which contains p-dichlorobenzene. He used THERdbASE exposure model and experimentally determined emission data to calculate indoor air concentrations and daily intake values. The emission data were used. The sublimation rates reported were between 1.6 and 4.6 mg/min; the value of 1.6 mg/min was used for further calculations. The exposure concentrations were modelled for the bathroom (9 m^3) as well as for the other areas of the apartment. The calculated concentrations were 1.53 and 0.492 mg/m^3, respectively.

The sublimation rate of the toilet block/air freshener presented in this report is 2.645 mg/min – within the range reported in the Aronson's article, but higher than the value used by Aronson in modelling.

The size of the toilet used for the worst case scenario assessment and the ventilation rate are significantly lower than used by Aronson for the modelling of exposure. The combination of these factors explains higher exposure concentrations presented as the worst case scenario.

Sax *et al*. (2006) presented a study targeting exposure to urban pollutants. This study was conducted among teenagers in New York and Los Angeles. Samples were taken in winter and summer in 1999 (NY) and winter and autumn 2000 (LA). Mothballs and room deodorisers were listed as potential sources of the pollutants. The measured concentrations of 1,4-dichlorobenzene were highest indoor: in NY, the maximum concentration was 1.452 mg/m^3, in LA –0.261 mg/m^3, with total maximum personal concentrations exceeding 0.300 mg/m^3 in both cities. The mean percent contribution to personal cancer risk was calculated for each measured contaminant, for indoor, outdoor and other microenvironments. For 1,4-dichlorobenzene, indoor exposure contribution to cancer risk was 45%, while outdoor exposure accounted for less than 25% of risk.

Logue *et al.* (2011) has presented the results of 77 published studies reporting measurements of chemicals in residents in the United States and countries with similar lifestyles, including Germany, United Kingdom, Finland, France, Belgium. The potential sources of contaminants were not listed. 1,4-dichlorobenzene was identified as a substance with a very large variability of results – the difference between the highest and lowest summary statistic values was a

factor of 500. The presented indoor concentration range was 10^{-6} to 0.0005 mg/m^3. Interestingly, 1,4-dichlorobenzene was also one of the substances identified in new homes, though at significantly lower concentrations.

Chin *et al*. (unpublished, 2012) have presented the results of monitoring performed in a sample of 287 homes in the US in four cities, over two seasons. Before monitoring was undertaken, it was not asked if p-dichlorobenzene (PDCB) was used in the household – the measurements were intended to indicate the use of the product. Indoor samples were taken in the living rooms, and in some locations also in a bedroom. 1439 valid samples were collected. PDCB was detected in 95% of the homes. The concentrations measured were from below detection limit (<0.00002 mg/m^3) to 2.1 mg/m^3. One result was 4.2mg/m^3. The mean value was 0.021 mg/m^3, and median – 0.00036 mg/m^3, indicating a significant number of low concentrations measured. The 95th percentile was 0.046 mg/m^3, 99th – 0.430 mg/m^3 and the maximum value for all houses – 2.1 mg/m^3.

According to the authors, the sharp raise in concentrations can be used to differentiate the residences where PDBC products were actually used.

According to the article, the 90th percentile concentrations can be linked to the emissions generated by the single moth ball - smaller than 10g. The maximum concentrations can be linked to emission rates generated by, for example, 85g toilet rim block (referenced source: tests by the US Consumer Product Safety Commission, 1991, Aronson 2007) – similar to used in the report 80g air freshener block. The maximum concentration measured is also within the range of concentrations estimations presented in this report.

Measured concentrations and odour threshold

For 1,4-dichlorobenzene, to have effective odour masking properties, it has to reach a concentration in the air at least equal to the odour threshold. There are two differend values quoted in available sources.

B.9.3.2.3 Literature review - outdoor exposure to 1,4-dichlorobenzene

Some studies presenting exposure to 1,4-dichlorobenzene include information about the concentration of the substance in the outdoor air. The exposure resulting from spending time outdoors has not been taken into consideration in calculations of exposure levels for workers or consumers.

Below, some of the studies are presented.

In parallel with monitoring indoor exposure to 1,4-dichlorobenzene Djohan *et al*. (2007) has conducted measurements outdoor, at sites located at least 5 m from the houses. The concentrations measured outdoor were significantly lower than indoor. The median for the 1st house was 0.00034 mg/m^3 compared with median of 0.0467 mg/m^3 in the toilet and 1.5 µg/m^3 in other rooms. In the second house the values were, respectively, 0.00013, 0.0128 and 0.0017 mg/m^3. In the third house, where the 1,4-dichlorobenzene was not used, the values were 0.00003, 0.00005 and 0.00015 mg/m^3.

Sax *et al.* (2006) also have included outdoor monitoring in the sampling strategy. In 77 % of samples taken in New York and 60% in Los Angeles the concentrations measured were above the detection limit (compared to 100% and 93% respectively for indoor samples). Mean values were 0.0049 mg/m^3 in New York and 0.00265 mg/m^3 Los Angeles (indoor mean values – 0.075 and 0.0474 mg/m^3, respectively).

Dodson *et al.* (2007) have developed a personal exposure model using volatile organic compound data collected for teachers and office workers. Concentration measurements of residential outdoor microenvironment were included, along with residential indoor and workplace microenvironments. Average concentrations in dining, retail and transport

microelements were also taken into consideration. The models presented were considered to provided an unbiased estimate for a number of compounds, including 1,4-dichlorobenzene. The study concludes that the concentration of most substances measured, including 1,4-dichlorobenzene, were lower than indoor concentrations.

The results measurements of outdoor concentrations of 1,4-dichlorobenzene presented in these studies indicate that even where there is no obvious source of 1,4-dichlorobenzene in the house, the humans may be exposed via outdoor air. However, the concentrations measured outdoor are significantly lower than those measured indoor, as reported in the literature presented. They are also very significantly lower than estimated exposure levels presented in this report. Therefore, the impact of the outdoor exposure will not significantly alter calculated exposure levels and RCRs.

B.9.3.2.2 Workers exposure

The discussion of exposure of professional workers to 1,4-dichlorobenzene in toilet blocks/air fresheners has not been included in the EU RAR (2004).

The 'Guidance on information requirements and chemical safety assessment Chapter R14 - Occupational exposure estimation' (2010) presents the description of methodology for developing exposure estimations for workers. The recommendations of this Guidance have been followed here in estimation of exposure of professional workers involved in hygiene tasks – cleaning, maintenance and toilet attendants.

Measured data

1,4-dichlorobenzene is used as an air freshener/deodorant in public (and workplace) toilet facilities. As a result, toilet attendants and cleaners are exposed to the vapour of 1,4-dichlorobenzene by inhalation. However, there are only two studies conducted in Germany (Globol Werke GmbH, 1986) presenting airborne concentrations of 1,4-dichlorobenzene in public toilets.

As a rule, the measured data is preferred to modelling in the evaluation of exposure. However, monitoring data have to fulfil quality criteria, presented in the Guidance on occupational exposure estimation, Chapter R14, to be used in exposure scenarios. Among other requirements, data have to be representative for the use of the substance presented in the exposure scenario, it has to be reliable (the methodology) and there has to be a sufficient number of samples taken. Unfortunately, the data presented in the study mentioned above do not fulfil these requirements as it is not representative for the EU: it was collected in two facilities in one Member State, and the number of measurements is too small considering the uncertainties related to the number of blocks used, the area/volume of the public toilets facilities, the rate of ventilation and the temperature. The values can only be considered as approximations of toilet facilities in general as the concentration of 1,4-dichlorobenzene vapour depends on several variables, including the number of 1,4-dichlorobenzene blocks used, the internal volume of the facility, the type and rate of ventilation and the temperature.

Therefore, while the number of toilet blocks used per volume of air presented in the study by Globol Werke GmbH (1986) will be used as an indication of cleaning industry work practice, exposure estimations will be developed using modelling tool.

The more detailed analysis of the measured data in relation to results of modelling will be presented in the section 'Literature review' below.

In conclusion it is well justified to use modelling data for exposure assessment as:

- no representative measurements for the EU are available,

- modelled scenarios are certainly conservative assessments due to the chosen parameters.

Use of modelling tools

The Guidance Chapter R14 presents a description of methodology used for developing exposure estimations for workers. The recommendations of this Guidance have been followed in generating estimations of exposure of professional workers involved in hygiene tasks such as cleaning and maintenance of toilets.

The tier 1 exposure modelling tool – **ECETOC TRA** - is not appropriate for generation of estimate of exposures for tasks related to cleaning and maintenance tasks. The exposure estimates are built on the basis of uses (PROCS), as defined in the Guidance Chapter R12. However, in ECETOC TRA, there is no defined use reflecting maintenance or cleaning activities sufficiently well.

More advanced tools such as **Stoffenmanager** and **ART** are also inappropriate due to the limits of applicability of the tools and specificity of the source of the exposure. In the ART tool, modelling of exposure arising from gas/vapour is outside of the applicability of the model. As in Stoffenmanager 4.5, in ART there is no option allowing estimating of exposure arising from vapour generated in the sublimation process from a substance in a solid state.

The substance, 1,4-dichlorobenzene, is in the solid state, but the exposure is to the vapour – the solid form is subject to sublimation. This form of exposure is outside of the capabilities of these tools.

Therefore, **ConsExpo** version 4.1 has been selected to generate the exposure estimations. According to its designer/owner, "*Using the models in ConsExpo and the default values for consumers presented here as background data, it is nonetheless possible to calculate the exposure and uptake of cleaning products by professional users*" (ConsExpo website, Update of Fact Sheets for ConsExpo 4.1).

The tool is described in greater detail in the section on modelling of consumer exposure.

Workers exposure to 1,4-dichlorobenzene

To develop the professional worker's exposure estimation to 1,4-dichlorobenzene the following parameters were provided:

Table B19: Parameters used to develop exposure estimation for professional workers

Parameter	**Value**	**Source/Description**
Product and compound information		
Compound name	1,4-dichlorobenzene	
CAS Number	106-46-7	
Application temperature	20°C, 25 °C and 30 °C	Suggested average ambient temperatures in public toilets
Molecular weight	147	EU RAR (2004)
KOW	log Pow = 3.37-3.39	EU RAR (2004)

Vapour pressure	170 Pa at 20°C 320 Pa at 30°C	RIVM, 2010 SDS – Merck (Merck, 2006) *Note: It was not possible to use value provided in EU RAR (2004) as the values were provided for different temperatures*.
Exposure scenario		
Body weight	70 kg	Guidance R8 (ECHA 2010a)
Use frequency	220 days/year	Guidance R8 (ECHA 2010a)
Exposure route – Inhalation		
Total exposure duration	8 hours/day	Guidance R8 (ECHA 2010a)
Product amount	80g	RPA (2010)
Weight fraction compound	1	RPA (2010): concentration of the substance in the toilet block may be >95%
Room volume	5 m^3 and 15 m^3	Based on Globol Werke GmbH 1986 study
Ventilation rate	3 air exchanges per hour	CIBSE Guidance
Emission duration	21 days – at 20°C 10 days – at 30°C 15.5 days at 25 °C	Based on RPA (2010); (longevity for 25 °C is based on average value, between 20 and 30 °C)
Mode of release		
Constant rate		The chemical is released with a constant rate in a certain time, and it is simultaneously removed from the air by ventilation of the room. This scenario is recommended for use when details of evaporation are not exactly known, but the time period during which the compound evaporates can be estimated. It is used for calculating the steady air concentration.
Uptake		

Uptake fraction / absorption	100%	Based on Guidance R.8 (ECHA 2010a)
Inhalation rate	10 m^3/8h	Based on Guidance R.8 (ECHA 2010a) - inhalation rate for male adults

There are three options for the mode of release. In addition to the selected 'constant rate':

- Instantaneous release – all of the chemical is released into the room at once. It is recommended for a first tier approach, as will usually result in a relatively high exposure.
- Evaporation – describes the release of the compound from the surface of the product by evaporation. This model is to be used when details of evaporation are known.

The air concentration of the compound at time *t* for the constant rate release mode, selected for this product, is calculated as follows:

$$C_{air} = \frac{A_o \times w_f / t_r}{qV} \times (1 - e^{-qt}) \qquad \text{exposure } t < t_r$$

where:

- C_{air} : concentration of compound in the room air [kg/m^3]
- t_r : release time [s]
- A_o : amount of product used [kg]
- wf : weight fraction of the compound in the product [fraction]
- V : room volume [m^3]
- q : ventilation rate of the room (number of air changes per time) [1/s]

The exposure of workers varies depending on a number of parameters. The duration of shift for the toilet attendants may be different, however for regulatory purposes the exposure is calculated for 8 hours. The estimation of the exposure of professional workers was developed for the analysis of the socioeconomic impact of the use of 1,4-dichlorobenzene in toilet blocks and air fresheners and possible effect of its replacement with alternative substances. There is a large number of options of the work patterns of cleaning workers. For this analysis, it has been assumed that a cleaner is exposed to the substance for 2 hours in a working day. The other parameters of exposure are the same.

Ventilation plays a significant role in the air concentration of a sublimating substance and subsequent exposure to it. The range of options for ventilation of public toilets is significant. The ventilation rate selected in the dossier is 2 air exchanges per hour. This input parameter is

based on air exchanges from ConsExpo guidance for ventilation in the home. This is not considered appropriate for a public toilet as by its very nature of use as a public facility would result in greater air exchanges resulting from public traffic, the opening and closing of the doors. There is no harmonised Building Regulations for ventilation rates across the EU and the dossier does not provide the range of the minimum ventilation rates across the 27 member states. The CIBSE guidance B2 on ventilation rates (2009) provides for a minimum design of 3 air exchanges per hour in non-domestic toilets. The engineering toolbox website suggests a minimum of 4 air exchange per hour for public buildings and other guidance recommends between 5 and 7 air exchanges. RAC considered that a ventilation rate of 2 air exchanges per hour in ConsExpo for consumer homes is not appropriate ventilation rate for a public toilet and has used the minimum air exchange value stated in the CIBSE guidance of 3.

Another significant parameter affecting exposure level is the number of blocks used in the facility per unit volume of the facility. There is no guidance or information on general practice in this area. In developing the worst case scenario, the use of one 80g block per 5 m^3 in urinals in the public toilet is assumed. In the literature (Globol Werke GmbH, 1986r it is noted that urinal blocks are of a smaller size (41.3g) than toilet blocks or air fresheners therefore this conservative worst case use of one 80g block per 5m^3 area will lead to an overestimation of exposure. It is possible that the alternative purpose and method of use described – as air freshener – can also be used in public amenities. Therefore, the alternative exposure estimation has been calculated, for use of 1 block for 15 m^3. RAC initially considered a number of exposure scenarios for toilet attendants using two average daily temperatures of 20 and 30 ^oC however for professional users RAC considered than an average temperature over an 8 hour shift of 30 ^oC was not appropriate for a reasonable worst case scenario and agreed that in order to reduce the level of uncertainties in the modelling of exposure scenarios an average temperature over an 8 hours of 25 ^oC was acceptable.

Table B20: Estimated exposure levels for professional exposure – toilet attendants and cleaners

Scenarios	**Exposure Parameters**	**mg/m^3**	
		20^oC	25^oC
Worst case 1 - toilet attendant and cleaner	Based on spending a full 8 hour day inside the public toilet area with a ventilation rate of 3 air exchanges per hour where one 80g product is used for each 5m^3 of public toilet room area	10.1	13.7
Worst case 2 - toilet attendant and cleaner	Based on spending a full 8 hour day inside the public toilet area with a ventilation rate of 3 air exchanges per hour where one 80g product is used for each 15m^3	3.38	4.58
Worst Case 3 - toilet attendant and cleaner	Based on spending 2 hours per day inside the public toilet area and 6 hours in the vestibule area. Ventilation rate of 3 air exchanges per hour where there is high usage of products inside the public toilet (80g of product for every 5m^3 of public toilet area) and the concentration in vestibule area is 1/3 the concentration in public toilet.	4.4	5.95

Realistic Case - toilet attendant and cleaner	Based on spending 2 hours per day inside the public toilet area with a ventilation rate of 3 air exchanges per hour, where one 80g product is used for every 15m^3 of public toilet area and 6 hours per day in the vestibule at a concentration of 1/3 the toilet area.	1.5	1.99

Source: ConsExpo 4.1 - exposure modelling results

The calculated mean exposure values for professionals are 7.02 mg/m^3 for the reasonable worst case scenario and 1.75 mg/m^3 for the realistic scenario.

Literature review: Workers exposure to 1,4-dichlorobenzene – comparison with data presented in the literature

Only one report was identified presenting concentration of 1,4-dichlorobenzene in public toilets relevant to use of the substance as an air freshener/toilet block and the exposure of professional workers (Globol Werke GmbH, 1986). Two studies were presented in this report.

In the first study, the source of 1,4-dichlorobenzene were 41.3g blocks placed in urinals in two public lavatories, (lavatory 1) containing two urinals and (lavatory 2) only one. Three toilet blocks (41.3 g/block) were placed in each urinal. The volumes of the rooms were 39.56 m3 and 15.42 m^3. Approximately, one 41.3 g block was used per 7 m^3 or 5 m^3. Ventilation of the rooms was not controlled and depended on the lavatory users. Temperature varied between 16 and 22°C. The blocks were used up within 67 and 57 days, respectively. In the morning, airborne concentrations of 1,4-dichlorobenzene were 0.3-5.8 mg/m^3 (mean 1.8 mg/m^3) in lavatory 1 and 0.6-13.3 mg/m^3 (mean 3.5 mg/m^3) in lavatory 2; in the afternoon they were 0.6-10.1 mg/m^3 (mean 3.6 mg/m3) and 0.6-7.5 mg/m^3 (mean 3.9 mg/m^3), respectively.The maximum measured levels of the substance were 10.1 and 13.3 mg/m^3 respectively.

In the second study, air freshener tablet was used in a room of approx. 15 m^3. In a lavatory, an air freshening tablet (77.4 g) was attached to the wall, 1.6 m above the urinal. The ventilation was not controlled and depended on the lavatory users. The experimental period was 30 days; during this period, the tablet was not used up completely. The temperature varied between 16 and 22°C. The volume of the room was 15.42 m^3. The air concentrations of the substance were within a range of .1.7-23.0 mg/m^3 in the morning, 1.9 22.4 mg/m^3 in the midday and 1.5-23.8 mg/m^3 in the evening. The respective mean values over the day were: 3.6, 4.2 and 7.5 mg/m^3.

The measured data presented in this study are not representative for the EU. Therefore they are of limited use for legislative purposes.

The exposure of cleaning workers

The estimation of the exposure of cleaning workers was developed to support the analysis of the socioeconomic impact of the use of 1,4-dichlorobenzene in toilet blocks and air fresheners.

There is a large number of options of the work patterns of cleaning workers. For this analysis, it has been assumed that a cleaner is exposed to the substance for 2 hours in a working day.

The other parameters of exposure are the same as presented in Table B19.

Table B21: Estimated exposure levels for professional exposure – cleaners, reasonable worst case and realistic scenario

Activity	Parameters	Exposure averaged over 8 hours in mg/m^3
Cleaner, room volume per block - 5 m^3, worst case scenario	Duration – 2 h, temperature – 20°C	1.54
	Duration – 2 h, temperature – 25°C	2.97
Cleaner, room volume per block - 15 m^3,realistic scenario	Duration – 2 h, temperature – 20°C	0.735
	Duration – 2 h, temperature – 25°C	0.995

Source: ConsExpo 4.1 - exposure modelling results

The calculated mean exposure values for cleaners are 2.25 mg/m^3 for the reasonable worst case scenario and 0.865 mg/m^3 for the realistic scenario.

B.9.3.2.4 Summary of the estimated exposure levels for professional workers and consumers

The estimations of exposure have been derived for workers and consumers, to evaluate the level of their exposure and compare it against the derived DNEL values. The estimations were done for a range of conditions, grouped as 'reasonable worst case' and 'realistic' scenarios.

For consumers, the calculated values over a 24 hour period were between 0.33 and 5.6 mg/m^3.

For professional workers – the calculated levels of exposure over 8 hour period are between 3.4 and 13.7 mg/m^3 for worst case and 1.5 and 1.99 mg/m^3 for realistic case scenarios.

In addition, exposure estimations were performed for two additional exposure patterns – consumers using public toilets and workers, for whom cleaning of toilets is only a fragment of their work. This second group of exposures was calculated to estimate the size of the population at risk and support an assessment of the socioeconomic impact of possible restriction, presented in section F of the report. For these values, RCRs will not be calculated as these exp[osures will not be greater than the exposure calculated for consumers exposure at home, and for toilet attendants.

B.9.3.2.5 Indirect exposure of humans via the environment

The asessment of the exposure to the environment is outside of the scope of this report. Therefore, the exposure of man via environment, resulting from use of 1,4-dichlorobenzene as air freshener / toilet block has not been calculated.

However, the exposure to the environment due to various uses of the substance, has been assessed previously. The exposure of man via the environment has also been assessed.

According to EU RAR (2004), based on the regional concentrations, the total daily intake of 1,4-dichlorobenzene for humans is 3.8 x 10^{-5} mg/kg bw/day. This value can be presented as exposure to 2.66 x 10^{-4} mg/m^3 for professional workers and 1.14 x 10^{-4} mg/m^3 for consumers.

Table B22: Total daily intake due to local environmental exposures

Scenario	Dose total (mg/kg bw/day)
Production	0.0109
Use as an intermediate	0.00052
Formulation of moth repellents and air fresheners	0.0049
Use of moth repellents and air fresheners	0.00179
Use in the production of grinding wheels	0.00172

Source: EU RAR (2004)

The highest indirect exposure is estimated for production processes. Use of moth repellents is banned in EU, therefore it can be expected that this component would be lower.

EU RAR (2004) includes also a breakdown of the human intakes via ingestion and inhalation, from different sources, as presented in Table B23.

Table B23: Different routes of intake from human exposure via the environment due to local exposure due to production of 1,4-dichlorobenzene

Source	Dose in mg/kg bw/day
Daily dose through intake of drinking water	0.00013
Daily dose through intake of fish	0.0046
Daily dose through intake of above ground plants	0.00011
Daily dose through intake of below ground plants	0.00003
Daily dose through intake of meat	< 0.00001
Daily dose through intake of milk	< 0.00001
Daily dose through intake of air	0.00597

Source: EU RAR (2004)

The highest exposures are to be expected from consumption of fish and through inhalation.

The indirect exposure via the environment can be considered negligible, compared to occupational exposure of professional workers in public toilets and consumers at home, presented in sections B.9.3.2.1 and B.9.3.2.2.

The combined exposure for both professional workers and consumers, therefore, depends mainly on the exposure they are subject to, respectively, at work and at home, through the use of air fresheners / toilet blocks.

ATSDR (2006) indicates that while 1,4-dichlorobenzene may be present in a wide variety of foodstuffs, the concentrations remain so low, that the main route of exposure is inhalation.

B.9.3.2.6 Environmental exposure

Not relevant.

B.10 Risk characterisation

As required by REACH, the risk characterisation was performed for the leading health effect.

The leading health effect is a threshold effect with a DNEL calculated; therefore the quantitative risk characterisation is calculated as follows:

Risk Characterisation Ratio (RCR) = Exposure / DNEL

The result supports the conclusion:

- If Exposure < DNEL → Risk is adequately controlled.
- If Exposure > DNEL → Risk is not controlled.

B.10.1 Use of 1,4-Dichlorobenzene in toilet blocks/air fresheners

B.10.1.1 Human health

B.10.1.1.1 Consumers

In evaluating exposure of consumers using toilet block/air fresheners containing 1,4-dichlorobenzene only respiratory exposure is relevant.

For exposure of consumers, the exposure estimations are presented in section B.9.3.2.2 'Consumer exposure' are used and compared with the DNEL derived for consumer exposure - mg/m^3.

Scenario	Conc. mg/m^3	DNEL mg/m^3	RCR
Reasonable Worst Case consumer exposure at 20 °C, 0.2 air exchanges	**2.68**	**0.64**	**4.19**
Reasonable Worst Case consumer exposure at 30 °C, 0.2 air exchanges	**5.63**	**0.64**	**8.8**
Reasonable Worst Case consumer exposure at 20 °C, 2 air exchanges	**1.6**	**0.64**	**2.5**
Reasonable Worst Case consumer exposure at 30 °C 2 air exchanges	**3.4**	**0.64**	**5.3**
Realistic Case consumer exposure at 20 °C	**0.333**	**0.64**	**0.52**
Realistic Case consumer exposure at 30 °C	**0.690**	**0.64**	**1.08**

Even though within European Union there is a significant variation in relation to temperature, the fact that 1,4-dichlorobenzene toilet block/air fresheners are used in indoor toilets reduces this variability. In fact, it seems likely that the average daily temperature in the toilets, especially in private residences, would be close to 25 °C, especially in the southern regions. However, RAC considers temperatures could be between 25 and 30°C where consumers are elderly and infirmed. Therefore, it is likely that the exposure estimations and RCRs calculated for 20 °C underestimate the levels of exposures and risk experienced by consumers.

For exposure of consumers at both 20 °C and 30 °C the calculated RCRs exceed 1 (2.5-8.8) in both worst case scenarios and in the realistic case the RCR exceed 1 at 30°C (1.1). Therefore, the conclusion that the risk of health effects resulting from consumers' exposure to 1,4-dichlorobenzene are not controlled, appears to be justified for reasonable worst case conditions. However, taking account of the hazard profile of the substance (a non genotoxic Category 2 carcinogen) whose carcinogenicity to humans is uncertain and that exposure sufficiently long and high to induce liver cancer would be required, RAC considers that it is questionable whether consumers have developed liver cancer as a result of exposure.

B.10.1.1.2 Workers

In evaluating exposure of professional uses of 1,4-dichlorobenzene in toilet block/air fresheners only respiratory exposure is relevant.

For long-term workers' exposure, the results of the modelling presented in section B.9.3.2.1 'Workers exposure' are used and compared to the DNEL calculated for the workers, presented in section B.5.11.

RAC noted the use of the product in masking odours in public facilities which have high traffic and are infrequently cleaned. RAC considered that a scenario, where a toilet attendant were to work for a full 8 hours per day inside the toilet area rather than in a vestibule with the use of one 80 g block per 5 m^3 would not be an appropriate reasonable worst case scenario. Therefore, risk characterisation ratio is calculated for this scenario, where one 80 g block is used per 15 m^3.

Table B24: RCR for professional workers, 8 hours exposure estimation

Scenario	Conc. mg/m^3	DNEL mg/m^3	RCR
Reasonable Worst case : 8 hours per day in the public toilet area, ventilation rate of 3 air exchanges per hour. 80 g of product is used for each 15 m^3, at 20 °C	**3.38**	**3.62**	**0.94**
Reasonable Worst case: 8 hours per day in the public toilet area, with a ventilation rate of 3 air exchanges per hour. 80 g of product is used for each 15 m^3 of public toilet area, at 25 °C	**4.58**	**3.62**	**1.26**
Reasonable Worst case: 2 hours per day inside the public toilet area and 6 hours in the vestibule area, ventilation rate	**4.4**	**3.62**	**1.21**

of 3 air exchanges per hour 80g of product for every 5m^3 of public toilet area and the concentration in vestibule area is 1/3 the concentration in public toilet, at 20 °C			
Reasonable Worst case 2: 2 hours per day inside the public toilet area and 6 hours in the vestibule area, ventilation rate of 3 air exchanges per hour 80g of product for every 5m^3 of public toilet area and the concentration in vestibule area is 1/3 the concentration in public toilet, at 25 °C	**5.95**	**3.62**	**1.64**
Realistic case toilet attendant 2 hours per day in the public toilet with a ventilation rate of 3 air exchanges per hour one 80g product is used for each 15m3 of public toilet room area 6 hours vestibule 1/3 conc in bathroom at 20 °C	**1.5**	**3.62**	**0.41**
Realistic case toilet attendant 2 hours per day in the public toilet with a ventilation rate of 3 air exchanges per hour one 80g product is used for each 15m^3 of public toilet room area 6 hours vestibule 1/3 conc in bathroom at 25 °C	**1.99**	**3.62**	**0.55**

In the estimated scenarios prepared for workers the RCR are greater than 1 for most of the worst case scenarios (1.21-1.64). RAC also considered the uncertainties around the fact that work breaks were not taken into account in the scenario and looked at RCR's calculated on a 7 hour period but concluded that the RCR's were still above 1 (1.1-1.5). Taking into account the hazard profile of the substance, a non genotoxic Category 2 carcinogen, whose carcinogenicity to humans is uncertain and that exposure sufficiently long and high to induce liver cancer would be required. RAC considered that it is questionable whether professional toilet attendants and cleaners have developed liver cancer as a result of exposure. Nevertheless, The RCR's greater than 1 indicate that the exposure needs to be reduced for workers working in high temperature, poorly ventilated environments (<3 air exchanges per hour).

Evaluation of workers and consumers exposure to 1,4-dichlorobenzene – comparison with reported data

The risks of inhalatory exposure to 1,4-dichlorobenzene has been addressed in some recent publications. Apart from the study by Djohan *et al*. (2007) these studies present exposure to ambient 1,4-dichlorobenzene (sources not specified) and compare the exposure to cancer risk estimates established by linear extrapolation (US EPA 2006). More details on the exposure measured in these studies is given in section B.9.3.2.2.

The risk characterisations presented by Djohan *et al*. (2007), based on the exposures measurements presented in the section B.9.3.2.2, lead to the conclusion that the exposure was not significant for the public health – the risk to consumers was low. However, according to authors, for those suffering from some pre-existing conditions, such as blood, kidney, central nervous system, liver or metabolic disorders, the probability of adverse effects was assessed as moderate to high.

Chin *et al*. (unpublished, 2012) presents measurements taken in living rooms and in bedrooms, never in toilets / bathrooms. If we accept the assumption that the air fresheners and / or toilet blocks were used in the households were the highest concentration were measured - the maximum air concentration (2.1mg/m^3) and the 99th percentile (DT – 0.86mg/m^3) - then the concentrations found are comparable to the results of the modelling for consumer exposure.

In the modelling, the concentration of the substance in the other than toilet or bathroom areas of the house is considered to be 1/3 or 1/20 of the concentration found in the toilet or bathroom.

Therefore, if the the maximum concentration was to be accepted as the concentration in other than bathroom area of the house (on the basis of identified in the article location where the measurement was taken), the averaged exposure over the 24 hours can be calculated (for duration of exposure 30 min in the bathroom and 23.5h in the other areas) as 2.19 mg/m^3 where the concentration of the substance in the living areas is 3 times lower than in the bathroom (worst case parameter), and 2.93 mg/m^3 if the respective concentration is 20 times lower (realistic scenario parameter).

B.10.1.1.3 Indirect exposure of humans via the environment

The level of the indirect exposure of humans via the environment to 1,4-dichlorobenzene, presented in EU RAR (2004), is very low - 2.66 x 10^{-4} mg / m^3 for professional workers and 1.14 x 10^{-4} mg / m^3 for consumers (3.8 x 10^{-5} mg/kg bw/day). It is well below the calculated values of DNEL for both professional workers (3.627 mg / m^3) and consumers (0.64 mg / m^3).

This result is in line with the EU RAR assessment, resulting in conclusion ii: 'There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.'

B.10.1.1.4 Conclusion

The risk characterisation shows that RCRs for consumers are above 1 for all worst case scenarios at 20 and 30 °C and marginally above 1 for a realistic case where the average temperature over a 24 hour period is 30°C. Consequently, the exposure to 1,4-dichlorobenzene from using toilet blocks and air fresheners is not adequately controlled. For professionals the risk characterisation shows that RCRs are above 1, (1.21-1.64) for all worst case scenarios at 20 and 25 °C indicating that the exposure needs to be reduced for professional users.

B.11 Summary on hazard and risk

Summary of identified hazards

The Annex XV proposal focuses on the human health hazards of 1,4-dichlorobenzene, since the adverse effect from the uses of concern, which is the object of the proposal, mainly affect human health. Special attention has been given to endpoints which are directly related to the use of air fresheners and toilet blocks, i.e. effects by inhalation. The hazard assessment carried out by ECHA builds on the work carried out in the context of the EU Risk Assessment Report (EU RAR, 2004), taking also into account more recent work.

The following is an overview of the relevant hazard properties of 1,4-dichlorobenzene listing all endpoints and conclusions drawn. The literature sources used to draw main conclusions are mentioned below. More literature sources can be found in the core part of the report.

- The **acute toxicity** of 1,4-dichlorobenzene is low regardless of the route of exposure (EU RAR, 2004).

- 1,4-dichlorobenzene has slight **irritation** properties for skin, eyes and the respiratory system (EU RAR, 2004).

- 1,4-dichlorobenzene is a weak **sensitiser** (EU RAR, 2004).

- Regarding the **repeated dose toxicity**, 1,4-dichlorobenzene is associated with liver toxicity in dogs (oral NOAEL of 10 mg/kg/day, ATSDR, 2006). There is evidence of

kidney toxicity in rats, leading to a NOAEC of 75 ppm for inhalation exposure. It can also cause slight local lesions of the nasal (olfactory and respiratory) epithelium in rats following inhalation exposure which allows establishing a NOAEC of 75 ppm (Aiso *et al.*, 2006). Liver and kidney toxicity were also noted in mice at the highest dose tested following oral exposure (NOAEL of 300 mg/kg/day for both endpoints).

- 1,4-dichlorobenzene is considered a **non-genotoxic substance** (EU RAR, 2004). This conclusion is important as it supports the finding that 1,4-dichlorobenzene is a threshold carcinogen.

- The **carcinogenic** effects of the substance have been demonstrated as liver carcinogenicity in mice after oral exposure (NOAEL of 300 mg/kg/day), developing of kidney adenocarcinoma in rats (which are not of relevance to humans) after oral exposure (LOAEL of 150 mg/kg/day) and liver carcinogenicity in mice after inhalation exposure (NOAEC of 75 ppm) (EU RAR, 2004). A threshold mechanism for carcinogenicity was considered as the most appropriate in the EU RAR. Recent reviews (ATSDR, 2006; Butterworth *et al.*, 2007) provide further support on the non-genotoxic threshold approach. The carcinogenic effects are considered to be the leading health effect for risk assessment.

- Recent literature contains information on the possible **endocrine** activity of the substance (inhalation NOAEL of 250 ppm in mice and rats, Takahashi *et al.*, 2007).

- Data from a two-generation oral reproductive toxicity study indicates toxicity in offspring at the highest dose tested. Toxicity is also noted at the mid dose in one generation of pups only (NOAEL of 30/mg/kg/day). Data from a two-generation study in rats via inhalation route and four developmental toxicity studies on rats and rabbits via oral and inhalation exposure did not reveal any evidence of reproductive or teratogenic effects in the absence of parental toxicity.

- A reported correlation between blood concentrations of 1,4-dichlorobenzene and **decrease in lung function** was considered (Elliot *et al.*, 2006), however, a causal link between decreased lung function and 1,4-dichlorobenzene exposure cannot be established based on the available data.

Summary of DNEL derivation

DNELs were derived and used for the risk characterisation, as required by the relevant parts of Annex I of the REACH Regulation and further explained in the Guidance on Information Requirements and Chemical Safety Assessment (ECHA, 2010a). The same experimental studies as used for establishing margins of safety in the EU RAR (2004) were used.

DNELs for different endpoints were derived for consumers, ranging from 0.36 to 0.64 mg/m^3 and for workers, ranging from 2 to 3.62 mg/m^3 (Table B25). For use in the risk characterization, DNELs of 0.64 mg/m^3 for consumers and 3.62 mg/m^3 for workers based on hepatic tumours in mice were selected as the most appropriate (despite the lower values for hepatic effects noted in the sub-chronic feeding study in dogs), as carcinogenicity is considered as an endpoint of higher relevance for human health assessment and the route of exposure of concern is inhalation.

Table B25: Derived DNELs for consumers and workers

DNEL	**DNELs for consumers**		**DNELs for workers**	
(endpoint)	**Resulting**	**Resulting**	**Resulting**	**Resulting**

	DNEL **mg/m³**	**DNEL** **mg/kg/day**	**DNEL** **mg/m³**	**DNEL** **mg/kg/day**
Oral, Systemic (hepatotoxicity) Dog	0.36	0.12	2	0.29
Long-term Inhalation, Systemic (carcinogenicity)	**0.64**	0.21	**3.62**	0.51

Source: Table B13 and Table B14

Summary of the exposure assessment

The exposure of both professionals and consumers from the uses of 1,4-dichlorobenzene in air fresheners and toilet blocks was estimated. The available measured data were not considered to be representative for the EU and conditions of use. Therefore, exposures were estimated by modelling using the ConsExpo 4.1 tool, which was considered to be the most appropriate tool for this purpose. The available measured data were, however, used to derive some of the modelling parameters. Exposure level estimates are presented for the following scenarios:

Consumers: estimates were calculated using different temperatures, ventilation rates, exposure durations and assumptions on air concentrations of 1,4-dichlorobenzene in the rest of the house in relation to the toilet (since exposure to the substance takes place also in other parts of the house from a source located in the toilet).

In addition, the exposure of consumers using a public toilet where 1,4-dichlorobenzene is used, was also estimated.

Professional workers: toilet attendants and toilet cleaners were chosen for the worst case scenario. Estimates were calculated for two different temperatures and different product usage per unit volume of air space.

Exposures were also estimated for cleaners in order to evaluate the size of the exposed population for the analysis of the socio-economic impacts.

For both professional workers and consumers exposure estimates, conservative values were chosen for "reasonable worst case scenarios", while "realistic" scenarios were built on less conservative estimates that are expected to represent average real life conditions. The exposure estimates obtained range from 1.5 to 5.95 mg/m^3 for workers and from 0.33 to 5.63 mg/m^3 for consumers.

Summary of the risk characterisation

The estimated exposure levels are compared against DNELs to calculate the risk characterisation ratios. In all but one of the realistic case consumer scenarios the risk characterisation ratios are above 1, ranging between 2.5 and 8.8 for consumers. In conclusion, the exposure from the uses of 1,4-dichlorobenzene in air fresheners and toilet blocks are not adequately controlled for consumers.

In the case of professionals the risk characterisation ratios are above 1 for most of the reasonable worst case scenarios (three out of four), ranging from 1.2 to 1.64.

C. Available information on alternatives

C.1 Identification of potential alternative products and techniques

There are several air fresheners and toilet blocks not containing 1, 4 dichlorobenzene available on the market. Most of them are substances or compounds used as deodorisers. Furthermore, (additional) cleaning, better drainage and better ventilation are alternative techniques to control odour levels. In this section, different air fresheners and toilet blocks products and techniques for air fresheners and toilet blocks are described. The use of 1,4-dichlorobenzene in air fresheners and toilet blocks is described in section B.2.2.

Alternative products

Air fresheners

The use of air fresheners has increased in the society in the last decades (RPA, 2010).

The alternative air fresheners can be categorised into the following groups (RIVM 2006):

Room perfume in holders

This is a large group of scented products, comprised of perfumes enclosed in a container, such as a glass disc or plastic flask, from which the scent is released slowly over time. The perfume can be in the form of a water-based or solvent-based liquid, a gel, or a solid soap-like substance.

Fragrant wax candles

Candles made of a fragrant wax, or only wax. The scent is released by burning the candle or heating the wax.

Ethereal oils

Fragrant oils that generally need heating before the scent is released fully. Candles or other warm objects such as lamps can heat the oils.

Fragrant sachets

Bags of textile such as lace or cotton filled with synthetic or natural scented products, for example lavender bags. The sachets can be placed in a room, but usually are placed between clothes and in linen cupboards.

Sprays

Many scented products are available in the form of aerosol spray cans or bottles. The product is often dissolved in volatile solvents, although some sprays may be water-based.

Potpourri

Mix of (dried) flowers, fruits or other material, with natural scent or impregnated with perfume. The mix is placed in an open container.

Incense

Cones or sticks of resin-like material that release the scent when burned.

Vacuum perfumes

A ball of material to be placed in the vacuum cleaner. The scent is released when the appliance is switched on.

Toilet bowl blocks

The following alternative toilet bowl blocks are identified by RPA (2010).

In-cistern blocks

Blocks placed inside the water tank slowly release the ingredients every time the toilet bowl is flushed.

In-bowl blocks

Tablets that are deposited in the standing water in the bowl where they offer cleaning rather than deodorising action.

Solid rim blocks

Solid cylinders or cuboids (with surfactants), which release small quantities of chemicals with every flush.

Liquid toilet rim blocks

More modern surfactant-based liquids contained in plastic containers, which are released in the toilet bowl with every flush. Some of these products may have two separate compartments, one containing a cleaning liquid with the other containing a deodoriser.

Solid rim block with deodorising gel

Recently developed multi-compartment rim blocks which contain both cleaning (solid) and deodorising (gel) components.

Toilet discs

Also recently developed, these are gel discs which are directly attached to the inside surface of the toilet bowl (i.e. they do not come inside a container) and gradually release cleaning and deodorising ingredients every time the toilet bowl is flushed. They are promoted as method avoiding the risk of the development of deposits of dirt or germs on and around the cage that toilet rim blocks usually come with.

Urinal blocks

The urinal blocks are deposited in the urinal above the urinal drain. The following types of alternative urinal blocks have been identified from the literature.

Surfactant based urinal blocks

Traditionally the main alternatives have been surfactant based blocks, which aim at cleaning the bowl and drain pipes to prevent the accumulation of deposits (RPA, 2010).

Urinal blocks containing bacteria cultures

Modern urinal blocks containing bacteria cultures, which actively prevent the micro-organisms to develop unpleasant odours (RPA, 2010).

Camphor urinal block

Camphor crystals, balls and tablets may contain more than 96% camphor (Fisher, 2011) and are available on the market to be used in urinals (Suomen Sanimex, 2011) as deodourisers.

Alternative techniques

As 1,4-dichlorobenzene air fresheners and toilet blocks are used to mask unpleasant odours, any measure to prevent the odours from developing and being released, or to remove the existing odour can be seen as an alternative technique. More frequent and more thorough *cleaning* can prevent the unpleasant odours to be developed when the source of the odour is from the toilet/urinal or from spillages e.g. spatters of urine or deposits on the walls and floors. Furthermore, *better ventilation* can remove the unpleasant odours from toilets. *Different types of urinals* may also be used to prevent mal-odours being formed and released from toilet bowls and urinals. These types of urinals can use different flushing patterns (e.g. manual, timed or automatic). Another possibility is the use of waterless urinals, a recently developed technique which do not operate with flushing (RPA 2010). A more detailed description of functioning of different urinal types, including waterless urinals, can be found in RPA (2010). However, installing these types of urinals/toilets will not address odours from spillages.

Substances used in alternative air fresheners and toilet blocks

Most air fresheners and toilet blocks not containing 1,-4dichlorobenzene contain more than one active substance. In fact, many contain more than 70 different components (RPA, 2010). The components reported in RPA (2010) are listed in the Annex 1, Tables A5.4 to A5.7. The risks related to the use of these substances are discussed in section C.2.2 (Human health and environmental risks related to alternatives)[12].

To better understand the risks related to these products containing several components, it is essential to know the amounts of each component in the product. The typical amounts of different components in air care products are presented in Table C26. The categorisation for different types of alternatives used by AISE (International Association for soaps, detergents and maintanence products) in the table does not fully follow the categorisation presented above.

Table C26: Basis of formulations for different air care products (%)

	Air fresheners			**Toilet bowl cleaners**			
Products / **Substance**	**Liquid gel**	**Aerosol**	**Electronic**	**Solid**	**Liquid**	**Thick bleach**	**Acidic**

[12] The isomer 1,2-dichlorobenzene (ortho-dichlorobenzne) is reported to be used in deodorisers (Merck Index, 2006). However, the physico-chemical and odor properties of 1,2-dichlorobenzene are different from the properties of 1,4-dichlorobenzene, for example it is a liquid whereas 1,4-dichlorobenzene is a solid in ambient conditions (Ullmann, 2006). There is no information if this substance is used in air fresheners and toilet blocks that could be used as alternatives to 1,4-dichlorobenzene.

family (%)							
Colour agent	< 1	0	<1	<1	<1	<1	<1
Fragrance	1-10	0.5-5	25-100	0-5	0-5	<1	<1
Preservatives	<1	<1	<1	<0.5	<0.5		
Solvents (e.g. alcohols or water or aliphatic hydro-carbon)	>50	>50	<75	-			
Surfactants and/or emulsifiers	5-50	<5	0	Anionic 15-30 Non-ionic 15-30	Anionic 5-20 Non-ionic 5-20	Anionic 1-2 Non-ionic 1-2 Soaps <1	Anionic 1-10 Non-ionic 1-10
Additives				Citric acid 5-15	Citric acid 5-15		Citric acid 10-15 Hydro-chloric acid 10-15 Sulfamic acid 10-15
Builders				Citrates 0-5	Citrates 0-5		
Bulking agents				Sodium sulphate 0-60	-		
Sequestrants				Phospho nates 0-5	Phospho nates 0-5		

Water				Balance to 100	Balance to 100	Balance to 100	Balance to 100
Oxidizing agents						Chlorine-based bleaching agents 1-5	
Viscosity Controlling agents						<1	

Source: AISE, 2011

The deodorising function of products not containing 1,4-dichlorobenzene is provided by the fragrances which if released continuously until used up may be considered to be direct alternatives for 1,4-dichlorobenzene. The non-fragrance substances often form a significant proportion of these products. They are used e.g. as surfactants, preservatives, colorants, builders, complexing/descaling agents, solvents, thickeners, anti-caking agents and stabilisers.

Conclusions

There are different kinds of air fresheners and toilet blocks not containing 1,4-dichlorobenzene available in the market. Furthermore, any measure to prevent the mal-odours to be developed or to remove the existing odour can also be achieved through alternative techniques.

C.2 Assessment of alternatives

C.2.1 Availability of alternatives

Air fresheners and toilet block products not containing 1, 4 dichlorobenzene started to develop in the 1990s. The fragrances are widely used in the cosmetics and detergents industry. The non-fragrance constituents of the alternative toilet blocks are also commonly used chemicals, both in the cleaning products and cosmetics industry, as well as elsewhere. These products are currently available on the market in a variety of formulas (RPA, 2010).

The use of 1,4-dichlorobenzene-based air fresheners and toilet blocks is decreasing, and other air fresheners and toilet block products already dominate the market.

C.2.2 Human health risks related to alternative products

The constituents in other products can be categorised as fragrances and non- fragrances. Since 1,4-dichlorobenzene is used to mask unpleasant odours, the fragrances have (more or less) a similar function as that of 1,4-dichlorobenzene. The non-fragrance substances can be grouped according to their function as fillers, anti-caking agents, stabilisers or preservatives. They constitute a significant proportion of the products not containing 1, 4 dichlorobenzene (Table C26). On the contrary, camphor may constitute the main part of the block in a similar manner to 1,4-dichlorobenzene. As urinal blocks made of camphor may be seen as the most similar alternative to the 1,4-dichlorobenzene blocks, the hazard profile of camphor is described in C.2.2.3.

C.2.2.1 Fragrances

The physicochemical and hazardous properties of fragrances are in general poorly characterised. A thorough review of all potential fragrance substances is not feasible as their

number is very large. However, risk assessments have been made of several fragrances due to their use in food. RPA (2010) also reviewed the available information for the six fragrances that are most frequently used in alternative toilet block and air freshener products. Based mainly on these two sources of information the following fragrances are addressed in this report:

- α-hexyl cinnamaldehyde
- citronellol
- geraniol
- citral
- d-limonene
- pin-2(10)-ene (beta-pinene)

The physiochemical and hazard properties of these fragrances are compared with the properties of 1,4-dichlorobenzene in Annex 1 Table A.5.4 (from RPA, 2010).

Irritation and sensitisation

RPA (2010) concluded that, in similarity with 1,4-dichlorobenzene, all of the six fragrances considered have irritating properties. Furthermore, all of these substances (except pin-2(10)-ene (beta-pinene)) have been documented to be able to cause sensitisation by skin contact. d-Limonene has also been identified as a respiratory allergen (HSDB, 2011).

Repeat dose toxicity

Of the fragrances assessed in this report, only citronellol and citral have been given a specified Acceptable Daily Intake (ADI) by the Joint FAO/WHO Expert Committee on Food Additives (Table C27). This ADI of 0.5 mg/kg body weight is based on a 2-year NTP feeding study in rats and mice with a NOEL of 60 mg/kg/day (JECFA, 2003).

Available repeat dose toxicity studies for the six fragrances were compiled by RPA (2010) (see Annex 1 Tables A.5.4 to A.5.7). The data-base was very limited. The lowest effect level identified for these substances was for α-hexyl cinnamaldehyde in a 90 day rat dermal study, where changes in the gastro-intestinal tract were noted at 125 mg/kg, and in addition, changes in the liver, kidney, blood and bone marrow at 250 mg/kg or above[13]. No NOAEL was determined.

Table C27: Evaluations of flavouring substances (fragrances)

Substance name	Year of assessment	Daily intake in humans	Details on the assessment	Conclusions based on current intake
α-hexyl cinnamaldehyde	2000	1 µg/kg bw/day (Europe)		No safety concern.

[13] This could be compared with the LOAEL of 300 mg/kg/day for nephrotoxicity of 1,4-dichlorobenzene in a 13 week study in rat (NTP, 1987, as cited in the EU RAR).

		0.2 µg/kg bw/day (USA)		
Citronellol (3,7-dimethyl-6-octen-1-ol)	2004	6.2 µg/kg bw/day (Europe) 13 µg/kg bw/day (USA)		A group ADI of 0-0.5 mg/kg bw, expresses as citral, was established for citral, citronellol, geranyl acetate, linalool, and linalyl acetate by JECFA. Use of citronellol and citral as flavouring agents is subsumed in the group ADI.
Citral	2004	114 µg/kg bw/day (Europe) 117 µg/kg bw/day (USA)	The NOEL of 60 mg/kg bw/day (National Toxicology Program, 2003) for citral is >500 times more than the estimated daily intakes in Europe and the USA when used as a flavouring agent.	
Geraniol	2004	11 µg/kg bw/day (Europe) 5.2 µg/kg bw/day (USA)		No safety concern.
d-Limonene	2005	660 µg/kg bw/day (Europe) 210 µg/kg bw/day (USA)		Given that there is an ADI "not specified" for d-limonene, the daily intakes in Europe and USA were considered not to pose a safety concern.
Pin-2(10)-ene	2005	26 µg/kg bw/day (Europe) 13 µg/kg bw/day (USA)		No safety concern.

Source: JECFA, 2000, 2004, 2005

Assessment of d-limonene in SCHER evaluation of the BEUC report on air fresheners

The Scientific Committee on Health and Environmental Risks (SCHER) published a review of the Bureau Européen des Unions de Consommateurs (BEUC) (2005) report: "Emission of

chemicals by air fresheners: Tests on 74 consumer products sold in Europe" (SCHER, 2006). Of the six fragrances addressed here, only d-limonene was discussed in detail in the BEUC report. A summary of SCHER's assessment is given below, due to the widespread use of d-limonene as an alternative to air freshener and toilet block products containing 1,4-dichlorobenzene.

SCHER concluded that around 65 % of inhaled d-limonene is absorbed and readily metabolized. Its major health effects are associated with irritant (skin and eye) and sensitizing properties, the latter being strongly dependent on the oxidation status of the molecule. In this respect, it has been proposed that the reaction products between d-limonene and ozone or other free radicals present in the atmosphere are actually responsible for irritation. A NOAEC of 225 mg/m^3 and a LOAEC of 450 mg/m^3 for short term d-limonene inhalation have been identified on the basis of decreased lung function (vital capacity) (Falk Filipsson *et al.*, 1993 as cited by SCHER 2006). Neither limonene nor the corresponding epoxide are genotoxic.

No information is available on long term effects of chronic respiratory exposure to d-limonene neither in animals nor in humans. Oral administration of d-limonene causes renal tumours in male rats but the mechanism is not considered relevant to humans (involvement of α2-u-globulin in male rats). IARC has concluded that there is no adequate evidence for limonene's carcinogenicity in human (IARC, 1999a).

A guidance value for inhalation of d-limonene has not yet been established, since only oral uptake has been considered by WHO. An exposure limit value of 450 µg/m^3 has been proposed in the Flavouring Index (INDEX) of Joint FAO/WHO Expert Committee on Food Additives (JECFA) report for long-term exposure, calculated by applying 1000 as the safety factor to the above mentioned LOAEC (INDEX 2005). According to SCHER, application of 100 on the NOAEC would have resulted in an exposure limit of 2250 µg/m^3, and as the values are based on effects in humans, even lower uncertainty factors may be appropriate.

Classification

Of the six fragrances considered, only limonene and citral are classified and included in Annex VI to Regulation 1272/2008 on Classification, Labelling and Packaging of substances and mixtures. Limonene (index number 601-029-00-7) has the following classification: Flam. Liq. 3, H226; Skin Irrit. 2, H 315; Skin Sens. 1, H 317; Aquatic Acute 1, H 400; Aquatic Chronic 1, H 410. Citral, (index number 601-019-00-3) is classified as Skin Irrit. 2, H 315 and Skin Sens. 1, H 317.

Human exposure

Fragrances are used in concentrations less than 5 % in almost all of the alternative products, while 1,4-dichlorobenzene constitutes the main part of the block. The vapour pressure for most, but not all, fragrances is also considerably lower than that of 1,4-dichlorobenzene. Thus, the potential for human exposure to alternative fragrances would usually be expected to be lower for fragrances than for 1,4-dichlorobenzene.

To verify this conclusion, exposure to the two fragrances addressed in this section with the highest vapour pressure, d-limonene and beta-pinene, was calculated for a child (see Annex 6) living in a household using fragrance-containing gel-based toilet discs. As inhalation exposure to the same concentrations results in a higher body burden in children than in adults the child was used as a model to ensure protection of the whole population. Applying the same ConExpo model as for 1,4-dichlorobenzene the resulting exposure for d-limonene and beta-pinene was 0.093 mg/m^3 (93 µg/m^3), expressed as a 24 h average concentration, or a body burden of 0.052 mg/kg/day (52 µg/kg/day[14]). Both fragrances resulted in the same exposure due to their identical molecule weight. These values were calculated for exposure at 25 ^{o}C. Using the

[14] The corresponding body burden in an 60 kg adult was 31 µg/kg/day (Annex 3).

same assumptions for 1,4-dichlorobenzene resulted in an exposure of 10.72 mg/m^3, or 6.00 mg/kg/day at 20 °C and 22.5 mg/m^3 , or 12.6 mg/kg/day at 30 °C for a child.

Comparison of fragrance levels to the INDEX value

As mentioned in the SCHER evaluation above, an exposure limit value for d-limonene of 450 µg/m^3 has been proposed in the INDEX report for long-term exposure (INDEX 2005). The calculated exposure concentration of d-limonene from a fragrance-containing, gel-based toilet disc of 93 µg/m^3 is considerably lower than that value.

Comparison of inhalation exposures to fragrances and food intakes of flavourings

The intake of d-limonene in Europeans from food has been estimated at 660 µg/kg/day (JECFA 2006). This figure might under-estimate the intake in children as a 2.5 year old child with a body weight of 12.5 kg (20 % of that of an adult) consumes approximately 50 % of the food of an adult. The exposure calculated for d-limonene from a gel-based toilet disc (52 µg/kg/day) is considerably lower compared to the food intake of limonene. JECFA (2006) concluded that the intake of d-limonene of 660 µg/kg/day from food was not considered to pose any safety concerns.

The daily intake of alfa-pinene in European adults from food was estimated to be approximately 36 µg/kg/day (JECFA 2006). No intake was given for beta-pinene, but the use of the two substances seem to be similar in food. The inhalation exposure of beta-pinene from a gel-based toilet disc (52 µg/kg/day for a child) is similar to the exposure to the pinene in food. Based on the discussion of safety concerns for d-limonene JECFA concluded that the intake from food of the structurally similar pinenes (alfa and beta) was not considered to pose any safety concerns.

Comparison of 1,4-dichlorobenzene and fragrance/surfactant-based alternatives

Aronson *et al*. (2007) made a comparative analysis of the health risks of toilet rim blocks with 1,4-dichlorobenzene and fragrance/surfactant-based alternatives.

For the purposes of risk comparison the author assumed that the compounds of interest in the products were the volatile substances (1,4-dichlorobenzene and the fragrance components found in the alternative rimblocks). Cancer and non-cancer health risks of the substances were considered and their dose-response relationships were reviewed. A comparison of the exposure-based estimates of health risks was presented.

The estimated exposures to the fragrances and surfactants in the toilet rimblocks were of about one order of magnitude lower than the estimated exposure concentrations of 1,4-dichlorobenzene. The fragrance content in the products were much lower compared to 1,4-dichlorobenzene content in the toilet rimblocks. Aronson concluded that the fragrances would have to have a higher level of toxicity than 1,4-dichlorobenzene in order to present a similar risk.

Aronson and co-workers concluded, based on the low concentrations of fragrances in the alternative products, their safe, historical use and their natural occurrence in food, that these substances would be less hazardous to human health than 1,4-dichlorobenzene.

Conclusions for human health risks related to fragrances

The available toxicological information for fragrances is very limited for most of the substances. Based on JEFCA's evaluation of fragrances for their use as flavourings in foods it can be concluded that exposure to fragrances from gel-based air fresheners may, in specific cases, be of the same order of magnitude as that from food intake or even higher. However, the exposure to most of the fragrances can be expected to be low due to their low concentration in the alternative products.

The exposure to the commonly used fragrance d-limonene is expected to be considerably lower than the proposed INDEX (2005) long-term inhalation value. The food intake of the six fragrances discussed in this section is not considered to be a safety concern, and it is unlikely that the additional exposure to these substances from air fresheners would change this conclusion.

One potential concern with fragrances in air fresheners may be their irritating and possibly sensitising properties. However, as also 1,4-dichlorobenzene is an irritant and a weak sensitiser, this seems to be a common concern for many of the deodorising substances.

In conclusion the use of fragrances in alternative products is considered safer from a health viewpoint than the use of 1,4-dichlorobenzene.

C.2.2.2 Non-fragrance substances

RPA (2010) reviewed the human health hazards of non-fragrance constituents of toilet block/air freshener products not containing 1, 4 dichlorobenzene. The section included below builds on information compiled by RPA. The hazard properties of the most commonly used non-fragrance constituents are presented in Tables A5.5, A5.6 and A5.7 in Annex 1.

Surfactants

RPA (2010) considered three of the most common used surfactants in the products not containing 1, 4 dichlorobenzene: sodium dodecylbenzene sulphonate, alcohol ethoxylates C_{12-18} (AE) and sodium lauryl ether sulphate. The substances have been subject to Human and Environment Risk Assessments on ingredients of household cleaning products (HERA projects). The main concern identified is their potential for skin irritation.

For sodium dodecylbenzene sulphonate consumer exposure has been estimated at 4.0 µg/kg/day from direct and indirect skin contacts, inhalation and via oral route through drinking water. A systemic NOAEL of 680 mg/kg/day and a margin of exposure (MOE) of at least 170,000 have been estimated for sodium dodecylbenzene sulphonate (read-across with linear alkylbenzene sulphonates (LAS)).

For alcohol ethoxysulphates (AEs) the aggregated consumer exposure has been estimated at 6.48 µg/kg/day. The lowest systemic NOAEL for AEs for repeat dose toxicity was set at 50 mg/kg/day based on hepatic changes. The MOE of 7716 has been estimated for this substance.

For sodium lauryl ether sulphate the estimated consumer exposure has been estimated at 29 µg/kg/day. Compared with the lowest systemic NOAEL for repeat dose toxicity was set at 75 mg/kg/day this resulted in a MOE of 2586.

The surfactants are typically present in the products in concentrations below 10% (Table C26). The three surfactants considered by RPA are used in concentrations of 1-10 % for sodium lauryl ether sulphate, less than 5 % for C_{12-18} ethoxylated alcohols, but from 25 to 50 % for sodium dodecylbenzene sulphonate. The health concerns related to the use of these substances in products seem very limited.

Preservatives

Two preservatives were covered in the RPA review.

Benzyl salicylate (CAS 118-58-1) is widely used as a perfume and preservative in soaps and as a flavouring agent in foodstuffs. The estimated adult exposure from its use in soaps is 0.45 µg/kg/day (Danish Environmental Protection Agency, 2006 as cited by RPA 2010). The available toxicological data is limited but indicate low acute toxicity, lack of genotoxicity and suggest a weak sensitising potential.

1,2-benzotiazoline-3(2H)-one (CAS 2634-33-5), the second preservative reviewed by RPA, is classified as a skin sensitiser for concentrations ≥ 0,05 % (R 1272/2008, Annex VI, index number 613-088-00-6, Accute Tox 4 - H 302, Skin Irrit. 2 – H 315, Skin sensitizer 1 - H 317, Eye Dam. 1 – H 318, Aquatic Acute 1 – H 400). The available data indicate a potential for skin and skin sensitisation as well as for causing eye damage. By the oral route the substance is rapidly metabolised and eliminated and shows only limited mammalian acute toxicity. An estimated oral repeated dose NOAEL has been set at 8.42 mg/kg/day, and foetotoxicity was apparent at a maternally toxic dose of 40 mg/kg/day. No carcinogenicity data were found and mutagenicity assays suggest limited evidence of genotoxicity.

Benzyl salicylate is used in concentrations of less than 5 % and 1,2-benzotiazoline-3(2H)-one in concentrations in the range of 0.01-0.02 % in products. The health concerns related to the use of these preservatives in alternative products seem very limited.

Colorants

RPA assessed the colorant CI 21095 (CAS 5468-75-7), also named C.I. Pigment Yellow 14, which is considered as a frequently used colorant in the alternative products. The scarce toxicity data available indicate low acute toxicity. The substance is used in concentrations of less than 1 %. According to information in the RPA report toxicological studies do not indicate any human health concerns related to the substance as used in other air freshener and toilet block products.

Builders

The builder reviewed by RPA, sodium carbonate (CAS 497-19-8), is a common food constituent and it is included in the GRAS (Generally Recognised As Safe) list of food constituents in the US. The human health concern is limited to contact irritating (but not sensitising) effects (R 1272/2008, Annex VI, index number 011-005-00-2, Eye Irrit. 2 – H 319) - . There is an occupational exposure level established in one EU country (UK) of 10 mg/m^3 for 8 hours exposure. In some toilet blocks sodium carbonate is used as a builder in considerable quantities (>40 %, RPA, 2010). The health concerns related to its use in alternative products seem very limited.

Complexing/descaling agents

Citric acid (CAS 5949-29-1) occurs naturally in fruits and other foodstuffs and is an intermediate in the metabolism (Krebs' cycle) of living organisms. It may cause irritation at higher concentrations. Its repeat dose NOAEL is relatively high at 1,200 mg/kg/day, which indicates a low risk (RPA, 2010). Carcinogenicity and genotoxicity studies are negative. Reproductive NOAEL for rat is 2500 mg/kg/day. Citric acid is used in the range of 1 to 5 % in alternative toilet blocks. The health concerns related to its use in products seem very limited.

Solvents

Ethanol (CAS 64-17-5) may be present as a solvent in products. It is used in foodstaffs and pharmaceutical products, but also in industry. There is no occupational exposure level (OEL) on the EU level, however in some EU countries national OELs have been established. The lowest OEL reported in RPA is 950 mg/m^3. Ethanol can cause eye irritation, but it is not classified for this effect (R 1272/2008, Annex VI, index number 603-002-00-5, Flam. Liq.2 – H225). Repeated dose toxicity studies indicate that the main target organ of repeated exposure is the liver, where steatosis and inflammation may progress to cirrhosis and

potentially cancer development. Reproductive toxicity has been observed in humans following long term high dose exposure and ethanol is an established human foeto-toxin and developmental toxin, as well as a mutagen and carcinogen. Ethanol is used in alternative air fresheners in concentrations below 5 %. The health concerns related to its use in products seem limited.

Thickeners

Xanthan gum (CAS 11138-66-2), is a high molecular polysaccharide which is widely used in the food industry. The dietary and pharmaceutical daily intake has been estimated at 884 mg/person/day in the US (Burdock Group Consultants, 2006, as cited in the RPA). It is generally regarded as safe (Oxford University, 2003b; US FDA, 2009, as cited in the RPA). Toxicological studies indicate that 5% solutions cause skin irritation in rabbit, which does not appear with concentration < 2 % in rats. OELs were established in some countries. The lowest is 3 mg/m^3 (ACGIH). Its use in alternative products is in the range of 1 to 5 %. The health concerns related to its use in alternative products seem very limited.

Anti-caking agents

The anti-caking agent sodium sulphate (CAS 7757-82-6) was reviewed by RPA. It is widely distributed in nature and occurs in foodstuffs. The daily intake from all sources (anthropogenic and natural) has been estimated at 7.5 mg/kg. The estimated consumer exposure from its use in detergents is 0.1 mg/kg/day. Sodium sulphate demonstrates low mammalian acute and repeat dose toxicity (oral NOAEL of 320 mg/kg/day in rats). There are OELs established at the national level in EU, the lowest at 6 mg/m^3. The substance is used in products in the range of 25 to 50%. The health concerns related to its use in alternative products seem very limited.

Stabilisers

The non-ionic surfactant and foam stabiliser coconut oil monoethanolamine (also named Cocamide MEA, CAS 68140-00-1) was reviewed by RPA. The substance shows low acute and repeat dose toxicity (oral NOAEL 750-1500 mg/kg/day in rats) and tests negatively in the Ames assays. It does not appear to be a sensitiser, however, some skin irritation was observed in rabbit and mouse. The substance is classified as R 41 – risk of serious damage to eyes. However, the substance is not included in the Annex VI of the Regulation 1272/2008. Its use in products is in the order of 5 to 10 %. The health concerns related to its use in alternative products seem very limited.

Conclusion on human health risk for non-fragrance substances

The non-fragrance constituents of the products not containing 1, 4 dichlorobenzene are mainly commonly used chemicals with limited potential for toxicity to humans. In most cases the products only contain low amounts of the substance in question and the consequent exposure is likely to be very low. Thus, the human health risks for non-fragance substances are expected to be lower than from 1,4-dichlorobenzene.

C.2.2.3 Camphor

According to publicly available information (Suomen Sanimex, 2011) camphor tablets (CAS number 76-22-2) are marketed as urinal blocks. Concentrations are similar to those of 1,4-dichlorobenzene, that is 96 % or above (Fisher, 2011). Given the relatively similar vapour pressure for the two substances (87 Pa at 25°C15 for camphor and 80 Pa at 20°C for 1,4-dichlorobenzene) exposures are supposedly within the same range. The substance is not classified under neither Directive 67/548/EEC nor Regulation 1272/2008.

[15] US EPA Action Memorandum. January 27. 2006

According to RPA (2010), camphor can also be found as a fragrance in alternative air fresheners in concentrations below 5%.

To briefly assess the hazard profile of camphor some information is given below and a summary of physico-chemical properties is presented in Annex 5.

Occupational Health Limits

Occupational health limits have been established by a number of organisations, in particular in the US. There is no harmonised limit for EU, but national limits which are in accordance with those of the US bodies have been set in some MS, for example in Germany and Finland (Table C28).

Table C28: Occupation health limits for camphor

	OSHA PEL	**ACGIH TLV**	**NIOSH REL**	**BAUA AGS**	**HTP values**
TWA **(Time-weighted average)**	0.3 ppm; 2 mg/m^3 (8-hours time-weighted)	2 ppm; 12 mg/m^3 (8-hours time-weighted)	0.3 ppm; 2 mg/m^3 (10-hours time-weighted)	2 ppm; 13 mg/m^3 (8-hours time-weighted)	0.3ppm; 1.9 mg/m^3 (8-hours time-weighted
STEL **(short-term exposure level)**		3 ppm; 10 mg/m^3			0.9 ppm; 5.7 mg/m^3

Source:
OSHA PEL – OSHA Permissible Exposure Limits
ACGIH TLV – American Conference of Governmental Industrial Hygienists Threshold Limit Value
NIOSH REL – The National Institute for Occupational Safety and Health Recommended Exposure Level
BAUA Bundesanstalt für Arbeitsschutz und Arbeitsmedizin,
AGS Ausschuss für Gefahrstoffe
HTP values – Finnish occupational health limit values

Studies in animals

Information from animal studies is scarce. The most relevant information includes three subchronic inhalation studies presented in Table C29. However, it has not been possible to find the original studies and very limited information is given in the available summaries.

Table C29: Multiple-dose inhalation studies with camphor

Parameter	**Study details**	**Level of exposure**	**Effect**	**Reference**
Subchronic	Mouse 7-weeks	Lowest published	Lung, thorax or	GISAAA 22(11),

Inhalation,	study, intermittent (3-hour periods of time; days per week not specified)	toxic concentration: 210 mg/m^3/3hour (33 ppm)	respiration: emphysema	83, 1957; as cited in RTECS (2005)
Subchronic Inhalation,	Rabbit 7-weeks study, intermittent (3-hour periods of time; days per week not specified)	Lowest published toxic concentration: 33 mg/m^3/3hour*[16] (5 ppm)	Lung, thorax or respiration: emphysema Brain and coverings: other degenerative changes Cardiac: other changes	GISAAA 22(11), 83, 1957; as cited in RTECS (2005)
'Prolonged duration', inhalation	Severe injuries in experimental animals (species not specified)	6 mg/m^3	Convulsions, congestion, changes in the gastrointestinal tract, and damage to the kidneys and brain	Flury and Zernik 1931b /Ex. 1-996 (in German), as cited in NIOSH (1988)

Source: RTECS Registry of Toxic Effects of Chemical Substances of NIOSH.

Data from humans

Several cases of oral intoxication in humans have been reported, as well as symptoms in workers after occupational exposure. However, only a few cases of intoxication following inhalation exposure have been reported (Table C30).

National Institute for Occupational Safety and Health (NIOSH, 1988) referred to a case of industrial exposure in which workers were directly in contact with camphor vapours (Gronka *et al*. 1969 as cited by NIOSH). Camphor concentrations ranged from 24 to 43 mg/m^3 and six employees examined showed inflammation of the nose and throat. One individual also reported occasional numbness of the fingers. After the plant installed local ventilation concentrations remained at or below 2 ppm. After the improvements, the authors reported that exposure up to 10 months did not produce eye or nasal irritation.

Based on the results of Gronka *et al*. American Conference of Governmental Industrial Hygienists (ACGIH) adopted new threshold limit values – a time weighted average (TLV-TWA) of 2 ppm and a threshold limit value for short term exposure level (TLV-STEL) of 3 ppm (the previous TLV-TWA was 2 mg/m^3, 0.3ppm). However, the regulatory body, Occupational Safety and Health Administration (OSHA), considered that, due to the lack of comprehensive medical examinations after exposures, the study by Gronka *et al*. did not provide an adequate basis for increasing of the permissible exposure level (time weighted average (PEL-TWA)). OSHA also took into account the severe effects in animals exposed for prolonged periods in a study conducted by Flury and Zernik (1931b/Ex. 1-996). Based on the information available OSHA decided to maintain its 2 mg/m^3 (0.3 ppm) limit for camphor.

[16] 33 mg/m^3/3hour is considered equivalent to approximately 4 mg/m^3/24 hour

Table C30: Data on humans exposed to camphor

Cases of exposure in humans			
Parameter	**Level of exposure**	**Effects**	**Reference**
Inhalation	Not given	Fatality	Flury, *et al*., 1931, as cited in NIOSH (1988)
Chronic exposure, Inhalation Industrial exposure to camphor	24-43 mg/m^3 2 ppm (12 mg/m^3)	Repeated exposure at this range produced inflammation of the nose and throat; occasional numbness in the fingers No eye or nasal irritation for concentrations maintained at or below 2 ppm	Gronka *et al*., 1969, as cited in NIOSH (1988) ibid

Conclusions on human health risks for camphor

Based on a very incomplete database it can be assumed that exposure to camphor via inhalation may induce systemic toxicity in experimental animals at exposure levels of a few mg/m^3. Occupational exposure limits are also considerably lower than those for 1,4-dichlorobenzene, which has an OEL of 10 ppm in the EU. It can thus be concluded that while camphor is an alternative to 1,4 dichlorobenzene, it is not a suitable alternative from a human health point of view however there is currently no restriction on the use of camphor as urinal blocks and it is the only chemical equivalent alternative to 1,4 dichlorobenzene.

C.2.3 Environmental risks related to alternatives

The RPA (2010) report provides some information in relation to environmental toxicity of substances used in toilet blocks and air fresheners products not based on 1,4-dichlorobenzene. The detailed information is provided in the tables presented in Annex 4.

RPA summarised the environmental hazards of alternatives as follows:

Box C1: Summary of Environmental Hazards of Selected Components of Alternative Room Air Freshener and Urinal Block Formulations

Fragrances: while the environmental toxicity data available on the fragrances is limited, only α-hexyl cinnamaldehyde has been suggested as possibly moderately bioaccumulative and of quite high acute toxicity to aquatic species (EPA, 2009b) and four others (citronellol, d-limonene, 2,4-dimethyl-3-cyclohexene-1-carboxaldehyde and pin-2(10)-ene) are classified as dangerous to the aquatic environment. However, most are readily metabolisable in various organisms and, particularly given their low inclusion levels, the uses considered here are considered unlikely to pose a significant risk.

Surfactants: for linear alkylbenzene sulphonates (LASs), a detailed environmental risk characterisation has suggested that Predicted Environmental Concentration (PEC) to: Predicted No Effect Concentration (PNEC) ratios were below 1 for all environmental compartments (HERA, 2009b). The alcohol ethoxylates (AEs), which include the C_{12-18} ethoxylated alcohols specifically considered in Annex 6, are also of low concern with regard to environmental risks, with PEC:PNEC ratios below 1 (HERA, 2009c).

Sodium lauryl ether sulphate has little specific data but belongs to a class of substances the alcohol ethoxysulphates (AESs) for which environmental risk characterization (PEC:PNEC) ratios are less than 1 (HERA, 2009d).

Preservatives: the preservative 1,2-benzotiazoline-3(2H)-one is classified as potentially harmful to humans and the environment. QSAR calculations have suggested that it is probably aerobically degradable and has low bioaccumulation potential in aquatic organisms (Madson *et al.*, 2000) and it was not prioritised by Environment Canada in their Domestic Substances List (Environment Canada, 2007) therefore, given that it is included in the alternative products considered in only very small amounts (0.01-0.02%), use in these applications are unlikely to constitute a significant risk.

Dyes: very little information has been identified on the dye CI21095. Its environmental toxicity has recently been considered by a European expert committee, which concluded that it did not meet the B (or vB) or T criteria but was likely to meet the P (and vP) criteria in order to meet its technical specification. However, it was concluded to be neither PBT nor vPvB (ECB, 2005).

Complexing agents: citric acid, monohydrate also rapidly dissociates into ions in the presence of water and, given that citric acid plays a vital role as an intermediate in Kreb's cycle metabolism in eukaryotes, its presence in the alternative articles is considered of little human or environmental concern (HERA, 2005b).

Solvents: for ethanol, on release into the environment it distributes mainly to air and water and, while stable to hydrolysis, it is readily biodegraded. It has a tropospheric half life of 10-36 hours and is unlikely to bioaccumulate suggesting little cause for concern.

Thickeners: xanthan gum is of low environmental concern being generally regarded as safe (Oxford University, 2003b; FDA, 2009) while coconut oil monoethanolamine, with an estimated log Pow value >4 it might be considered potentially bioaccumulative but is only 'toxic' to 'moderately toxic' to aquatic organisms and is considered unlikely to be considered a PBT. A PNEC of 0.23 µg/L has been estimated for a closely-related substance cocamide DEA which would equate to a MOE of 427.1 based on estimates of its PEC (Danish Environmental

Protection Agency, 2006). Given that cocamide DEA appears slightly more toxic than the monoethanolamine, it is likely that the MOE for coconut oil monoethanolamine would also prove adequate.

Builders: sodium carbonate dissociates into its component ions readily in the presence of water. HERA (2005b) has established that its use in detergents poses no significant risk to the aquatic ecosystem.

Anti-caking agents: There is similarly little concern with regard to the anti-caking-agent sodium sulphate, which is widely distributed in nature, occurs in almost all fresh and salt waters, and is a normal constituent of natural foodstuffs. It has low aquatic toxicity and enters the sulphur cycle and so is not considered a major environmental hazard although it has been suggested that local peak concentrations may be greater than the PNEC of 1.9 mg/L and could therefore conceivably damage un-adapted flora and fauna (HERA, 2006).

Stabilisers: benzyl salicylate is widely used in a range of other consumer products. As it is used in only small amounts (<5%) in alternative air freshener and toilet block products, these sources are unlikely to be of concern. However, predicted BCF values are 547.7 - 652.47 (depending on pH) and little ecotoxicity data were identified, so it is not possible to adequately assess the risk posed to the environment at this time.

For easier comparison, the tables presented in Annex 4 also include the eco-toxicological information related to 1,4-dichlorobenzene.

A more detailed analysis of the environmental hazard of 1,4-dichlorobenzene has been presented in the EU RAR (2004) report. Considering the analysis of use of interest – 60 % of the substance used as an air freshener and 40% as toilet block - and the properties of the substance, it was concluded that the main compartment affected is air. It was not possible to evaluate the impact of the 1,4-dichlorobenzene released into the atmosphere on living organisms due to the lack of validated data. Abiotic effects, however, could be evaluated. The substance has an atmospheric lifespan of 50 days, which indicates that the stratospheric ozone will not be affected. For surface water, sediment and secondary poisoning PEC and PNEC values were calculated. The PEC/PNEC ratio for the use of 1,4-dichlorobenzene as a toilet block was calculated to 0.17 for each of the surface water and sediment compartments. The PEC/PNEC ratios for the secondary poisoning were: for fish-eating birds 0.84 and for earthworm-eating birds and mammals 0.04 .

These findings lead to the conclusion in the EU RAR that '*at present there is no need for further information and testing and for risk reduction measures beyond those which are being applied already*'. This conclusion was drawn for air, surface water, sediment and secondary poisoning.

The terrestrial compartment is affected mainly by the production of 1,4-dichlorobenzene and its use as an intermediate. It is, therefore, outside of the scope of this report.

On the basis of the information presented above it can be concluded that there is no reason to expect that the environmental impact resulting from use of other air freshener and toilet block products would be more pronounced than the effect of 1,4-dichlorobenzene used as air freshener and toilet block.

C.2.4 Technical feasibility of the alternatives

The 1,4-dichlorobenzene products are used mainly to mask unpleasant odours with its own, strong aroma. Other air fresheners are used for the same purpose, but the emphasis is more on providing pleasant odours than masking the bad ones. Other toilet blocks not containing 1-4,dichlorobenzene are used to prevent unpleasant odours by cleaning and disinfecting, but they also release fragrances. In this section the main aspects of the technical feasibility of air

fresheners and toilet blocks not containing 1-4,dichlorobenzene (that is deodorising, cleaning and longevity) are discussed.

Deodorising

1,4-dichlorobenzene products vs. alternatives

1,4-dichlorobenzene releases a very strong moth-ball like odour. Other air fresheners and toilet blocks on the other hand, can provide a variety of scents (citrus, pine, etc.). A pleasant fragrance may have little positive impact if a product is not capable of effectively reducing or masking malodours (RPA, 2010).

Quantitative comparison of the odour masking properties of 1,4-dichlorobenzene and other products is challenging. Simple comparison of odour thresholds and air concentrations would not be meaningful. Firstly, to evaluate the effectiveness of the substance in relation to masking odour, we would need to know the odour threshold and concentration in the air of the substance to be masked, e.g. urine. In addition, the odour threshold of fragrances could be influenced by interactions with the other ingredients in the products. Secondly, knowledge of the concentration at which the substances can be smelled/detected in the air is not sufficient to estimate at which concentration the aroma of the substance would dominate the smell to be masked. However, with typical hygiene conditions **at homes** and in domestic toilets, there should not be a need for a very strong odour masking capacity, and other air fresheners products which do not contain 1,4 dichlorobenzene are considered to be able to provide this function.

In public toilets, frequent use combined with inadequate cleaning may result in significant malodour problem. According to manufacturers of 1,4-dichlorobenzene products, other air freshener products and toilet blocks do not release sufficient amount of fragrance of sufficient strength to ensure that malodours are masked, especially in frequently used toilets (RPA, 2010)[17]. With the exception of Camphor this statement seems justified because other products typically contain up to 5% of fragrances, compared to almost 100% in the case of 1,4-dichlorobenzene (see Table C26). This means that the amount of product (i.e. the fragrance constituent) used to mask odours is significantly less in the case of other products. However, as previously discussed, it is difficult to compare the efficiency of different fragrances in odour masking. Odour may also be a problem in public toilets where the plumbing to the sewers is old and inadequate resulting in odour returning to the public toilets though openings e.g. urinals

Release patterns

According to a manufacturer of 1,4-dichlorobenzene urinal blocks deodorising is more important than simply removing malodours; as positive scent is noticeable to customers and unconsciously related to a facility being clean. The manufacturer argues that simply eliminating malodours does not have the same impact on a consumer (RPA, 2010).

Products that release scent constantly are the most similar to 1,4-dichlorobenzene products, and consequently suitable to replace them. However, the air fresheners with alternative pattern of release, for example peak release, are also reported to be used to mask bad odours

[17] Additional views stating that 1,4-dichlorobenzene has very strong odour masking properties (RPA, 2010):
Manufacturer of air fresheners, urinal blocks and toilet rim blocks (USA): *1,4 dichlorobenzene-based toilet rim blocks are not a necessity these days because the design of a toilet (the fact it keeps water in the bowl) means that they are not a long term source of constant malodours that should be controlled by a deodoriser as strong as 1,4 dichlorobenzene*
Industry expert: *warmer weather could make toilet rooms develop strong unpleasant odours that require deodorisers with good odour masking properties. 1,4 dichlorobenzene offers such functionality.*

(RIVM, 2006), Release patterns and use locations for different types of alternative air fresheners are presented in Table C31.

Table C31: Location, application and scent release pattern for different air fresheners

Product type	Location of use	Application types	Scent release pattern
Room perfume in holders	Living-room, bedroom, kitchen, toilet, garage, car, office, stores	Electric plug, ventilation, no specific action	Constant
Fragrant candles and wax	Living-room, bedroom, stores	Heating, Burning	Peak
Ethereal oils	Living-room, bedroom, sauna, office, stores	Heating	Peak
Fragrant sachets	Living-room, bedroom, kitchen, toilet, garage, car, office, stores	No specific action	Constant
Sprays	Living-room, bedroom, kitchen, toilet, garage, car, sauna, office, stores	Spray on targeted spot, general surfaces, or in air space	Peak
Potpourri	Living-room, bedroom, kitchen, toilet, garage, car, office, stores	No specific action	Constant
Incense	Living-room, bedroom, stores	Burning	Peak

Source: RIVM (2006) as cited in the RPA (2010)

Cleaning (relevant only for toilet blocks)

Toilet blocks which do not contain 1,4-dichlorobenzene do not only release pleasant odour, but also support cleaning and disinfecting of toilet bowls and urinals. To the contrary, 1,4-dichlorobenzene does not have cleaning or disinfecting properties (HSDB, 2011; Ullmann's Encyclopedia, 2006; RPA, 2010). However, it seems that many suppliers and users of 1,4-dichlorobenzene toilet blocks assume that 1,4-dichlorobenzene would also provide an additional cleaning function (RPA, 2010).

The cleaning and disinfecting properties of other toilet blocks at least to some extent prevent the malodours to be formed. However, they do not prevent malodours related to spillages and general lack of cleanliness of the toilet to be evident in the air (RPA, 2010).

Traditionally the main non-1,4-dichlorobenzene urinal blocks have been surfactant based blocks. In addition, urinal blocks containing bacteria cultures are nowadays available. The products with bacteria cultures can remove the fats and solids that build up in urinal traps and in pipework. They are also promoted to reduce build-up of organic matter and preventing formation of scale in pipework (RPA, 2010).

Longevity

1,4-dichlorobenzene products

The 1,4-dichlorobenzene products are solid at room temperature and sublimate gradually into surrounding air. Their longevity is mainly affected by i) size of the product and ii) the surrounding room temperature. If the block is wet – the sublimation rate may be reduced; instead, some substance may be dissolved into water. As both 1,4-dichlorobenzene air fresheners and toilet blocks are about the same size, there is no significant difference in their longevity. Based on information from RPA (2010), it is assumed, that an 1,4-dichlorobenzene air freshener or toilet block will last 21 days in a temperature of 20 ºC and 10 days in a temperature of 25 ºC (see also section B.9 on exposure). In the exposure assessment an average product (air freshener or toilet block) is assumed to weigh 80g. Table C32 presents the available data on the longevity of 1,4-dichlorobenzene and other urinal blocks. As the 1,4-dichlorobenzene toilet bowl blocks and air fresheners are assumed to be of same size as urinal blocks, the same estimate on longevity is applied also for these products.

Other air fresheners

There is no comprehensive information available on the longevity of other air fresheners. However, it is clear that it varies between the different types. Some of the products require user's manipulation to release scent (for example flushing the toilet, compressing the container, electrical impulses), and the longevity of the product depends on the user's behaviour. The longevity of the air fresheners with constant, continuous release is mainly determined by the component constituting the matrix, in which fragrances are suspended, for example the gel, and surface of the release area.

As an example, one of the air fresheners, room perfume in holder with gel, is advertised to last around six weeks (Biltema, 2012).

Other toilet bowl blocks

The alternative toilet bowl blocks are water soluble products. It is necessary for their functioning as cleaning and disinfecting agents. The main parameter affecting the longevity is the frequency of flushing. The longevity is also affected by the size of the block, which varies between products.

One toilet rim block is advertised to last up to 1000 flushes (ezee-shop, 2012). Around 48 flushes per day would give the same longevity of 21 days, that is assumed for 1,4-dichlorobenzene. This is much more than what can be expected for domestic toilet bowls. In public toilets, the frequency of flushing varies to some extent, and may exceed 48 times per day.

In the exposure calculations for a toilet block which did not contain 1,-4 dichlorobenzene (see section C.2.2.1 and Annex 3), it is assumed that the product would last for 9 days. This assumption should be considered together with the small size (6g) of this specific product, and does not represent an average longevity for toilet blocks. In fact, 6g is a single dose of the product – the whole package contains 6 doses, and is expected to last for up to 8 weeks.

As the longevity of the these toilet bowl blocks is mainly defined by the flushing pattern, the temperature should not affect them as much as it affects the products, whose mode of action is based on evaporation or sublimation, such as 1,4-dichlorobenzene. This means that these toilet bowl blocks should last relatively longer in higher temperatures.

Other urinal blocks

Table C32 summarises the available information on the longevity of different urinal blocks. As the other urinal blocks are water soluble, their longevity is highly affected by flushing frequency. Similar to toilet bowl blocks, the temperature should not affect these products, as much as it affects 1,4-dichlorobenzene. The urinals in public toilets have potential to be used frequently and consequently flushed frequently. In addition to number of customers, the

flushing frequency depends on the type of urinal in question and users habits. RPA (2010) provides a thorough overview on different types of urinals in their report.

Table C32: Longevity of Different Urinal Block Products[18]

Supplier	Nominal weight (g)	Longevity (days)	Notes
1,4 dichlorobenzene-based blocks			
A	85 – 115	30	Non-EU made
B	25 – 80	21	For a product with >95% 1,4 dichlorobenzene
B	25 – 80	14	For a product with 70% 1,4 dichlorobenzene
1,4 dichlorobenzene-free blocks			
V	Not known	30	Theoretical – aim is to last for 1,000 flushes
W	100	200 flushes	
X	100	21-28	For high flush urinals
X	100	7-10	For high flush urinals; half-price per kg compared to product above
Y	25	8-10	If an attempt were made to slow down the dissolution process, it would impair the efficacy of the product as well as the intensity of the perfume.
Z	35	4-6 but possibly up to 10	Biological urinal block If the product lasted for more than 10 days, it would not work properly (the perfume would be too weak), if it lasted fewer than 3 days, there would not be sufficient biomass build up so it could not be effective. 4-6 days is the optimal for efficacy but this also depends on the number of blocks. Most users tend to use 2-3 at any time. The use instructions advise the user to place one biological urinal block into each urinal bowl once a week. The product is formulated so the correct level of bacteria will be released over one week, so even if there is some of the previous block in the bowl, this should be removed and replaced with a new block.

Source: RPA, 2010

The most durable alternatives seem to offer around 1000 flushes. According to a manufacturer of both 1,4-dichlorobenzene and othertoilet blocks, a urinal of high traffic toilet will be flushed more than 100 times per day (RPA, 2010). This would result in longevity of less than 10 days for these products.

[18] No data were available on the longevity of camphor based blocks.

Alternative techniques

Any measure to prevent the odours from being released or to remove the existing odour can be seen as an alternative technique for 1,4-dichlorobenzene air fresheners and toilet blocks.

Additional cleaning

The additional cleaning is more relevant option for public toilets than in the other premises including domestic toilets. With typical hygiene conditions at homes, there should not be any need for more frequent cleaning if 1,4-dichlorobenzene is replaced with alternative household air freshener and toilet block products.

In professional settings frequent cleaning can prevent any mal-odours related to spillages and can help to establish good level of cleanliness. In addition, techniques to encourage users to maintain the premises clean could be used (for example, installing signs inviting users to respect the cleanliness of toilets or special devices designed to limit spillages e.g. Uro-Goal (2012)). Finally, taking care that the drain pipes are installed and maintained appropriately will also help to prevent forming of malodours.

Improving ventilation

Ventilation can be used to remove existing mal-odours outside the building. However, it does not prevent the odours being formed or remove them completely. Improving ventilation may not be technically feasible in all cases.

Modern urinals

The 1,4-dichlorobenzene urinal blocks are relatively more competitive in older than in more sophisticated modern urinals. This is mainly due to effect of water consumption on the longevity of the alternative urinal blocks. Furthermore, modern urinals are often better designed to prevent the mal-odours to be released from the urinal and drainpipes. RPA (2010) provides a fairly detailed presentation on different urinal types, discussing also their water consumption. However, it wil not address mal odours coming from spillages.

Conclusions

Table C33 provides an indicative scoring of characteristics related to technical feasibility of use of 1,4-dichlorobenzene and other products. The deodorising function is divided into two aspects, odour masking and scenting to allow scoring for both functions. This division reflects the fact that 1,4-dichlorobenzene can be used to mask the mal-odour, whereas the fragrances in other products are used to provide a positive scent to a room without mal-odour. The importance of these functions may vary between the users. The technical properties vary between different product groups and the scoring is provided for a so called representative product, that could replace the 1,4-dichlorobenzene products.

Table C33: Comparison of technical characteristics of 1,4-dichlorobenzene and a "representative" alternative

Product group		Deodorising		Longevity	Cleaning properties
		Odour masking	Scenting		
Air fresheners	1,4-DCB	+++	+	++	-
	Other products	+	+++	++	-
Toilet bowl blocks (domestic use)	1,4-DCB	+++	+	++	-
	Other products	+	+++	+++	+++
Toilet bowl blocks (public toilets)	1,4-DCB	+++	+	++	-
	Other products	+	+++	+	+++
Urinal blocks	1,4-DCB	+++	+	++	-
	Other products	+	+++	+	+++

Note: The score is between '+' and '+++', where '+++' indicates highest level functioning. The'–' indicates that the function in question is not offered by the product.

The technical properties and functioning of 1,4-dichlorobenzene and the other identified air fresheners and toilet blocks differ to some extent, which makes their comparison challenging. In most of the applications, they seem to be able to provide the same service. In fact, most of them even offer additional properties. From technical feasibility point of view, the replacement seems to be most difficult in circumstances where strong odour masking properties are requested in professional settings. These are mainly high traffic toilets, with poor hygienic conditions. However, even if a product which provides exactly the same function as 1,4-dichlorobenzene has not been identified (apart from camphor which is not proposed as a suitable alternative due to it's adverse effects on human health) it is concluded that technically feasible alternatives exist. For both consumer and professional uses the alternatives aim to provide the same effect (i.e. combatting the unwanted odours) by different means (i.e. cleaning instead of masking, or a combination of cleaning and deodorising in the same product).

C.2.5 Economic feasibility of the alternatives

In this section the economic feasibility of use of the alternatives is assessed from the end-users point of view. The potential impacts on producers of air fresheners and toilet blocks are discussed in section F.

As discussed under Technical feasibility of alternatives (section C.2.4), the 1,4-dichlorobenzene and alternative products are challenging to compare as they have different deodorising, cleaning and longevity properties. These differences should be considered when assessing the economic feasibility of use of the alternatives. However, the available data does not allow

taking into account the deodorising and cleaning properties quantitatively in the calculations, and consequently their potential impacts are described qualitatively or semi-quantitatively. All the referred prices and assumptions on prices are without VAT, if not otherwise indicated.

Air fresheners

According to RPA (2010), a typical 1,4-dichlorobenzene air freshener costs €2. According to AMEC (2012) adjusting RPA prices for inflation and removing VAT gives an average price of €2.1 for 1,4-dichlorobenzene air fresheners. An overview of the prices per unit for alternatives is presented in Table C34. The information is from a leading UK-based retailer, who is also active in other Member States. These prices include VAT. The presented unit prices do not consider the longevity of the product, and consequently are not directly comparable with unit prices of 1,4-dichlorobenzene products.

Table C34: Overview of the Cost of Alternative Air Freshener Products (including VAT)

Type of air freshener alternative	Price range per unit
Aerosol	€0.32 - €3.50 per 300 ml
Automatic aerosol refill	€2.28 - €4.05
Automatic aerosol unit	€7.41 - €16.29
Gel	€0.43 - €3.42
Manual spray refill	€2.85
Manual spray unit	€3.50 - €6.84
Plug-in refill	€4.08 - €5.09
Plug-in unit	€6.99 - €10.49
Pot pourri	€3.42
Scented oil	€1.14 - €7.98
Wick in liquid	€1.93 - €2.62

Source:RPA, 2010
Note: prices for products available from a leading supermarket in the UK as of 20 April 2010; used an exchange rate of £1 = €1.14

The alternative air fresheners are available in wide range of prices. There are alternatives (e.g. in aerosol and gel products) available with lower unit prices.

For further assessment in this report, it is assumed that a suitable alternative air freshener costs €0.4 and lasts for 21 days. Gel-based products provide constant release like 1.4-dichlorobenzene in the same (lower end) price range. For these reasons it is assumed as a representative alternative. For example, a retailer operating in Finland supplies a gel-based air freshener for €1.69 (including VAT) with around 6 weeks longevity (Biltema, 2012). The

assessment by AMEC (2012) is based on the price of bottom-of-range aerosol spray (€0.28 per unit). For further information on longevity and deodorising properties of the product, see the section on technical feasibility.

Toilet bowl blocks

According to RPA (2010), a typical 1,4-dichlorobenzene toilet rim block costs €1.5. According to AMEC (2012) adjusting the RPA prices for inflation and removing VAT gives an average price of €1.32. An overview of the prices per unit for alternatives is presented in Table C35. The information is from a leading UK-based retailer, who is also active in other Member States. The presented unit prices do not consider the longevity of the product.

Table C35: Overview of the Cost of Alternative Toilet Block Products (including VAT)

Type of toilet block alternative	Price range per unit
Adhesive in-bowl disc	€0.57
Cistern block	€0.18 - €1.14
In-bowl block	€0.31
Liquid	€1.48 - €1.74
Liquid - refill	€1.12 - €1.14
Solid in cage rim block	€0.23 - €1.12
Solid with gel rim block	€2.05 - €2.71

Source: RPA, 2010
Note: prices for products available from a leading supermarket in the UK as of 20 April 2010; used an exchange rate of £1 = €1.14

Alternative toilet bowl blocks are available in prices between €0.18 and €2.71 - the alternatives are in average less expensive than 1,4-dichlorobenzene product (RPA, 2010). However, the straight comparison of the prices is not meaningful as the longevity of the products differs and is related to the flushing frequency. Nevertheless, some solid in cage rim blocks are reported to last up to 1000 flushes, indicating that the cost per day would be competitive with a reasonable assumption for the number of flushes per day[19].

In this report, it is assumed that a suitable alternative toilet block costs €0.2 and lasts for 21 days in domestic use and 10 days in public toilets. The price is chosen near the lower end[20] of the price range for solid in cage rim blocks (€0.23-1.12) which are most similar to 1,4-dichlorobenzene products. The assessment by AMEC (2012) is based on the price of bottom-of-range cistern-block (€0.16). This is derived from RPA by adjusting for inflation and removing VAT. For further information on longevity and information on deodorising properties of the products, see the section on technical feasibility.

[19] Around 48 flushes per day gives the same longevity as assumed for 1,4-dichlorobenzene product at 20ºC (21 days). Even higher flushing frequency could be compensated by the lower unit price for these alternatives.
[20] It is considered that users will choose the cheapest alternatives, if they provide as similar functionality as possible. There are no reasons to assume that the more expensive alternatives would be more similar from the functionality point of view, including the odour masking property. If some users choose more expensive alternatives, this is because these alternatives offer an additional functionality (e.g. cleaning properties), which is not offered by 1,4-dichlorobenzene. Consequently it would not be justified to compare these alternatives (with additional functionalities) with 1,4-dichlorobenzene.

Urinal blocks

According to RPA (2010), the typical price of 1,4-dichlorobenzene urinal block is estimated to be €0.7. According to assessment by AMEC (2012), an average price of 1,4-dichlobenzene urinal block is €0.58. An overview of the prices of 1,4-dichlorobenzene and alternative urinal blocks per unit and per kg is presented in Table C36. The alternative products have in average higher price per kg, and lower price per unit. It is not clear from literature why the alternative blocks seem to be available in smaller units.

Table C36: Prices of Selected 1,4-dichlorobenzene-based and 1,4-dichlorobenzene-free Urinal Blocks (including VAT)

Product name	Price in € (incl. VAT)	Member State of sale	Quantity	Price (€)		Source
				Per kg	Per unit	
1,4 dichlorobenzene-based products						
Ribo Special	6.90	DE	1 kg	6.90	-	HygieneVetrieb (2009)
Dr Becher Extra	34.05	DE	2.5 kg	13.62	-	Dr Becher (2009)
Fresh Urinal Para Block	10.75	CZ	1 kg (12 pieces)	10.75	0.90	Davkovace (2009)
Lemon Channel Blocks	19.40	UK	3 kg	6.46	-	E-Shop Supplies (2010)
Citrus Channel Cubes	28.40	UK	3 kg	9.47	-	MSC J&L Industrial Supply (2010)
1,4 dichlorobenzene product A	6.25*	DK	1 kg	6.25	-	Consultation
1,4 dichlorobenzene-free products						
Ribo Bio	8.62	DE	n/a	-	-	HygieneVetrieb (2009)
Dr Becher Gruene	17.62	DE	35 pieces	-	0.50	Dr Becher (2009)
Dr Becher Standard	11.88	DE	30 pieces	-	0.40	Dr Becher (2009)
Fresh 40	9.64	CZ	750 g (~ 40 pieces)	12.85	0.24	Davkovace (2009)
Fresh Urinal Toss Block	33.00	CZ	20 pieces	-	1.65	Davkovace (2009)

Biological Toss Blocks	13.70	UK	1.1 kg (50 pieces)	12.45	0.27	Gentworks (2010)
Biological product A	35.00*	DK	1 kg (20 pieces)	35.00	1.75	Consultation
Biological product B	17.50*	DK	1 kg (38-42 pieces)	17.50	0.42-0.46	Consultation
Surfactant product C	8.75*	DK	1 kg	8.75	-	Consultation

Source: RPA, 2010
*Notes: (a) high value order discounts not taken into account; retail prices in the Czech Republic quoted in Czech Koruna (CZK) and converted using exchange rate of 23 November 2009 (€ 1 = CZK 25.9); exchange rate £1=€1.14 * includes VAT at 25%*

Similar to the toilet bowl blocks, the cost per day is affected by the longevity of the products. Table C32 presents overview on the relative longevity of different urinal blocks. However, the longevity of alternatives (which are water soluble) is highly affected by the flushing frequency, whereas the longevity of 1,4-dichlorobenzene urinal blocks (which sublimates to surrounding air) is highly affected by the temperature.

The total costs of urinal blocks may be increased with the use of plastic screens with integrated block compartments (RPA, 2010). The screens prevent fragmented block to fall into pipes and to cause blockages. 1,4-dichlorobenzene has very good mechanical properties (RPA 2010) and does not break easily. However, this will not prevent it from falling into the pipes when its size is gradually reduced. According to RPA (2010) the screens may cost up to €4 per screen. However it is assumed that the screens do not need to be replaced frequently and the impact on the total costs is insignificant.

As described in the section on technical feasibility alternative toilet blocks both mask the odours and prevent odours from being formed. They also facilitate cleaning. The latter properties increase the hygienic conditions in the toilet, which has a value of its own. However, it can also be argued that there is a need for additional cleaning with the alternative products, as they do not mask the unpleasant odour as effectively as 1,4-dichlorobenzene (RPA, 2010). According to RPA (2010), around 70% of the users would need additional cleaning to obtain the same level of deodourisation, with an annual cost estimated to be between €58.50 and €258.75[21] per urinal depending on the number of visitors in the toilet. However, those managing toilet facilities are free to decide on the appropriate level of additional cleaning to undertake to compensate for any reduction in deodourising capability of alternatives, and the cost estimation approach employed in Section F takes account of this possibility.

For the calculations on the economic feasibility, it is assumed that an alternative urinal block costs €0.5 and lasts for 10 days. The price is chosen near the lower end of the price range representing a surfactant based alternative. According to AMEC (2012) surfactant based urinal block costs €0.4. In the assessment of economic impacts, it it is assumed that there are no suitable alternatives available for 1,4-dichlorobenzene urinal blocks (see Chapter F). This reflects the conclusion that the replacement is most difficult in the public toilets. For further information on longevity and information on deodorising properties of the products, see the section on technical feasibility.

Alternative techniques

[21] RPA assumptions: i) cleaning of urinal 5 minutes; ii) additional cleaning 1 to 5 times per week; iii) cost of cleaning services €13,50 per hour.

Any measure to prevent the odours from being released or to remove the existing odour can be seen as an alternative technique for 1,4-dichlorobenzene air fresheners and toilet blocks. The annual cost of using one deodoriser product (for both 1,4-dichlorobenzene or alternative) is estimated at around €10-30. On the other hand the cost of other techniques to control odour (additional cleaning, improving ventilation or retrofitting the urinal facility) is considered to be significantly higher. For that reason it seems plausible that many users would opt for using alternative air fresheners and toilet blocks if a ban for placing on the market of 1,4-dichlorobenzene enters in force. However, installing waterless urinals may be competitive option for many users as demonstrated in RPA (2010), regardless of the potential restriction.

Conclusions

Consumer preferences in relation to the characteristics of the products affect their decisions on which product to use. For example, the moth-ball like odour does not appeal to everyone but may be more familiar (and consequently appealing) for older persons (RPA, 2010). It is not possible to take this variety and personal preferences into account in the cost calculations. Furthermore, there is no information available in relation to the differences in odour masking properties and the cleaning function of alternative toilet blocks that could be used in the cost estimates.

Considering only the prices and the longevity of the products, some of the available alternatives are estimated to be less expensive per day for the users. This is in line with the fact that alternative products already dominate the market. For urinals in frequently used toilets with very high flushing frequency the alternatives may be more expensive per day.

Table C37 summarises the assumptions used to calculate the costs per year of using 1,4-dichlorobenzene and a "representative" alternative. This alternative is considered to offer as similar functions as possible with relatively low price. If the end user opts for more expensive alternatives, it is assumed that they offer additional features for the consumer. The results in Table C37 are further used for the socio-economic analyses (in section F) to assess the financial costs of the proposed restriction. In addition, the data is used to assess changes in the consumer surplus. However, in section F, it is assumed that the whole professional use of toilet blocks are in urinals, and no 1,4-dichlorobenzene toilet bowl blocks would be used in public toilets. This is based on the information on RPA (2010), idenfying urinal blocks as the main use in public toilets. There is no data available on the potential amount of 1,4-dichlorobenzene toilet bowl blocks used in the public toilets. However, there is no data available to exlude this possibility either.

Table C37: Costs of 1,4-DCB and alternative products

Product group		**Unit price (€)**	**Longevity (days)**	**Annual cost (€)**	**Additional cost of switching to alternatives (€ per year)**
Air fresheners	1,4-DCB	2.1	21	36.5	
	Alternative	0.4	21	7.0	29.5
Toilet bowl blocks (domestic use)	1,4-DCB	1.5	21	26.1	
	Alternative	0.2	21	3.5	22.6
Toilet bowl	1,4-DCB	1.5	21	26.1	

blocks (public toilets)	Alternative	0.2	10	7.3	18.8
Urinal blocks	1,4-DCB	0.7	21	12.2	
	Alternative	0.5	10	18.3	-6.1

Source: section C.2.5
Note: *Positive values indicate savings, negative values indicate costs*

C.3 Summary of available information on alternatives

Identification of potential alternative products and techniques

There are different kinds of air fresheners and toilet blocks non-containing 1,4-dichlorobenzene available in the market, and they dominate the market. With the exception of Camphor many alternative products contain more than 70 different substances, including fillers, anti-caking agents, stabilisers or preservatives. Furthermore, any measure to prevent the mal-odours to be developed or to remove the existing odour can be seen as an alternative technique.

Risks related to alternatives

The available toxicological information for fragrances is very limited for most of the substances. Based on JEFCA's evaluation of fragrances for their use as flavourings in foods it can be concluded that exposure to fragrances from gel-based air fresheners may, in specific cases, be of the same order of magnitude as that from food or even higher. However, the exposure to most of the fragrances can be expected to be low due to their low concentration in the products.

The exposure to the commonly used fragrance d-limonene is expected to be considerably lower than the proposed INDEX (2005) long-term inhalation value. The food intake of the six fragrances discussed in this section is not considered to be a safety concern according to JECFA, and it is unlikely that the additional exposure to these substances from air fresheners would change this conclusion.

One potential concern with fragrances in air fresheners may be their irritating and possibly sensitising properties. However, as also 1,4-dichlorobenzene is an irritant and a weak sensitiser, this seems to be a common concern for many of the deodorising substances.

In conclusion the use of fragrances in air freshener and toilet products is considered safer from a health viewpoint than the use of 1,4-dichlorobenzene.

The non-fragrance constituents of the other products are mainly commonly used chemicals with limited potential for toxicity to humans. In most cases the products only contain low amounts of the substance in question and consequently the exposure is likely to be very low. Thus, the human health risks for non-fragance substances are expected to be lower than for 1,4-dichlorobenzene.

Technical feasibility of alternatives

The technical properties vary between 1,4-dichlorobenzene products and other air freshener and toilet block products. An indicative scoring (Table C33) is used to describe the odour masking, scenting, longevity and cleaning properties of a so called representative product that could be assumed to replace the 1,4-dichlorobenzene products.

These technical properties differ to some extent, which makes the comparison of 1,4-dichlorobenzene and other products challenging. In most of the applications, other products seem to be able to provide the same service. From technical feasibility point of view, the replacement seems to be most difficult in circumstances, where strong odour masking properties are requested. These are mainly high traffic toilets, with poor hygienic conditions.

Economic feasibility of alternatives

Consumer preferences in relation to the characteristics of the products affect their decisions on which product to use. For example, the moth-ball like odour does not appeal to everyone but may be more familiar (and consequently appealing) for older persons (RPA, 2010). It is not possible to take this variety and personal preferences into account in the cost calculations. Furthermore, there is no information available in relation to the differences in odour masking properties and the cleaning function of toilet block products that could be used in the cost estimates.

Considering only the prices and the longevity of the products, some of the available products are estimated to be less expensive per day for the users. This is in line with the fact that other products already dominate the market. For urinals in frequently used toilets with very high flushing frequency other products may be more expensive per day.

D. Justification for action on a EU-wide basis

D.1 Considerations related to human health risks

As described in section B.9, consumers can be exposed to 1,4-dichlorobenzene at home and in public toilets. Cleaning/maintenance personnel or workers managing/supervising public toilets can be exposed to the substance at their place of work. The concern from inhalation exposure to the substance is carcinogenicity. Based on available information 1,4-dichlorobenzene is potentially used in all Member States while the use is higher in some Eastern and Southern Member States. The human health concern is thus an EU-wide problem.

D.2 Considerations related to internal market

Air fresheners and toilet blocks containing 1,4-dichlorobenzene are traded freely and used in all Member States (apart from Sweden, see D3). These products are both manufactured and imported in the EU. An EU-wide measure, like a restriction, would remove the potentially distorting effect that a national ban (or other national measure) may have on the free circulation of goods. In the case of 1,4-dichlorobenzene, these distortions concern the actors of the supply chain of air care products. The second justification is that regulating through EU-wide action ensures that the producers of air care products in different Member States are treated in an equitable manner. Finally, acting at EU level would ensure a 'level playing field' for all producers and importers of these products.

D.3 Other considerations

To date, Sweden has restricted nationally the placing on the market and use of 1,4-dichlorobenzene in chemical products intended to mask odours. According to ECHA's knowledge no other Member State is considering a national ban. To achieve a similar level of protection of human health across the EU, each Member State would need to implement national legislation. However, this would not be cost-effective and contrary to the functioning of the internal market. It appears also administratively more efficient to introduce legislation at EU level.

D.4 Summary

The main reason to act on an EU-wide basis is to reduce the exposure to 1,4-dichlorobenzene to protecthuman health from the effects of 1,4-dichlorobenzene. Furthermore, the fact that the goods need to circulate freely within the EU stresses the importance of the EU-wide action. Currently one Member State has a national restriction on 1,4-dichlorobenzene. Thus, to ensure a similar level of protection of human health across the EU and enhance the good functioning of the internal market, action needs to be taken on a EU-wide basis.

E. Justification why the proposed restriction is the most appropriate EU-wide measure

E.1 Identification and description of potential risk management options

E.1.1 Risk to be addressed – the baseline

Trends in the use of 1,4-dichlorobenze in air fresheners and toilet blocks in the EU

Recent information (RPA, 2010) suggests that consumer use (i.e. in households) is more important in some Member States (central and eastern Europe) than others. Professional use (i.e. in public toilets) is assumed to occur throughout the EU, apart from countries that have in place national legislation banning its use. Sweden is the only MS that has in place this type of legislation (see section B.9.1.1). There is only one manufacturer in the EU that continues to supply 1,4-dichlorobenzene to both EU and non-EU producers of air fresheners and toilet blocks (AMEC, 2012). A small number of EU-based companies (up to 15) continue to produce the final products and an unknown number (possibly hundreds) of companies are importing these products in the EU market (AMEC, 2012).

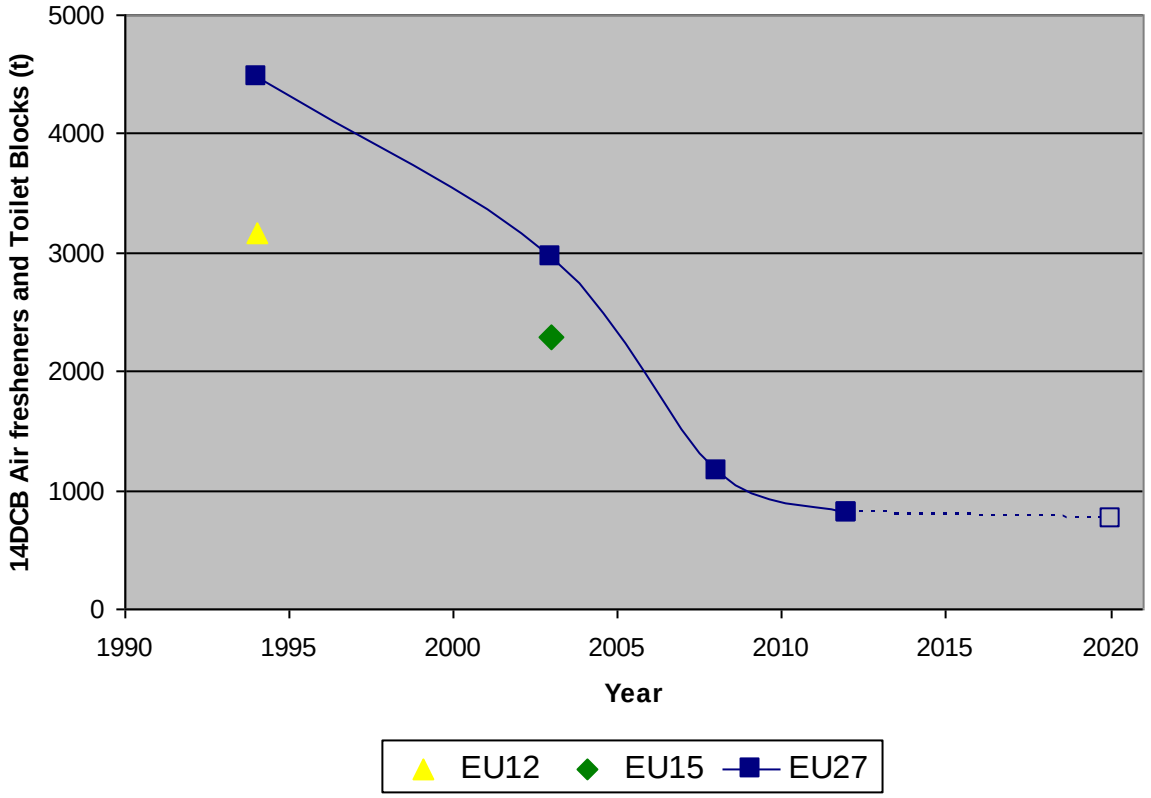


Figure E1: Amounts of 1,4-dichlorobenzene in air fresheners and toilet blocks in the EU [22]

Figure E1 shows the amount of 1,4-dichlorobenzene used in air fresheners and toilet blocks in the EU. This amount has been decreasing since the early nineties, presumably due to the demand for air fresheners and toilet blocks with different characteristics (e.g. more pleasant and varied smell, cleaning properties) which begun to dominate the market. A further decrease in the use of the substance in air fresheners and toilet blocks took place around 2004, when the substance was classified as carcinogen category 2 (Regulation (EC) No 1272/2008, on classification, labelling and packaging of substances and mixtures). Manufacturers of 1,4-dichlorobenzene who supplied producers of air care products and also these producers themselves started to move away from this market. Indeed, some EU companies have either ceased manufacturing the substance or they continue manufacturing but do not supply anymore for production of air fresheners and toilet blocks. Producers of air fresheners and toilet blocks have moved to the production of alternatives. This has incited end users to also look and find alternative products.

[22] Data used in Figure E1 (figures for EU12 and EU15 have been extrapolated to EU27 using population data):

Year	Geographical coverage	Source	Type of information
1994	EU12	EU RAR	Amount of 1,4-dichlorobenzene used for the production of air fresheners and toilet blocks (not considering imports and exports)
2003	EU15	RPA 2010	
2008	EU27	RPA 2010	Amount of 1,4-dichlorobenzene placed on the market in air fresheners and toilet blocks (considering imports and exports)
2012	EU27	AMEC 2012	
2020	EU27	Market information from AMEC 2012	

The estimated amount of 1,4-dichlorobenzene used in the EU for the production of air fresheners and toilet blocks is approximately 808 t/year in 2012, about 713 t/year for professional use (i.e. urinal blocks and air fresheners) and about 96 t/year for domestic use (toilet bowl/toilet rim blocks and air fresheners) (AMEC, 2012). Our information shows that after a dramatic decrease, the use of the substance seems to decline slowly and will probably remain at the same level also in the near future (AMEC, 2012), in the absence of any legislative measure. One reason for continued use seems to be the good performance of the substance in masking bad odours (e.g. in high temperature and low hygienic conditions), in particular in professional use configurations. Other reasons include users' habits or believing that the substance has cleaning properties, whereas in fact 1,4-dichlorobenzene only masks odour and does not provide any cleaning function. This explains continued use mostly in domestic uses (see also section F.2).

Population at risk

The concern to be addressed emerges from the use of 1,4-dichlorobenzene in air fresheners and toilet blocks by consumers and relates to concerns for human health. The main health concern associated to these uses is carcinogenicity. Carcinogenicity by inhalation, explained by a threshold mechanism, was considered to be the effect of highest concern in the risk assessment and risk characterisation was conducted for this effect. The risk characterisation demonstrated that exposure of consumers to air fresheners and toilet blocks containing 1,4-dichlorobenzene are not adequately controlled (section B.10).

Taking account of the hazard profile of the substance, a non genotoxic Category 2 carcinogen, whose carcinogenicity to humans is uncertain, there is concern that the calculated exposure is greater than the derived DNEL for workers in the reasonable worst case scenarios. In addition there is also concern as the derived DNEL for workers is significantly lower than the current IOEL.

In order to estimate the number of consumers in the EU who are at risk from these products, the exposure levels of the different user groups have been compared to the DNELs used for the risk characterisation. Table E38 shows the different groups of exposed populations together with estimates of their number (see Table F45, the size of each group was estimated using the total amount of product in the EU market in 2012). It also shows the modelled exposure levels (calculated with Consexpo, section B.9) and the DNELs for workers and consumers. The table shows that cleaning personnel, toilet attendants and consumers using the substance at home are exposed above the respective DNEL.

Table E38: Estimated population at risk in the EU for 2012 – time averaged exposure levels*

Population at risk	Exposure level (mg/m^3)		DNELs (mg/m^3) ***	Exposed Population ****	Estimated fraction of population above DNEL*****	Population exposed above the DNEL
	Realistic**	Worst case				
Cleaning personnel	0.865	2.25	3.62	21,000	0	0
Toilet attendants	1.75	7.02	3.62	500	28%	140
Consumers using public toilets	0.000367	0.0011	0.64	15,000,000	0	0
Consumers using the substance at home	0.51	3.64	0.64	165,000	49%	80,850

* Workers exposure is averaged over 8 hours, consumers exposure is averaged over 24 hours.
** Calculated mean exposure value for realistic exposure, see section B.9.3.2. The realistic scenarios contain less conservative assumptions for room volumes (for workers) and for exposure duration, room volume and concentration of the substance in other areas of the house (for consumers).
*** DNELs for consumers and professional workers (see section B.10)
**** Estimates taken from Table F45. Populations calculated assuming that 800 t of products per year are used in the EU market.
***** Fraction estimated assuming a normal distribution of the exposed population where the Realistic scenario is taken as the mean and the Worst case scenario as the 95th percentile. Note that the normal distribution was chosen as a proxy for the distribution of the exposed population, which is unknownbut was considered sufficient to provide the order of magnitude of the population exposed above the DNEL.

Impacts from the uses of concern

The use of 1,4-dichlorobenzene in air fresheners and toilet blocks may cause health impacts in the exposed population. The impact assessment concluded on the following impacts (section F.1):

- Possibly some cancer cases due to the mitogenic properties of 1,4-dichlorobenzene (a threshold effect).

Current occupational safety and health related legislation in the EU

Currently, MS have in place different Occupational Exposure Limits (OEL) for 1,4-dichlorobenzene (section B.9.1.1). These OELs are higher than the DNELs derived for workers in this report and are thus not regarded as fully protective according to REACH. The Strategy for Limiting Risks (EC, 2008) has recommended that the Commission Scientific Committee on Occupational Exposure Limits (SCOEL) reviews the current EU OEL. If the OEL was to be adapted in order to be more protective for workers in the applications of concern, this could change the baseline situation for these applications. The current indicative OEL does not provide adequate protection to workers employed in public toilets where 1,4-dichlorobenzene

is used, considering the derived DNEL value for workers (see Table E38 for "cleaning personnel" and "toilet attendants").

Conclusion

The use of 1,4-dichlorobenzene in air fresheners and toilet blocks has decreased by about 80% in the past 20 years. It has been replaced by alternatives which now dominate this market. Currently, some 800 t of the substance is used per year for these applications in the EU.

The concern from the exposure of consumers to air fresheners and toilet blocks containing 1,4-dichlorobenzene are currently not controlled i.e. exposure is not below the derived DNEL. Legislative measures which aim to warn the users of the risks associated with their particular use (e.g. labelling according to CLP) are in place, and have contributed to reduce the amounts of 1,4-dichlorobenzene products in the market. However, they have not eliminated the exposure from the uses of concern.

Although the amounts placed on the market and the related exposed population have declined, the use is expected to continue at the current level. Given that the exposure associated with the use of the substance in air fresheners and toilet blocks is greater than the derived DNEL, action to reduce this exposure is warranted. The section below elaborates on which type of action is the most appropriate.

E.1.2 Options for restrictions

This section presents a preliminary screening of the various restriction options identified. The characteristics of each option are discussed to assess which options can be discarded at an early stage and which options should be assessed further. The scope and target population of these options are presented in the Table E39. In addition, one more risk management option, has been identified. It is presented in section E.1.3, under Other EU-wide risk management options.

Other identified options for restrictions focussed on use conditions under which the products could continue to be placed on the market, subject to compliance with these conditions (RPA, 2010). The conditions assessed were a weight limit or a concentration limit for the 1,4-dichlorobenzene based air fresheners and toilet blocks or temperature and ventilation conditions for the locations where these products would be used[23]. It would be very difficult to ensure that these conditions were in place and there would thus be an apparent risk that RMOs built on such conditions would not provide sufficient means to reduce exposure to safe levels. They would then not remove the health concern. In consequence, RMOs with specific use conditions were not included in the preliminary screening.

[23] Weight limit: the exposure is assumed to be reduced due to reduced surface of the product. However users could still use e.g. two products instead of one in order to achieve the same odour masking effect.
Concentration limit: the concentration in 1,4-dichlorobenzene is limited by using an adequate inert filler, e.g. salt. In the case of salt the exposure to 1,4-dichlorobenzene is even increased when salt dissolves in water (RPA, 2010).
Ventilation conditions: if good ventilation conditions are in place, there is less a need to use a product with such strong odour masking properties like 1,4-dichlorobenzene. This option would require costly solutions (e.g. installation of mechanical ventilation system).
Temperature conditions: the longevity of the toilet block is longer in lower temperatures, leading to lower exposure. This option would require costly solutions (e.g. installation of air conditioning).

Table E39: Restriction options

Option	Restriction on	Scope	Target population	Amount placed On the market (t/year)*
1	Consumer uses	Domestic use: • Air fresheners • Toilet bowl blocks	• Consumers using the products at home	96
2	Professional uses	Use in public toilets: • Air fresheners • Urinal blocks • Toilet bowl blocks	• Cleaning personnel • Toilet attendants	713
3	Consumer and professional uses	Air fresheners, urinal blocks and toilet bowl blocks in domestic use and public toilets	Consumers at home, cleaning personnel and toilet attendants	809

Source: AMEC, 2012

Option 1: Restriction on placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks for **consumer use**

This option addresses the exposure of consumers from domestic use of air fresheners and toilet blocks (in that case toilet bowl blocks for domestic use). The placing on the market of these products for consumers would be forbidden. Air fresheners and toilet blocks for professional use (i.e. in public toilets) would continue to be placed on the market. Consumers would need to use alternative products. Producers and suppliers of 1,4-dichlorobenzene based air fresheners and toilet blocks for consumer use would loose this market segment, but they would continue to supply the professional market.

This option would remove exposure for consumers using the products at home. Exposure from these products to the other considered populations (cleaning personnel, and toilet attendants) would remain unaltered. Our information shows that other products, suitable for consumers, are available in the market (section C). For consumer use the costs of the alternatives are comparable to the cost of 1,4-dichlorobenzene or even cheaper for both air fresheners and toilet bowl blocks (Table C37).

The end users concerned would be able to comply with the restriction, since alternative products are readily available. Since 1,4-dichlorobenzene based air fresheners and toilet blocks would remain in the market a labelling requirement would be needed specifying that these products are only for professional use. Regarding enforceability, it would be difficult to ensure that these products are used only by professionals. In many cases products labelled "for professional use only" can in practice be purchased and used also by consumers.

Option 2: Restriction on placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks for **professional use**

This option addresses the exposure of professionals employed in public toilets (cleaning/maintenance personnel and toilet attendants). Consumers using public toilets are exposed below the DNEL for consumers and are not considered at risk, according to our assumptions on exposure (section B.9) The placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks for professional use would be discontinued. These products would still be placed on the market for consumer use. Professionals will need to use alternative air fresheners and toilet blocks, which would entail additional costs (Table C37). Producers and suppliers of 1,4-dichlorobenzene based air fresheners and toilet blocks would continue to supply the consumer market. The impact to producers and suppliers would be bigger with respect to option 1 since the professional market is a lot bigger than the consumer market (Table E39).

This option would remove the risk for professionals employed in public toilets. Risk from these products to consumers using air fresheners and toilet blocks at home will remain. Given the estimates on population exposed above the DNEL (Table E38) this option has clearly an inferior risk reduction capacity in comparison to option 1. In addition, from an enforcement point of view, it will be difficult to ensure that these products are not used by professionals since they will be freely available in the market for consumer use.

Option 3: Restriction on placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks for **consumer and professional use**

This option addresses the exposure of all populations addressed in this report, i.e. both consumers and professional workers. In this option air fresheners and toilet blocks containing 1,4-dichlorobenzene would not be placed on the market. This would impact producers, suppliers and end users of 1,4-dichlorobenzene based air fresheners and toilet blocks who would need to look for alternative substances or alternative techniques.

This option would remove exposure from 1,4-dichlorobenzene in the uses of concern for both professional workers and consumers. It would entail costs to the actors concerned to substitute the substance with some alternative tecniques or products. For consumers there is a variety of suitable products and the switch to these products will even produce some savings (Table C37). Professionals will need to find an alternative suitable to their specific use conditions and the switch will be accompanied with some costs, the same as for option 2 above (Table C37). At a first approximation this option is easy to implement and enforceable, especially because the products will be completely removed from the market. There will be no need to ensure that these products are used by a specific category of end users (e.g. professionals only or consumers only), as is the case for options 1 and 2.

E.1.3 Other EU-wide risk management options than restriction

Voluntary agreement

An agreement could be proposed to industry (producers, suppliers and end users) of 1,4-dichlorobenzene based air fresheners and toilet blocks, to voluntarily phase out the use of these products without any legislative intervention. A timeline could be set which would include checking progress and reporting until complete phase out of the use. In theory some marginal use could still remain after the phase out period.

As described in E.1.1, the use of 1,4-dichlorobenzene in air fresheners and toilet blocks has already been phased out to a large extent, meaning that the phasing out that could reasonably be expected by a voluntary instrument has already taken place. It can thus be assumed that the uses that continue to exist today would not be removed by voluntary action (otherwise this should have already happened after the change in the classification to carcinogen category 2). Moreover, in practical terms, such an agreement would require that an EU institution negotiates the terms of the agreement with industry. However, according to ECHA's understanding no EU institution has such a mandate. Finally, it would be difficult to identify

importers and include them into a voluntary agreement. For these reasons it seems that a voluntary agreement would not be an efficient instrument to manage risks from the use of 1,4-dichlorobenzene in air fresheners and toilet blocks.

Limitations on the placing on the market of products classified as carcinogenic category 2

Germany has in place legislation that aims to control (but does not prohibit) selling of products containing substances classified as category 2 carcinogens, like 1,4-dichlorobenzene (E.1.1). These substances or mixtures can be sold only to a person who knows how to use them and cannot be sold to minors or in self service machines. These measures can contribute to control the risks depending on the use of the substance, but not in the case of 1,4-dichlorobenzene, for which exposure to the substance is unavoidable, given its use as deodoriser in domestic and public toilets.

Occupational Exposure Limit

This option addresses the exposure of professionals working in public toilets and as a consequence the exposure of consumers using them. From that point of view it is comparable with restriction option 2 on professional use. In this option an EU-wide OEL would be set in order to control risks from exposure of workers to the substance. This OEL would be risk based, i.e. the DNEL for safe use would need to be taken into account for setting the OEL. However, even if the indicative EU OEL would change, this does not automatically lead to the adoption of the same value by all MS. In addition, employers would be required to ensure that the OEL was taken into consideration in the worker risk assessment/exposure assessment under safety and health legislation.

In practice, if sufficiently low OEL would be set, it would be very difficult to continue the use of 1,4-dichlorobenzene and comply with the requirements of the OEL, i.e. it would be a "de facto" ban. This might not be clear to all the actors concerned, thereby affecting the implementability of this option. Public toilets and also the related cleaning/maintenance works are often run by SMEs or micro enterprises. The level of familiarity with safety and health requirements may not be adequate to ensure strict compliance with the requirements and protection of workers. If the use of 1,4-dichlorobenzene products would continue, it would be difficult to design and expensive to implement the required changes to reduce workers' (i.e. toilet attendants and cleaners) exposure levels to a level below the DNEL. This may require significant changes to the ventilation and design of the toilets. Finally, effective enforcement would require lot of resources, due to necessary inspections and exposure monitoring in a number of public toilets. This option will not be assessed further.

The option above could be combined with a restriction on consumer uses, similar to option 1. It would then remove the risk to consumers with sufficient certainty, while setting conditions of safe use for professionals. However, it would be expensive to implement and enforce for reasons discussed above. This option will not be assessed further.

E.2 Assessment of risk management options

The preliminary evaluation presented in the previous section shows that only options 1, 2 and 3 are in principle capable of reducing the risk with sufficient certainty. These three options are assessed further.

E.2.1 Restriction option 1 (Consumer uses)

E.2.1.1 Effectiveness

E.2.1.1.1 Risk reduction capacity

E.2.1.1.1.1 Changes in human health risks/impacts

This option would remove the human health concerns associated with the consumer use of the substance in air fresheners and toilet blocks. More specifically, exposure above the DNEL of consumers using these products at home (estimated at about 80,850 persons in 2012) would be avoided (Table E38), together with the related impacts described in the baseline. Air fresheners and toilet blocks for consumer use would not be available in the market after the restriction. Substances used in the alternative consumer products have been identified and they are considered safer, from a human health point of view than 1,4-dichlorobenzene (section C.2).

E.2.1.1.1.2 Changes in the environmental risks/impacts

Not relevant for this proposal.

E.2.1.1.1.3 Other issues

Not relevant for this proposal.

E.2.1.1.2 Proportionality

E.2.1.1.2.1 Technical feasibility

The technical characteristics of 1,4-dichlorobenzene have been qualitatively compared to a "representative" product, i.e. a products that would function in the most similar way. This comparison was made using three criteria; deodorising (further described as odour masking and scenting), longevity, and cleaning properties (Table C33). Whereas 1,4-dichlorobenzene has clearly better odour masking properties, other products provide a big variety and better "quality" of scents. The longevity of the products varies depending on the product and application (air freshener, toilet bowl block for domestic or public use, and urinal block). Finally, alternative toilet blocks offer additional cleaning properties, which is not the case for 1,4-dichlorobenzene.

It is assumed that end users will prefer to switch to products that resemble as far as possible to 1,4-dichlorobenzene. In reality, some of the users will shift to other products (see section C for an overview of those) that may have even better performance (especially considering the cleaning properties) than 1,4-dichlorobenzene. They could also use alternative techniques (e.g. additional cleaning, better ventilation or other types of urinals) in addition to, or in combination with such products. In conclusion, other air fresheners and toilet blocks are already on the market (and in fact dominate the market comparing to 1,4-dichlorobenzene) for consumer uses. The technical feasibility of this restriction option has been clearly established.

E.2.1.1.2.2 Economic feasibility (including the costs)

There are no additional costs for consumers (or society) since other products are already in the market at competitive prices (Table C36) for consumer use. In fact, consumers can save if they switch to cheaper alternatives. These savings are estimated at about 30 €/year for air fresheners and at about 23 €/year for toilet bowl blocks for domestic use per household if there would be a 100% shift from 1,4-dichlorobenzene to an alternative (Table C37).

Assuming that 1,4-dichlorobenzene products and the other products are functionally equivalent, switching to these would result in an increase in consumer surplus of about €2.8 million per year for domestic use (Table E40[24] and Table F48). Significant increases are associated with the lower costs of the alternatives compared with 1,4-dichlorobenzene, which stimulate significant increases in the use of these products. In conclusion, this option would increase the consumer surplus of domestic users (i.e. a saving) In addition, there are

[24] The figures presented here and in chapters C and F are estimates of the order of magnitude of costs that could be expected, based on the prices of the lower-end alternatives present in the market.

potentially reductions in cancer cases and in liver, kidney and/or nasal epithelium lesions that were not quantified due to insufficient information in humans (see section F1).

Table E40: Costs for consumer uses in 2012 (option 1)

Uses	**Change in consumer surplus (€)***		**Amount of 14DCB placed on the market (t/year)****
Air fresheners (domestic use)	2,500,000		96
Toilet bowl blocks (domestic use)	290,000		
Total	2,790,000		

Sources:
** Estimates taken from Table F49 (figures might not agree due to rounding)*
Note: Positive values indicate savings, negative values indicate costs
*** AMEC, 2012*

E.2.1.1.2.3 Other issues

Not relevant for this proposal.

E.2.1.2 Practicality

E.2.1.2.1 Implementability

As shown in section E.1.1, the use of 1,4-dichlorobenzene in air fresheners and toilet blocks has declined, inferring that the market has already moved to alternative products. For that reason there are no concerns regarding implementability of the restriction. Consumers, which are the end users concerned, will be able to comply with this restriction. Since 1,4-dichlorobenzene based air fresheners and toilet blocks will remain on the market, they will need to be clearly labelled as "for professional use only" (or another adequate labelling phrase).

E.2.1.2.2 Enforceability

The enforcement of the placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks for consumers would be difficult because the products would still be available for professionals. In reality, many products labelled "for professional use only" can in practice be purchased and used also by consumers.

E.2.1.2.3 Manageability

There are no specific concerns as to the manageability of this restriction. The way to implement it (by switching to alternative substances) is clear and understandable to all actors involved.

E.2.1.3 Monitorability

The monitoring of the restriction for 1,4-dichlorobenzene based air fresheners and toilet blocks would be done through enforcement, and no additional monitoring is envisaged.

E.2.1.4 Overall assessment of restriction option 1

This option fulfils the criteria used in the assessment of the risk management options. It does not completely remove the risk, since the products of concern will continue to be used by professionals, but it decreases the exposure for consumers to levels below the DNEL, and consequently reduces its related health impacts. It introduces savings to the society, as feasible alternatives are estimated to be less expensive to use. The health benefits are also estimated to be positive. Some concerns remain regarding the enforceability of this option.

E.2.2 Restriction option 2 (Professional uses)

E.2.2.1 Effectiveness

E.2.2.1.1 Risk reduction capacity

E.2.2.1.1.1 Changes in human health risks/impacts

This option would remove the human health concerns associated with the professional use of the substance in air fresheners and toilet blocks. More specifically, exposure above the DNEL of professionals employed in public toilets (estimated at about 140 toilet attendants in 2012), would be avoided (Table E38), together with the related impacts described in the baseline. Air fresheners and toilet blocks for professional use would not be available in the market after the restriction. Substances used in the alternative products have been identified and they are considered safer, from a human health point of view than 1,4-dichlorobenzene (section C.2).

E.2.2.1.1.2 Changes in the environmental risks/impacts

Not relevant for this proposal.

E.2.2.1.1.3 Other issues

Not relevant for this proposal.

E.2.2.1.2 Proportionality

E.2.2.1.2.1 Technical feasibility

The technical feasibility of this restriction option is similar to option 1, i.e. the technical feasibility of this option is clearly established. One technical issue to be mentioned is the longevity of the alternatives, which is worse than the longevity of 1,4-dichlorobenzene for both toilet bowl blocks and urinal blocks (Table C33).

E.2.2.1.2.2 Economic feasibility (including the costs)

For professional users additional costs might be required due to additional cleaning or due to a switch in more expensive alternatives in order to achieve similar odour masking performance. Alternatives for some applications are of comparable price or cheaper (air fresheners and toilet bowl blocks) but for other applications alternatives are more expensive (urinal blocks). The main strength of 1,4-dichlorobenzene that is not considered in the calculations on additional cost of alternatives is the very efficient odour masking, requested in situations of heavy traffic or inadequate cleaning (RPA, 2010). Alternative products perform less well in masking odours than 1,4-dichlorobenzene. However, it is questionable if mal odours should be simply masked instead of cleaning due to hygiene reasons (but also due to other reasons e.g. blockage of pipes, etc.).

Our calculations show that if professional users are able to switch to alternatives they can make savings of the order of about €19 per year for toilet bowl blocks and €30 per year for air fresheners. However, in the assessment of economic impacts, it is assumed that the whole professional use of toilet blocks are in urinals, and no 1,4-dichlorobenzene toilet bowl blocks would be used in public toilets. The alternative urinal blocks are estimated to be about €6 per year more expensive than alternatives (Table C37).

Assuming that professional users are fully informed on the properties of the products, and purchase 1,4-dichlorobenzene products because they attach a genuinely higher value to their performance, the cost of a restriction which prevents them to choose 1,4-dichlorobenzene products in future is equal to the 'consumer surplus' associated with their consumption (i.e. the additional value which users place on of 1,4-dichlorobenzene products compared with the alternatives). In other words, it is assumed that there are no perfect alternatives to 1,4-dichlorobenzene products for professional use. It is estimated that loss in consumer surplus for professional users is around €4 million per year (Table F48). However, there are potentially reductions in cancer cases and in liver, kidney and/or nasal epithelium lesions that are not quantified.

Table E41: Costs for professional uses in 2012 (option 2)

Uses	Change in consumer surplus (€)*	Amount placed On the market (t/year)**
Air fresheners (professional use)	-1,300,000	713
Urinal blocks (professional use)	-2,700,000	
Total	-4,000,000	713

**Estimate taken from Table F49 (figures might not agree due to rounding)*
Note: Positive values indicate savings, negative values indicate costs
***Source: AMEC, 2012*

E.2.2.1.2.3 Other issues

Not relevant for this proposal.

E.2.2.2 Practicality

E.2.2.2.1 Implementability

As shown in section E.1.1, the use of 1,4-dichlorobenzene in air fresheners and toilet blocks has declined, inferring that the market has already moved to alternative products. For that reason there are no concerns regarding implementability of the restriction. Industry actors and end users concerned will be able to comply with this restriction. Producers of 1,4-dichlorobenzene based products might need some transition time in order to adapt their production processes and techniques to the alternatives. Distributors and suppliers of these products might also benefit from a transition period in order to sell products in stock. 1,4-dichlorobenzene air fresheners and toilet blocks typically have an expiry limit of 1 year. A

transition period of 12 months is thus considered reasonable for this option. As a consequence, it is expected that the relevant actors will not have high stocks of 1,4-dichlorobenzene based products that will remain unsold due to the implementation of this restriction option.

E.2.2.2.2 Enforceability

The enforcement of this restriction option would be difficult because the products would still be available in the market for consumers and hence available also to professionals.

E.2.2.2.3 Manageability

There are no specific concerns as to the manageability of this restriction. The way to implement it (by switching to alternative substances) is clear and understandable to all actors involved.

E.2.2.3 Monitorability

The monitoring of the restriction for 1,4-dichlorobenzene based air fresheners and toilet blocks would be done through enforcement, and no additional monitoring is envisaged.

E.2.2.4 Overall assessment of restriction option 2

This option fulfils to some extent the criteria used in the assessment of the risk management options. It does not completely remove the risk, since the products of concern will continue to be used by consumers, but it decreases the exposure for professionals below the DNEL, and consequently reduces its related health impacts. The costs to society are estimated to be higher than the avoided health impacts. Concerns remain regarding the enforceability of this option.

E.2.3 Restriction option 3 (Consumer and professional uses)

E.2.3.1 Effectiveness

E.2.3.1.1 Risk reduction capacity

E.2.3.1.1.1 Changes in human health risks/impacts

This option is expected to remove the human health concerns associated with the use of the substance in air fresheners and toilet blocks. More specifically, exposure above the DNEL of consumers using these products at home, (estimated at about 80,850 persons in 2012), and of professionals employed in public toilets (estimated at about 140 toilet attendants in 2012), will be avoided (Table E38), together with their related impacts. Indeed these products will not be available in the European market after the restriction for neither professional use (in public toilets) nor consumer use. Substances used in the alternative products have been identified and they are considered safer from a human health point of view than 1,4-dichlorobenzene (section C.2).

E.2.3.1.1.2 Changes in the environmental risks/impacts

Not relevant for this proposal.

E.2.3.1.1.3 Other issues

Not relevant for this proposal.

E.2.3.1.2 Proportionality

E.2.3.1.2.1 Technical feasibility

See options 1 and 2.

E.2.3.1.2.1 Economic feasibility (including the costs)

This option is a combination of options 1 and 2. As discussed in option 1, assuming that 1,4-dichlorobenzene products and the alternatives are functionally equivalent (identical), switching to the alternatives would result in an increase in consumer surplus of just over €2.8 million per year for domestic use (Table F49). As discussed in option 2, assuming that professional users are fully informed on the properties of the products, and there are no suitable alternatives to 1,4-dichlorobenzene products for professional use, it is estimated that the loss in consumer surplus for professional users is around €4 million per annum. Consequently, the total cost to the society is estimated to be €1,2 million per annum.

In addition, there are potentially reductions in cancer cases and in liver, kidney and/or nasal epithelium lesions that have not been quantified.

Table E42: Costs for consumer uses and professional uses in 2012 (option 3)

Uses	Change in consumer surplus (€ per year)*	Amount placed on the market (t/year)**
Air fresheners (domestic use)	2,500,000	96
Toilet bowl blocks (domestic use)	290,000	
Air fresheners (professional use)	-1,300,000	713
Urinal blocks (professional use)	-2,700,000	
Total	-1,200,000	809

**Estimates taken from Table F48 and Table F49(figures might not agree due to rounding)*
Note: Positive values indicate savings, negative values indicate costs
***Source: AMEC, 2012*

E.2.3.1.2.3 Other issues

Not relevant for this proposal.

E.2.3.2 Practicality

E.2.3.2.1 Implementability

As discussed in option 2 above, a transition period of 12 months is considered reasonable also for this option.

E.2.3.2.2 Enforceability

The enforcement of the placing on the market of 1,4-dichlorobenzene based air fresheners and toilet blocks can be assessed mainly by verifying if producers, importers and distributors (wholesalers and retailers) still supply these products, e.g. by checking the product information

in their catalogues or packages. It is not foreseen that enforcement authorities should verify if an air freshener or toilet block contains 1,4-dichlorobenzene by testing. In addition, this restriction option is in-line with the non-inclusion in Directive 98/8/EC on biocidal products for the use of the substance in moth-balls which concerns exactly the same products. The non-inclusion decision resulted in the phase out of the use in mothballs, however the products remained in the market for use as air fresheners and toilet blocks. Option 3 is the only one that would remove the products from the market for the uses of concern.

In the original proposal by the dossier submitter (ECHA) a concentration limit was not proposed for this option. It was then considered that a concentration limit would be necessary if 1,4-dichlorobenzene was present as an impurity in low concentrations in the products concerned (or in alternative products). In the products concerned 1,4-dichlorobenzene is the only active substance. The 1,4-dichlorobenzene based air fresheners and toilet blocks are products containing typically 98% of the substance (the remaining being dye). In some cases products with as low as 70% of 1,4-dichlorobenzene have been found in the market (the remaining being a soluble filler like salt). Finally, "hybrid" products with concentration in 1,4-dichlorobenzene of the order of 50% are still in the R&D stage (in these products 1,4-dichlorobenzene could be found together with surfactants, detergents and binders, RPA, 2010). It could be envisaged to set a sufficiently low concentration limit, which would force users to stop manufacturing these products because of reduced efficiency and high costs. Based on the advice received from the Forum for exchange of information on enforcement, a concentration limit would enhance the enforceability of the restriction (Forum 1st advice, October 2012, Forum 2nd advice, April 2013). In consequence a concentration limit of 1% w/w was included in the proposed restriction wording[25].

E.2.3.2.3 Manageability

There are no specific concerns as to the manageability of this restriction. The way to implement it (by switching to alternative techniques or alternative products) is clear and understandable to all actors involved.

E.2.3.3 Monitorability

The monitoring of the restriction for 1,4-dichlorobenzene based air fresheners and toilet blocks will be done through enforcement, and no additional monitoring is envisaged.

E.2.3.4 Overall assessment of restriction option 3

This option fulfils to a great extent all the criteria used in the assessment of the risk management options. This option would remove completely the risk from the uses of concern. The annual costs of this option are estimated to be about €1.2 million while the benefits would be between €10.9 and €26.2 million per year. This restriction option is considered proportional to the risks considering the costs to the society, as well as implementable and enforceable.

E.3 Comparison of the risk management options

A simplified scoring approach is presented in Table E43 for the three options assessed in detail. The options are given a score using as criteria the effectiveness (broken down to risk reduction capacity and proportionality) and the practicality (broken down to implementability and enforceability) of each option. For a definition of these criteria see the Guidance for the

[25] For mixtures, the limit of concentration which triggers classification of the mixture as a category 2 carcinogen is ≥ 1,0 % (Regulation EC No 1272/2008 on classification, labelling and packaging of substances and mixtures). This option could be matched with a concentration limit of 1% w/w, below which the mixture would not be considered as carcinogenic. Methods to determine the quantitative composition of 1,4-dichlorobenzene are available in the market and are reliable (e.g. gas chromatography, Ullmann, 2006). Moreover their detection and quantification limits typically go beyond the above mentioned threshold for classification of a mixture (EPA, 2003, Spectrum, 2012).

preparation of an Annex XV dossier for restrictions (ECHA 2007). Based on this qualitative ranking, option 3 fulfils the criteria better than options 1 and 2.

Table E43: Comparison of the risk management options

	Effectiveness		Practicality	
	Risk reduction	**Proportionality**	**Implementability**	**Enforceability**
Option 1 Restriction on consumer use	++	+++	+++	+
Option 2 Restriction on professional use	+	-	+++	+
Option 3 Restriction on consumer AND professional use	+++	++	+++	+++

Legend - - : does not fulfil the criterion
+ : slightly fulfils the criterion
++ : fulfils the criterion largely
+++ : completely fulfils the criterion

Table E44 summarises the quantified information presented in Chapter F together with the main conclusions on the proportionality of the three restriction options. It includes only impacts on the consumer surplus. On other words, e.g. issues related to enforceability and other potential health impacts are excluded.

Table E44: Summary of information informing SEAC assessment

Restriction Option	**Exposures to 1,4-dichlorobenzene need to be reduced?**	**Costs (€)**	**Benefits**	**SEAC conclusion**
Option 1 **Restriction on consumer use**	*Yes*	*2.7 million** *2.0 million***	*Positive but figures not available*	*Proportionate*
Option 2 **Restriction on professional use**	*Yes*	*-4.0 million** *-0.6 million***	*Positive but figures not available*	*Taking account of the inferred health benefits and the scale of costs involved, SEAC concluded that the proposal may not be considered to be disproportionate.*

Option 3 **Restriction on consumer AND professional use**	*Yes for domestic* *Yes for professional*	*-1.2 million** *1.4 million***	*Positive but figures not available*	*Taking account of the inferred health benefits and the scale of costs involved, SEAC concluded that the proposal may not be considered to be disproportionate.*

Note: positive values indicate savings; negative values indicate costs
* consumer surplus approach
** substitution cost approach

E.4 Main assumptions used and decisions made during analysis

For the main assumptions used and decisions made during the analysis see:

- Section B.5 for the DNELs calculations
- Section B.9 for the exposure assessment
- Section C for the costs of the alternatives
- Section F for the qualitative and quantitative assessment of the health impacts

E.5 The proposed restriction(s) and summary of the justifications

The use of 1,4-dichlorobenzene in air fresheners and toilet blocks presents health concernsto humans. The main health concern is carcinogenicity.The risk characterisation demonstrated that exposure of workers and consumers to air fresheners and toilet blocks containing 1,4-dichlorobenzene are not controlled i.e. exposures are not below the DNELs.

The following populations were identified to be exposed at levels above the DNEL for carcinogenicity by inhalation, considered as the effect of highest concern:

- Cleaning personnel
- Toilet attendants
- Consumers using the products at home

The impact assessment concluded on the following impact:

- Possibly some extra cancer cases due to the mitogenic properties of 1,4-dichlorobenzene (a threshold effect).

Three restriction options were considered in detail. An option targeting consumer (i.e. domestic) use only, an option targeting professional uses (mainly in public toilets) and a combination of these two options. The third option was found as the most appropriate risk management option. This option is the only one that removes exposures from all populations of concern and is considered easier to enforce than the other two options. Whereas the proposed option might entail a bigger loss in consumer surplus than option 1, it is considered proportional. Some non-quantified possible health benefits have been identified, too. These are reductions in cancer cases and in liver and/or kidney lesions. These reductions were not quantified, though.

A restriction on both consumer (domestic use) and professional uses (mainly in public toilets but also in other indoor areas) of these products is proposed. The proposed restriction would remove exposure to 1,-4-dichlorobenzene from air fresheners and toilet blocks, together with their related impacts. These products will not be available in the European market after the restriction for neither professional use nor consumer use.

The proposed restriction is well targeted to the identified uses of concern, and would not unduly affect uses or actors in the supply chain which are not associated to these uses (see section F3 – F5). Different kinds of products and techniques for both 1,4-dichlorobenzene air fresheners and toilet blocks are available in the market, and the use of alternatives is considered safer from a health viewpoint than the use of 1,4-dichlorobenzene. Administrative and enforcement costs are considered to be low.

In conclusion:

A restriction is considered to be the most appropriate risk management option to manage exposure emanating from the use of 1,4-dichlorobenzene in air fresheners and toilet blocks.

A proposal for an Annex XVII entry is given below:

Designation of the substance, of the group of substances or of the mixture	**Conditions of the restriction**
1,4-dichlorobenzene EC No. 203-400-5 CAS No. 106-46-7	1. Shall not be placed on the market, or used, as a substance or constituent of mixtures in a concentration equal to or greater than 1 % by weight where the substance or the mixture is intended to be used as an air freshener or to de-odourise toilets, homes, offices and other indoor public areas. 2. Paragraph 1 shall apply from {*date* corresponding to 12 months after the Commission Regulation amending Annex XVII to REACH Regulation enters into force}.

This option would apply 12 months after the amendment of REACH Annex XVII comes into force.

F. Socio-economic Assessment of Proposed Restriction

In this section, the human health and economic impacts of the proposed restriction (restriction option 3 proposing a ban on both domestic and professional use) are assessed. In some cases, information related to domestic use (restriction option 1) and professional use (restriction option 2) is also presented separately. The assessment is based on the estimated annual amounts of 1,4-dihclorobenzene placed on the market in 2012 in air fresheners and toilet blocks. It is estimated that the annual amount used in 2020 without regulatory action would be around 90% of what it is currently (see the baseline in E.1.1). The declining trend in using 1,4-dichlorobenzene air fresheners and toilet blocks affects both benefits and costs of the proposed restriction in the same proportion, and consequently a longer temporal scope is not needed in the assessment. In section F7 a sensitivity calculation has been made for illustrative purposes.

In addition to economic and human health impacts, some other relevant impacts are described qualitatively.

F.1 Human health impacts

From experimental animal studies it can be concluded that the main health concern related to the use of 1,4-dichlorobenzene toilet blocks and air fresheners would be carcinogenicity. However, given the hazard profile of the substance the risk of carcinogenicity to humans is uncertain. The substance also has irritating properties (eye irritant) and is a possible weak sensitiser. The risk assessment (see section B), including the risk characterisation, is used as a basis for the description of human health impact in this section.

In the Annex XV report prepared by ECHA a quantification of health impacts based on effects on the lung function in humans was included. This assessment took data from Elliot *et al.* (2006) as a starting point. The study is described in section B but was not used in the risk assessment as it was not regarded to be suitable for DNEL derivation. Furthermore RAC did not find the study roboust enough to be used for quantification of impacts. For that reason the quantitative assessment by ECHA has been deleted from the main Background Document and placed in Annex 8 as its methodological approach remains valid.

Table F45 summarises the estimated populations exposed to 1,4-dichlorobenzene. In addition, populations estimated to be exposed above the DNELs are presented in section E.1 (Table E38).

Table F45: Assumptions on the exposed populations in 2012

Population group	Amount placed on the market[1] (t/year)	Use locations[3]	Exposed persons per use location	Exposed population[7]
Consumers exposed at homes	96	68,682	2.4[4]	164,836
Toilet attendants	713[2]	512,414	0.001[5]	512
Toilet cleaners			0.042[6]	21,351
Males visiting public toilets			28[9]	14,497,658[8]

Total	**809**	**581,096**		**14,684,357**

[1] *Source: AMEC, 2012*

[2] For this calculation air fresheners and toilet blocks are considered as identical products (also in terms of exposed populations).

[3] Assuming a continuous use of one product per location throughout a year. Use locations = $\frac{q}{w} \div \frac{365}{t}$ (q=amount placed on the market (t/year), w=weight of 1 product (80 g), 365=days per year, t=: longevity (days)
Domestic use: 1 product per location, i.e. toilet
Professional use: 1 product per urinal (1 toilet may contain several urinals)

[4] The average size of household in the EU in 2010 is 2.4 (Eurostat, 2012)

[5] Assuming 1 toilet attendant per 1000 urinals

[6] Assuming that urinals with 1,4-dichlorobenzene are cleaned once a day for five minutes each by cleaners exposed for two hours (120 minutes) per day. In other words one cleaner is able to finalise 24 urinals in a day (120/5=24).
Exposed persons per urinal = $\frac{1}{(120\,\text{min}/\,5\,\text{min})} \approx 0.042$.

[7] Population at risk = Use locations X Exposed persons per use locations

[8] Assuming 6% of urinals treated with 1,4-dichlorobenzene (RPA, 2010). 6% of the male population of the EU, i.e. 241,627,637(Eurostat 2012), is assumed to be exposed.

[9] Calculated by dividing the exposed male population by number of urinals (use locations).

Possible health impacts due to systemic toxicity and carcinogenicity

All effects identified from the experimental animal studies with 1,4-dichlorobenzene are considered to have thresholds. That means that even if DNELs are exceeded, the quantification of impacts is not straight forward. For this reason the experimental data used for the risk assessment was only used for describing impacts on human health in a qualitative manner.

To further understand the possible impact on human health by the exposures described in part B, Table F46 shows the margins of safety between the modelled exposures (section B.9.3) and the lowest exposure levels where adverse effects were seen in the experimental studies (LOAELs). The LOAELs have been adjusted for differences in exposure time, respiratory rate and in absorption but no other adjustment (such as for other inter- or intraspecies differences) have been made.

There is very little information from long-term studies in humans that can be used for the impact assessment. Hsiao *et al.* (2009; referred to in section B5.6.2) investigated biomarkers for liver and kidney function in workers without any clinical symptoms. It was found that the levels of both liver and kidney biomarkers were elevated in the 1,4-dichlorobenzene-exposed workers, indicating that occupational exposure may affect the function of these organs. It is difficult to predict the precise impacts related to elevated biomarker levels on kidney and liver function and to what extent such functional disturbances would lead to morbidity. However, the modelled exposure levels of professionals working in public toilets and consumers in this report are higher than those presented by Hsiao *et al.* (2009). Consequently, mild lesions cannot be excluded in exposed populations.

Apart from Hsiao *et al.* (2009) no relevant information related to systemic toxicity of 1,4-dichlorobenzene in humans has been found. No epidemiological studies of carcinogenicity in populations exposed to 1,4-dichlorobenzene have been identified, which makes carcinogenicity difficult to assess in terms of impacts. However, as margins between modelled exposures and adjusted LOAELs are limited a number of cancer cases due to the mitogenic properties of 1,4-dichlorobenzene cannot be excluded.

For illustrative purposes we have estimated expected cancer cases based on the unit risk values established by U.S EPA (2006), which builds on a non-threshold approach (Annex 7).

Table F46: Margin of safety between modelled exposures for 1,4-dichlorobenzene and adjusted LOAELs from experimental animal studies

Exposed group	Exposure range* (mg/m^3)	LOAEL** ($ppm/mg/m^3$)	LOAEL adjusted*** (mg/m3)	Margin of safety (MOS)
Toxicity of liver and kidney				
Workers	1.5-13.7	300/1840	277	20-185
Consumers	0.33-5.63	300/1840	98	17-297
Carcinogenicity				
Workers	1.5-13.7	300/1840	554	40-369
Consumers	0.33-5.63	300/1840	197	34-597

*Consexpo modelling results, see section B.9.3
**JBRC, 1995
***LOAELs were adjusted for differences between human and experimental conditions in exposure time. They were further adjusted for differences in absorption between rats, mice and men and for workers a higher respiratory volume at light work was assumed. For further details please see section B.11.

Conclusions on human health impacts

Based on experimental studies and exposure estimates which exceed DNELs it can be concluded that the use of 1,4-dichlorobenzene-containing air fresheners and toilet blocks may possibly induce cancer in some individuals who are sufficiently exposed to high levels repeatedly.

F.2 Economic impacts

The main economic impact from the proposed restriction comes from the need for the users of 1,4-dichlorobenzene products to cease their use and switch to alternatives. This cost element is considered to cover most societal costs, and other cost elements are described qualitatively.

The alternatives to 1,4-dichlorobenzene products differ in terms of their technical characteristics and performance, and users can be expected to respond in different ways to the restriction. Table F47 presents estimates of the financial costs of switching to alternative products. The calculations are based on alternatives that are assumed to be most likely to replace 1,4-dichlorobenzene products due to technical similarity. They are also chosen near the lower end of the price range. For further information on alternatives, including calculations for annualised additional cost per user, see Chapters C.2.3 (Technical feasibility) and C.2.4 (Economic feasibility).

In this section, it is assumed that the whole professional use of toilet blocks are in urinals, and no 1,4-dichlorobenzene toilet bowl blocks would be used in public toilets. This is based on the information on RPA (2010), identifying urinal blocks as the main use in public toilets. There is no data available on the potential amount of 1,4-dichlorobenzene toilet bowl blocks used in the public toilets. However, there is no data available to exlude this possibility either. From the estimates on the additional cost per user per year presented in Table C.46 (€6.1 cost for urinal blocks per year; €18.8 savings for toilet bowl blocks for public toilets per year), it can be seen that allocating some of the professional use for toilet bowl blocks instead of urinals, the total cost per year could be significantly decreased.

Table F47: Financial implications of switching to 1,4-DCB alternative products in 2012

Product group	1,4-DCB placed on the market (t)	Use locations*	Additional cost (€ per user per year)	Total cost (€ per year)	Restriction Option**	
Air fresheners (domestic use)	83	59,692	29.5	1,763,750	1	3
Toilet bowl blocks (domestic use)	13	8,990	22.6	203,125		
Air fresheners (professional use)	100	71,918	29.5	2,125,000	2	
Urinal blocks (professional use)	613	440,497	-6.1	-2,679,688		
Total	**809**	**581,096**		**1,412,188**		

Source for the amounts: AMEC (2012)

* *assuming a continuous use of one product per user throughout the year and weight of 80 grams per product*

** Option 1: Restriction on consumer uses
Option 2: Restriction on professional uses
Option 3: Restriction on both professional and consumer uses

Note: *Positive values indicate savings, negative values indicate costs*

It can be seen from Table F47 that switching from 1,4-dichlorobenzene urinal blocks to the next best alternative is estimated to cost €6.1 per urinal per year (an increase of around 50 per cent when compared with the current costs of using 1,4-dichlorobenzene urinal blocks (Table C37). However, alternatives to 1,4-dichlorobenzene air fresheners and toilet bowl blocks for domestic use are actually estimated to cost significantly less to use over the course of a year than the existing 1,4-dichlorobenzene products (reductions of around 80 per cent for air fresheners and 90 per cent for toilet bowl blocks).

Two basic explanations are possible for the continued use of 1,4-dichlorobenzene products when cheaper alternatives are already available. The first is that domestic and professional users prefer the characteristics of 1,4-dichlorobenzene products and are prepared to pay higher prices to secure them. In this case, the implication is that, although there might be alternative products on the market, none provides the exact service afforded by 1,4-dichlorobenzene products in terms of, say, odour-masking capability. The second explanation is that domestic and professional users are misinformed about the technical performance of 1,4-dichlorobenzene products relative to the alternatives and would use the cheaper products

if they had full information. This implies that the alternatives on the market are equally as good as 1,4-dichlorobenzene products but that users are unaware of this.[26]

If we assume that users are fully informed, and purchase 1,4-dichlorobenzene products because they attach a genuinely higher value to their performance, the cost of a restriction which prevents users to choose 1,4-dichlorobenzene products in future is equal to the loss of 'consumer surplus' associated with their consumption. Consumer surplus is the additional amount that domestic and professional users would be willing to pay for 1,4-dichlorobenzene products over and above what they currently pay. It reflects the value to users of the specific properties (or effectiveness of same) which 1,4-dichlorobenzene products have which the alternatives do not. It is a function of the price domestic and professional users pay, how much they use, and how sensitive their demand is to variations in price (the demand 'elasticity').

Table F48 presents estimates of the size of the consumer surplus associated with the current use of 1,4-dichlorobenzene products. The calculations are based on the annual amounts placed on the market and the prices of 1,4-dichlorobenzene and alternative products in 2012[27]. A price elasticity of demand of -1 is assumed implying that 1,4 dichlorobenzene-based products are a normal good.

[26] A third possibility is that users are unaware of the risks associated with the use of the product, and if they did, they would switch; this is a variant of the other two scenarios, since a lack of knowledge of the risks associated with use does not explain why the price difference alone is not sufficient to cause the switch.

[27] A first approximation to the size of consumer surplus when the price elasticity of demand is -1 is given by the equation (amount placed on the market / weight of the product) x price of the product x 0.5. A price elasticity of demand of -1 means that a one per cent increase in price leads to a one per cent reduction in demand. See the appendix to this chapter for further explanation.

Table F48: Change in consumer surplus from not using 1,4-dichlorobenzene air fresheners and toilet blocks in 2012 – assuming domestic and professional users have perfect information

Product group	kg used currently (q)	Price of product (€ per kg) (p)	Price elasticity of demand	Change in consumer surplus (€) (qxp/2)	Restriction Option**	
Air fresheners (domestic use)	83,000	26.3	-1	-1,091,450	1	3
Toilet bowl blocks (domestic use)	12,500	18.8		-117,500		
Air fresheners (professional use)	100,000	26.3		-1,315,000	2	
Urinal blocks (professional use)	612,500	8.8		-2,695,000		
Total	**808,000**			**-5,218,950**		

Source for the amounts: derived from AMEC, 2012
** Option 1: Restriction on consumer uses
Option 2: Restriction on professional uses
Option 3: Restriction on both professional and consumer uses
Note: *Positive values indicate savings, negative values indicate costs*

Assuming domestic and professional users are fully informed, the loss in consumer surplus associated with switching from their use of 1,4-dichlorobenzene air fresheners and toilet blocks is estimated to be around €5.2 million per year. This potential loss of consumer surplus is the high-end estimate of the costs for restricting the air fresheners and toilet blocks. The calculation is sensitive to the assumption about the price elasticity of demand – a higher elasticity reduces the estimate of consumer surplus lost, whereas a lower elasticity increases it.

If we assume domestic and professional users are unaware of the effective substitutes, and/or misperceive the technical characteristics of 1,4-dichlorobenzene products relative to the alternatives, then there will not generally be a consumer surplus loss directly from having to switch to an alternative product. This is because in reality, the alternative (under these assumptions) performs just as well as the original, and once users switch to alternatives, the utility they derive from their use will be just as high as with existing 1,4-dichlorobenzene products. There might, however, be a change in consumer surplus associated with the change in cost arising from using the new product. When price (cost) changes, there will also generally be a demand effect – price increases tend to reduce demand, while reductions increase it – and these will be associated with changes in consumer surplus. These demand changes are commonly assumed to be small enough that they can be ignored. However, when price differences between products are as significant as those referred to here, it is better to estimate the change in consumer surplus additionally.

Table F49: Change in consumer surplus from not using 1,4-dichlorobenzene air fresheners and toilet blocks in 2012 – assuming domestic and professional users have imperfect information

Product group	kg used currently (q1) 1,4-DCB	Price of product (€ per kg)	Price of product (€ per kg equivalent)	Price elasticity of demand	kg equivalent used after restriction (q2) Alternative	Change in consumer surplus (€)*	Restriction Option **	
		1,4-DCB (p1)	Alternative (p2)					
Air fresheners (domestic use)	83,000	26.3	5.0	-1	150,190	2,477,649	1	3
Toilet bowl blocks (domestic use)	12,500	18.8	2.5		23,333	291,146		
Air fresheners (professional use)	100,000	26.3	5.0		180,952	2,985,119	2	
Urinal blocks (professional use)	612,500	8.8	13.1		306,250	-2,009,766		
Total	**808,000**				**660,726**	**3,744,148**		

Source for the amounts: AMEC, 2012

* Change in consumer surplus is estimated as follows:
For price increases: (q1-q2)(p2-p1)/2
For price reductions: q1(p1-p2) + (q2-q1)(p1-p2)/2

** Option 1: Restriction on consumer uses
Option 2: Restriction on professional uses
Option 3: Restriction on both professional and consumer uses

Note: *Positive values indicate savings, negative values indicate costs*

Table F49 suggests that, assuming that 1,4-dichlorobenzene products and the alternatives are functionally equivalent, switching to the alternatives would result in an increase in consumer surplus of just over €3.7 million per year. Significant increases are associated with the lower costs of the alternatives compared with 1,4-dichlorobenzene, which stimulate significant increases in the use of these products. The use of professional urinal blocks is estimated to fall given the 50 per cent higher price of alternatives, meaning a reduction in consumer surplus.

It is worth considering the validity of assumptions underpinning each of these sets of estimates and their implications for the results and conclusions. First, a simple analysis comparing the

financial implications of alternatives to the current products suggests overall prices would fall relative to the baseline. However, if domestic and professional users are fully informed about the characteristics of 1,4-dichlorobenzene products, any savings are more than offset by the loss in the value of these products (€5.2 million per year). However, evidence from AMEC (2012) and RPA (2010) suggests that some users incorrectly perceive that 1,4-dichlorobenzene products have cleaning properties, and that they might be purchasing for habitual or other non-economic reasons. We might expect this behaviour to be most likely in domestic situations, since professional users generally have an incentive to identify the most appropriate product for their circumstances and to use cheaper alternatives when they are available – professional use might well reflect the particular needs of the use locations in question, therefore (e.g. difficult cleaning conditions generating strong odours). This implies that the loss in consumer surplus for professional users of around €4 million per year (full information, see option 2 in Table F48) could be the more likely result than the gain of around €1 million per year in the imperfect information case (option 2 in Table F49).

An additional assumption made in the analysis above is that prices for 1,4-dichlorobenzene and alternative products are 'correct', in the sense that they reflect opportunity costs of production. This is a standard assumption, but evidence from Amec (2012) suggests this might not be the case. This is because it reports that capital equipment currently used for the production of 1,4-dichlorobenzene-based air fresheners and toilet blocks could not be converted for any alternative use, and hence is effectively 'sunk'. However, Amec (2012) also report that this equipment has a positive market value which would be lost if the market for 1,4-dichlorobenzene products was restricted. This positive market value for sunk capital implies a divergence of prices from marginal cost, since the opportunity cost of sunk investments is actually zero. This loss will be felt by capital owners (firms) but is actually a transfer to producers from consumers, who face higher prices than otherwise. It has a value equal to the annualised value of residual capital, which is a function of the present value of the capital, the discount (interest) rate and the residual life of the capital. Assuming five companies[28] producing 1,4-dichlorobenzene air fresheners and toilet blocks in the EU, with capital equipment currently worth on average €55,000 per firm, with five years of life remaining. This gives a total current market value of capital of €275,000. The annualised value of this capital is a function of the market discount rate (or return on capital required). This is not simple to observe or calculate, and depends on a number of factors (such as investor risk). A figure of 10 per cent generates an annualised value of €72,000, with values of €63,000 and €91,000 derived from rates of five per cent and 20 per cent respectively (suggesting that the calculated value is not highly sensitive to choice of discount rate). This figure is an additional cost of the restriction to the figures reported in Table F48 and Table F49 above. Although a comparison with those figures indicates this is not a significant additional cost, it might well represent a significant cost for individual firms (see section F5).

Finally, as mentioned above, these estimates are sensitive to the choice of figure for the price elasticity of demand. No empirical evidence has been available to indicate what value is appropriate in this case. A figure of -1.0 is standard practice in economics in the absence of other evidence, as it indicates a 'normal good'. Demand is expected to be more elastic where there are many effective substitutes, whereas it is lower when a product provides specialist functions, or when the product accounts for a small part of total expenditure on a service (e.g. cleaning). Taken together, these points again might suggest that the imperfect information figure is most appropriate for domestic use, whereas the full information-based figure is valid for professional use, but in the absence of more reliable, this is speculative.

As discussed in section C.2.5 (Economic feasibility of alternatives), some users of 1,4-dichlorobenzene may wish to opt for additional cleaning to remove the unpleasant odours which are no longer masked by 1,4-dichlorobenzene. This assumes that alternatives with weaker odour masking do not offer the same service. This additional cleaning would entail extra costs, but would also have benefits in terms of additional cleanliness and (replacement)

[28] The number of companies producing 1,4-dihclorobenzene products in the EU is not known. AMEC (2012) reports it to be maximum of 15, but identified only one.

odour-masking. Users are free to decide on the most appropriate level of cleaning in their own situations following any change in the availability of 1,4-dichlorobenzene products. The consumer surplus-based approach to estimating the economic impacts of changes in availability accounts for this implicitly, and hence it is not necessary to consider these costs additionally in this analysis.

The proposed restriction (option 3) does not introduce specific administrative requirements to authorities or market actors, and the administrative costs are assumed to be low. The enforcement may be done with existing resources and the related costs are assumed to be low as well (see section E.2.3.2.2 on enforceability of the proposed restriction).

Uncertainties in the calculation of consumer surplus

Table F50 shows the variation in the values of the consumer surplus when different assumptions regarding the value of the elasticity and the shape of the demand curve are used. Regarding elasticity three options were taken. A relatively inelastic demand (-0.75), a relatively elastic demand (-1.25), as well as the original assumption of unitary elasticity.

Regarding the shape of the demand curve, both a linear demand curve (which was used for the consumer surplus calculations in the previous paragraphs) and a non-linear demand curve are considered as possible shapes of the demand curve. A linear demand curve has the following form: $q(p) = a - bp$ (where q is quantity, p is price and a and b are parameters), and consumer surplus = $q1 * (a/b - p1) * 0.5$. The parameters can be calculated as follows: $b = -\eta * (q1/p1)$ (where η = own price elasticity of demand) and $a = q + bp$.

A non-linear demand curve has the following general functional form: $q(p) = Ap^{\eta}$, where A is a parameter. Consumer surplus is then given by the integral of this function evaluated between the prevailing price (n) and choke price (m), i.e. consumer surplus = = $A/(\eta+1) * (m^{(\eta+1)} - n^{(\eta+1)})$. For a given price and quantity on the curve, $A = q1p1^{-\eta}$. A choke price of 2 was used for the calculations.

As can be seen from the table below, the uncertainty analysis indicates that although the precise values of the consumer surplus are subject to some variation, the conclusions from the original consumer surplus analysis are robust since the sign and order of magnitude of consumer surplus estimates are stable.

Table F50: Sensitivity of consumer surplus size

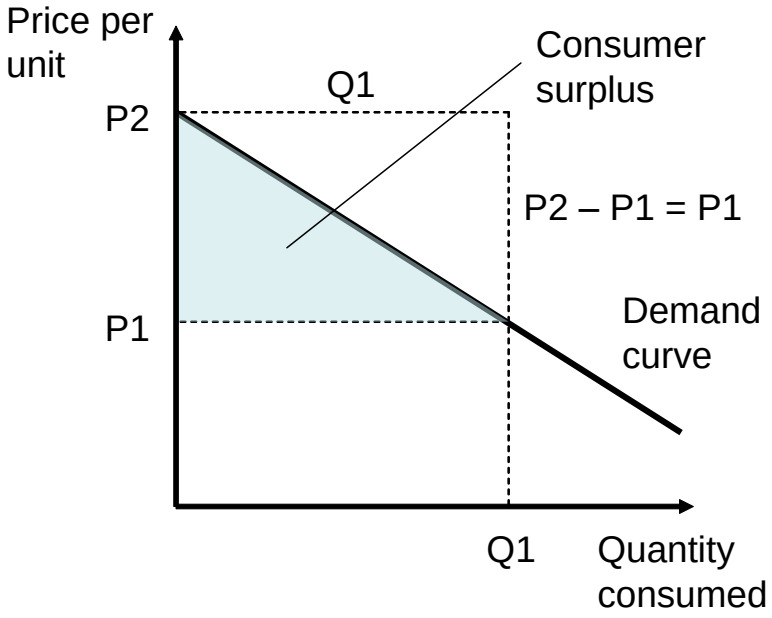
Elasticity	**-0.75**	**-1.00**	**-1.25**
Linear demand **Costs (€m)**			
Option 1	3.1	2.8	2.6
Option 2	-5.3	-4.0	-3.5
Option 3	-2.2	-1.2	-1.0
Non-linear demand **Costs (€m)**			
Option 1	3.3	4.1	5.1

Option 2	-6.1	-5.6	-5.1
Option 3	-2.7	-1.5	0.0

Appendix to Chapter F

Figure F A1 below is a simplified graphical representation of consumer surplus and explains how it can be calculated approximately using information on the price and quantity consumed of a good. The demand curve for a good shows the relationship between the price of a good and how much of it consumers demand. A higher price reduces demand – as the price falls, demand increases. The slope of this curve reflects how sensitive the quantity consumed (demanded) is to changes in price – that is, the price elasticity of demand. It is conventional to assume that a good has a price elasticity of demand of -1, meaning that a one per cent change in price leads to an opposite one per cent change in demand (i.e. a price increase results in a demand decrease and *vice versa*). Goods which are basic commodities and/or which have few substitutes might have elasticities between 0 and -1 (meaning that demand is less sensitive to changes in price), whereas goods which are relative luxuries or for which there are many substitutes might have elasticities greater than -1 in absolute terms (meaning that demand is more sensitive to changes in price).

Figure F A1 Graphical representation of consumer surplus



A negative price elasticity of demand effectively means that additional consumption has reduced additional value compared with existing levels – consumers are willing to pay less for additional consumption as the amount of consumption increases. This means that 'earlier' amounts of consumption have a higher value than 'later' amounts. The area under the demand curve represents the value of each additional unit of consumption. Thus, in Figure F A1, consumers would be willing to pay prices closer to P2 for relatively low quantities consumed, but would only be prepared to pay lower prices towards P1 for additional amounts of consumption.

However, in general, consumers are only required to pay a single price for each unit of a product they consume. With a market price of P1, consumers will be paying P1 for every unit

of a product they consume up to Q1, even though they value that level of consumption in total by more than this – as shown by the area under the demand curve. This excess of how much consumers value their consumption compared with how much they are required to pay for it is termed 'consumer surplus', and is denoted in Figure F A1 by the shaded area.

The value of the consumer surplus associated with the consumption of a product can be calculated approximately as follows. A starting position can be assumed where the price of the product is P1, resulting in a quantity consumed of Q1. With a price elasticity of demand of -1, a 100 per cent increase (i.e. a doubling) in price (from P1 to P2) would result in a 100 per cent decrease in the quantity consumed, i.e. would reduce demand to zero. Thus P2 is the price at which the demand curve in the figure crosses the y axis of the graph. As can be seen from the figure, the shaded consumer surplus area is given by the equation (Q1 × P2 / 2), or half the product of the current price (P1) and the quantity consumed (Q1). This is equal to half the total market value of consumption.

F.3 Social impacts

Restricting the placing on the market of 1,4-dichlorobenzene air fresheners and toilet blocks affects the employment of those who are currently producing them, or manufacturing flaked form of 1,4 –dichlorobenzene to be used in this production. According to AMEC (2012), one company is known to manufacture flaked 1,4-dichlorobenzene in the EU, and the number of companies producing the 1,4-dichlorobenzene products is below 15 (up to five producing toilet blocks and up to 10 air fresheners). It is not known how many of these producers have also alternatives in their portfolio. However, one company is known not to provide alternatives.

The number of importers of 1,4-dichlorobenzene toilet blocks into the EU is assumed to be below 10. There is no similar estimate available for the air fresheners. Most of the importers are assumed to import both 1,4-dihclorobenzene and alternative products. (AMEC, 2012)

Based on indications from a limited number of stakeholders, RPA (2010) assumed that several hundreds staff is employed in producing 1,4-dichlorobenzene products in the EU. The order of magnitude of the estimate could be correct considering the overall estimated market value of the products of €10,2 million[29], profit margins of the suppliers, the estimated price of 1,4-dichlorobenzene of €1,000-3,000 per tonne[30] and the annual labour costs of e.g. €12,000[31]. Furthermore, information from one producer suggests that 15 employees (for this company) may become redundant if the proposed restriction is implemented (RPA, 2010). However, there is no reason to assume differences in the labour inputs required in the production of 1,4-dichlorobenzene and alternative products (or other products/services if the end-users will not opt for the alternative air fresheners and toilet blocks), and the negative impact to employment in the supply chain of 1,4-dichlorobenzene products should mainly be offset by positive impacts in other sectors. In other words, the impacts on employment are mainly distributional and not a cost to the society as such. However, the redeployment of staff always includes some adjustment costs, e.g. related to temporary unemployment of workers when finding new jobs, although it is difficult to place a figure on these adjustment costs in practice.

F.4 Wider economic impacts

According to a manufacturer of 1,4-dichlorobenzene (RPA, 2010), the restriction on placing on the market of air fresheners and toilet blocks may cease the whole flaking of 1,4-dichlorobenzene in the EU (see section B.2.2 for description of production process of 1,4-dichlorobenzene). As 1,4-dichlorobenzene is a side product of 1,2-dichlorobenzene, this could

[29] Air fresheners: 183 tonnes / 0.08 kg x €2 = €4,6m; Toilet bowl blocks: 12,5 tonnes / 0.08 kg x €1,5 = €230,000; Urinal blocks: 612,5 tonnes / 0.08 kg x €0.7 = €5,4m
[30] Source for the price of 1,4-dichlorobenzne: RPA, 2010
[31] Examples of average monthly labour costs are available e.g. at http://epp.eurostat.ec.europa.eu/portal/page/portal/labour_market/labour_costs/main_tables

affect also the manufacturing of 1,2-dichlorobenzene, if alternative markets are not found for the flaked or liquid form of 1,4-dichlorobenzene. According to the manufacturer, this would impact the competitiveness of the EU manufacturers of 1,2-dichlorobenzene (RPA, 2010). It is possible that being located in the EU will become a disadvantage if the markets of flaked 1,4-dichlorobenzene will be concentrated outside the EU. However, the existing non-EU markets for flaked 1,4-dichlorobenzene, as well as the markets for liquid form would still be available. It is also possible that flaked form will be continued to be used in the EU to produce 1,4-dichlorobenzene air fresheners and toilet blocks for export.

F.5 Distributional impacts

The proposed restriction would impact different actors in the supply chain including manufacturers of 1,4-dihclorobenzene, producers of air fresheners and toilet blocks, resellers and the users of these products (both domestic and professional). In addition, some of the actors in the supply chain of alternative products will be impacted. The distributional impacts are not societal costs as such, as many of the negative impacts faced e.g. by producers of 1,4-dihclorobenzene products would be compensated by impacts on the producers of the alternative products.

Many of the impacted actors are assumed to be small and medium size enterprises (SME), including the producers of 1,4-dichlorobenzene products. Some of these producers may be significantly impacted by the proposed restriction as they may need to cease the production, especially if they do not produce also the alternatives and are not able to adapt their production. They might also face a reduction in the market value of their assets used in the production of 1,4-dichlorobenzene products (although these costs are not true economic costs – see section F2). Based on the information from the producers of the 1,4-dichlorobenzene products, RPA (2010) lists the following impacts from adapting the production to produce alternatives:

- costs of new machinery;
- production downtime;
- staff training costs;
- costs of numerous new materials for alternative formulations and of other inputs due to the longer production processes required;
- marketing costs; and
- employment costs if the restriction were to be implemented in the short-term.

Many of these cost elements are reflected in the prices of alternatives, and consequently considered in the calculations for the financial costs (Table F47) and changes in the consumer surplus (Table F48 and Table F49). The impact of the proposed restriction on employment is briefly discussed in section F.3 (Social impacts). The loss in the market value of capital equipment was estimated in section F2 to be in the region of €70,000 per year, or €275,000 over the course of the remaining lifetime of the equipment (€55,000 per company).

1,4-dichlorobenzene air fresheners and toilet blocks are used by both consumers and professional users including cleaning companies. Many of the professional users are probably SMEs. As the additional costs per user is assumed to be low (highest for the urinal blocks €6 per year per urinal), the financial impacts on users is small. No specific SME related impacts have been identified.

According to RPA (2010), at least the consumer use appears to be confined to Southern and possibly Eastern Member States. Consequently both costs and benefits related to consumer

use would be higher in these areas. It is not known if this applies also to professional use but this could be likely. Hence, the distribution of the costs and benefits of the restriction are likely to take place in Southern and Eastern EU Member States.

F.6 Main assumptions used and decisions made during analysis

Assumptions on the volumes of 1,4-dichlorobenzene and exposed populations are discussed below. Many of the main assumptions for assessment of human health and economic impacts are described under corresponding chapters. Furthermore, the assumptions for DNEL setting are described in section B.5.11 and for exposure assessment in section B.9. The uncertainty related to prices and longevity of 1,4-dichlorobenzene and alternative products is discussed in section C.

Volume of 1,4-dichlorobenzene in air fresheners and toilet blocks

The estimated amounts of 1,4-dichlorobenzene placed in the market in air fresheners and toilet blocks are based on the consultations of RPA (2010) and AMEC (2012). They are derived partly from estimates of some producers of 1,4-dichlorobenzene based products. Especially the estimate on the imported amounts is uncertain. However, as the amounts affect both costs and health benefits of the proposed restriction, this uncertainty does not impact the cost-effectiveness of the proposal.

Exposed population

The estimates on the volumes of 1,4-dichlorobenzene are used to derive the population at risk. The estimates are based on assumption that one 1,4-dichlorobenzene product weights 80 grams and that one product is used constantly by a user. The assumptions as well as some results are presented in Table F45 and Table AX60. Changing the assumptions on the populations at risk affects the inferred health benefits, while the costs remain the same. For instance, assuming breaks in the use of 1,4-dichlorobenzene products (i.e. not continuous use over whole year) would increase the population at risk. The health impacts could be similarly increased, if the exposure remains in a level where impact occurred.

F.7 Uncertainties

See Annex 8.

F.8 Conclusions on the socio-economic impacts

Based on experimental studies and exposure estimates which significantly exceed DNELs it can be concluded that the use of 1,4-dichlorobenzene-containing air fresheners and toilet blocks may affect liver and kidney and possibly induce cancer in some individuals.

SEAC has considered the two separate methodological approaches to analysing the costs of the restriction presented in the Background Document. The first is based on the financial costs of switching from 1,4-dichlorobenzene to an alternative (the so called 'substitution cost' approach), whilst the second is based on the consumer surplus change arising from the requirement to cease the use of 1,4-dichlorobenzene and switch to an alternative.

Although the two approaches can be considered as alternative methods for estimating costs, given the uncertainties surrounding the evidence and data necessary for their application they can be considered as complementary approaches in the sense that they provide a check

(triangulation) of the magnitude of costs (losses involved). In this respect the two approaches are in general consistent.

For the combined restriction, the analysis produces an overall estimate using the consumer surplus approach of €1.2m cost per year. With regards to the substitution (financial) costs approach, as the alternatives in general are less expensive, the financial impact is estimated to be a saving of €1.4 m per year for the combined restriction.

The quantitative analysis of the benefits of the restriction which was included in the original Annex XV report submitted by ECHA is based on a health impact assessment using an 'impact pathway' type methodology. This estimates the change in physical health impacts due to changes in exposures as a result of the restriction. The approach is based on linking quantitative relationships between exposure and the health impact of interest. This general procedure is widely used for the assessment of benefits related to air and other environmental pollutants and is considered to be an appropriate methodological approach. The particular health impacts considered in the quantitative health impact assessment are mortality impacts associated with decreases in lung functioning arising from exposure to 1,4-dichlorobenzene. It should be noted that this is not the same health endpoint (carcinogenicity) which was considered in the risk assessment. The use of the lung function endpoint for the assessment of benefits appears to be based on the greater availability of data for deriving quantitative estimates. However, SEAC noted the RAC conclusion that there is insufficient evidence to support the link between exposure to 1,4-dichlorobenzene and reduced lung function. Therefore, SEAC did not consider it appropriate to use the results of the quantitative health impact assessment to inform the SEAC position.

Overall, the cost assessment suggests that under the substitution cost approach, any positive (or even zero) value of health benefit would be sufficient to justify the restriction on proportionality grounds, though a higher level of health benefit would be needed in the case of the consumer surplus approach in order to justify the (positive) costs in this case.

For the proposed restriction on domestic use, SEAC concluded that this measure is proportionate, and can do so without the need to consider any quantitative estimate of health benefits in terms of lung function or other health endpoint. This is a consequence of the RAC conclusion that exposures to 1,4-dichlorobenzene need to be reduced for domestic users and that the proposed restriction on domestic use is the most appropriate risk management measure. This infers, qualitatively at least, that there are positive health benefits. The inferred health benefits, combined with the cost savings (consumer surplus gain) found in the cost analysis, allow SEAC to support the view that the proposal to restrict for domestic use is proportionate.

The evidence is less clear for the options to restrict professional use only or to jointly restrict domestic and professional use. While RAC has concluded that there is a need to reduce exposures for professional users, there is limited evidence to support any conclusions on health impacts. In this case, inferred health benefits do not offer sufficient justification for proportionality, since the analysis shows that professional users will incur positive costs as a result of the proposed restriction (in contrast to cost savings for domestic use). Therefore, the cost benefit analysis suggests that costs outweigh quantified benefits for both options involving professional use. This corresponds with the outcome of the cost benefit analysis done by RPA (2010) on a restriction on professional use which found that the costs of such a restriction would outweigh the resulting benefits to health. Based on their analysis RPA recommended against a restriction on professional uses. However, taking account of the scale of costs involved in the combined restriction proposal across all of the EU (-€1.2 million costs according to the consumer surplus approach and €1.4 million savings according to the substitution costs approach), SEAC considered that a discretionary case may be made for considering the proposal to not be disproportionate.

G. Stakeholder Consultation

G.1 Consultation during the preparation of the restriction proposal

Environment Infrastructure UK Limited (AMEC) carried out a stakeholder consultation, at the request of ECHA, in February 2012. This was part of the ECHA's project to assess abatement costs of certain hazardous substances. The goal of the consultation was to seek information on market data for 1,4-dichlorobenzene (quantities, prices, number of actors and trends) and for alternative products including costs of alternatives. Questionnaires were developed for:

- Producers, importers and suppliers of 1,4-dichlorobenzene based air fresheners and toilet blocks
- Cleaning companies currently or formerly using 1,4-dichlorobenzene based air fresheners and toilet blocks

In total 81 organisations were contacted, however only 17 provided information and 3 questionnaires were completed and returned. Table G51 lists the contacted stakeholders and companies who provided information.

Table G51: Organisations that were contacted by AMEC

Company	Information provided?
Aarti Industries / Alchemie Europe	
A.I.S.E	✓
Allegri Cleaning	
Allpura – Verband Schweizer Reinigungs-Unternehmen	
Amity International	
ANCST Legacoop	
Arkema	
Aronia N.V.	
Asociacion Profesional de Empresas de Limpieza – ASPEL	
Associação Portuguesa Facility Services- AFPS	
Biltrec SA	
Bogdol GMBH	
Bundesinnung der Denkmal-, Fassaden- und Gebäudereiniger – BIG	
Bundesinnungsverband des Gebäudereiniger-Handwerks – BIV	
Ceda Chemicals	

Company	**Information provided?**
Česka Asociace Úklidu A Cištění – CAC	
Chevron Phillips	✓
CLANDREX SERVICES	✓
Cleaning and Support Services Association – CSSA	
Cleenol	✓
Danish Service Industries Federation – DI	
DOSIM SA	
Dr. Sasse Gebäudereinigung AG	
EA Supplies	
Ecological	
Eurochlor	✓
European Federation of Cleaning Industries	
Evans Vanodine	✓*
FARE	
Fédération des Entreprises de Propreté et services associés – FEP	
Fédération Luxembourgeoise des Entreprises de Nettoyage – FLEN	
Federazione Imprese di Servizi – FISE – ANIP	
Finnish Property Maintenance Association	
Fresh Products	
Gebäudereinigung – Krankenhausservice Zehnacker GmbH	
GEPE-Gebäudereinigung PETERHOFF	
Global Group	
GRG – Grossberliner Reinigungs-Ges. Hans-Jochen Schwarz KG	
Halliburton	
HECTAS Gebäudedienste Stiftung & Co. KG	

Company	**Information provided?**
Initial (part of Rentokil)	
ISS Mediclean Limited	
James Briggs UK	✓
Jeyes	✓
Kalvei	
Klüh Cleaning GmbH	
Lanxess	✓
lassila-tikanoja	✓*
LSR Associates Ltd	
LUXELACALIS	
Master Cleaning Services	✓
MATISZ	
Multiclean	✓
NHO Service	
Obrtna Zbornica Slovenije	
OCS Support Services Limited	
Ondernemersorganisatie Schoonmaak en Bedrijfsdiensten – OSB	
ORKA d.o.o.	
PCC Rokita	✓
Piepenbrock Unternehmensgruppe GmbH & Co. KG	
Plural Servicepool GmbH	
Polish Cleaning Chamber of Commerce	
Principle Cleaning Services Limited	
Recochem	✓
Reiwag Facility Services GmbH	
Rtkpalvelu	

Company	Information provided?
SCUOLA NAZIONALE SERVIZI	
Serviceentreprenörerna – ALMEGA	
Sky Chemicals	
SSS	
Staples Disposables Ltd UK	✓
Stormindustriediensten	✓
TAKATA-PETRI	
Tampen and Tampen	
Ticona GmbH	
Toray International Europe GmbH	
TOSOH EUROPE B.V.	
Trust Hygiene	✓
Union Générale Belge du Nettoyage – UGBN/ABSU	
WISAG GEBÄUDEREINIGUNG HOLDING GMBH & CO. KG	
Zakład Produkcyjny IRBIS Dulanowicz	✓*

Source: AMEC, 2012
Notes:
* Questionnaire completed and returned.

The aim of this consultation was to complement the RPA consultation (see below) in areas where information was missing or was incomplete. For that reason the pool of stakeholders was more narrow (for example there was no need to consult again Member State competent authorities or manufacturers of 1,4-dichlorobenzene, since it was considered that sufficient information was already available).

The main results of the consultation regarding market information supports in general the findings of RPA and the assumption that there is a decreasing trend in the use of 1,4-dichlorobenzene in the uses of concern (AMEC, 2012). Not much additional information was found for example on the amounts of 1,4-dichlorobenzene imported to EU in air fresheners and toilet blocks.

G.2 RPA consultation

RPA was contracted by the EC to perform an economic and social analysis of the use of 1,4-dichlorobenzene in air fresheners and toilet blocks. This included a consultation of interested parties, which was carried out from September 2009 to April 2010. The stakeholders contacted were Member State competent authorities, manufacturers of 1,4-dichlorobenzene, producers, importers and suppliers of 1,4-dichlorobenzene based products, relevant associations and end users.

The main objective of RPA's work was to evaluate a restriction targeting only the domestic use of 1,4-dichlorobenzene based air fresheners and toilet blocks and excluding professional uses. That is why the consultation was designed to retrieve information mainly on domestic use, even if in practice information on professional uses was also collected and analysed. The following three types of questionnaires were prepared and sent to the stakeholders (1,4-dichlorobenzene questionnaires, DG ENTR):

- for Competent Authorities of EU Member States
- for manufacturers and importers of 1,4 dichlorobenzene
- for producers, suppliers and importers of air fresheners and toilet blocks

Information from the consultation was used to estimate the size of the EU market for air fresheners and toilet blocks for both consumer and professional uses, estimate the trends of this market in the future and describe the impacts of a restriction targeting these uses.

Information from stakeholders was used to estimate the size of the EU market (in tonnes) for air fresheners for consumer use (83 t) and toilet rim blocks for consumer use (17 t). Estimates for professional uses were also done by deducting these figures from the total amount of substance used for the production of air fresheners and toilet blocks.

Some of the general results of this consultation are given below:

- Manufacturers of 1,4-dichlorobenzene : only two EU manufacturers of the substance were identified. For both, sales of 1,4-dichlorobenzene for the production of air fresheners and toilet blocks is a very small part of their business. A restriction of consumer uses would probably affect also the professional market, because then the size of the professional market would become too small to be profitable. The substance is imported to the EU from China, India and eventually other countries. No information on tonnages is available.

- Producers/importers and suppliers of products: a small number of companies (approx. 10) are still producing these products in the EU. Most companies who were producing/supplying 1,4-dichlorobenzene products in the past have diversified their portfolio. For these companies impact from a restriction on consumer use small.

- Suppliers of 1,4-dichlorobenzene based products target mainly professional users (10 companies have been identified in RPA, 2010). It was confirmed from the consultation that these products are sold in at least 18 Member States plus Switzerland.

- Limited data were provided by Member State authorities regarding manufacturing, import and consumption of the substance (Table G52) or 1,4-dichlorobenzene based air fresheners and toilet blocks (Table G53).). Only 1 MS has in place legislation restricting the use of 1,4-dichlorobenzene based products (Table G54). Regarding accidents reported to health authorities in Member States, these relate mostly to accidental ingestion of products or to direct exposure to the substance (Table G55). They do not concern chronic exposure to 1,4-dichlorobenzene based air fresheners and toilet blocks, which is the object of this report. Finally, Member States are in general in favour of a restriction when compared to voluntary action or to a non-EU wide measure (Table G56).

Table G52: Manufacture, Import and Consumption of 1,4 Dichlorobenzene in EU Member States, Iceland, Norway and Switzerland

Country	Manufacture (tonnes)	Imports (tonnes)	Consumption (tonnes)	Source
Austria	No data	No data	No data	Austrian Federal Ministry of Environment (2009)
Cyprus	0	0	0	Cypriot Department of Labour Inspection (2009)
Denmark	0	0	0	Danish EPA (2009)
Estonia	0	2007: 0.0011	No data	Estonian Ministry of Social Affairs (2009)
	0	2008: 0.0018	No data	
Finland	No data	2009: amount not public	No data	Finnish National Supervisory Authority for Welfare and Health (2009)
Germany	No data	No data	No data	German Federal Institute for Occupational Safety and Health (2010)
Greece	0	No data	No data	Greek General Chemical State Laboratory (2010)
Latvia	No data	2004: Not specified 2007: 5.83 2008: 0.15	No data	Latvian Environmental, Geology and Meteorology Centre (2010); Latvian Environmental, Geology and Meteorology Centre (2009); Latvian Ministry of Health (2009)
Lithuania	2003-2007: 0	2003-2007: 0	2003-2007: 0	Lithuanian State Non Food Products Inspectorate (2009)
Malta	No data	No data	No data	Malta Standards Authority (2009)
the Netherlands	No data	No data	No data	RIVM (2009)
Poland	No data	No data	No data	Polish Bureau for Chemical Substances and Preparations

				(2009)
Slovak Republic	No data	No data	No data	Slovak Trade Inspectorate (2009)
Slovenia	2008: 0	2008: 9.84	2008: 8.52 +3.17 (export)	Chemicals Office of the Republic of Slovenia (2009)
	2007: 0	2007: 13.875	2007: 9.6776 +2.24 (export)	
	2006: 0	2006: 11.84	2006: 6.91 +3.135 (export)	
	2005: 0	2005: 8.77	2005: 6.516	
	2004: 0	2004: 6.6845	2004: 5.98	
	2003: 0	2003: 3.18	2003: 2.61	
	2002: 0	2002: 17.944	2002: 7.571 +10 (export to Croatia)	
	2001: 0	2001: 20	2001: 20 t (export to Croatia)	
	2000: 0	2000: 2.5	2000: 2.5	
Sweden	Confidential data	Confidential data	Confidential data	Swedish Chemicals Agency (2009)
Iceland	0	2008-9: 0	0	Environment Agency of Iceland (2009)
Norway	2008: 0	2008: 0	2008: 0	Norwegian Pollution Control Authority (2009)
Switzerland	No data	No data	No data	Swiss Federal Office of Public Health (2009)

Notes: the Norwegian Product Register has some information on this substance, however it is confidential. The substance occurs as technical impurities in another substance. The declaration of this substance to the product register was made by well known companies on the European market (Norwegian Pollution Control Authority, 2009).

Table G53: Manufacture, Marketing and Use of 1,4 Dichlorobenzene-based Air Fresheners and Toilet Blocks

Table 2.15: Information Provided by National Competent Authorities on the Manufacture, Marketing and Use of 1,4 Dichlorobenzene-based Air Fresheners and Toilet Blocks in Certain EU Member States, Iceland, Norway, and Switzerland											
Country	**Year**	**Air fresheners**					**Toilet blocks**				
		Manufacture in this country?	**(Number of) products on the market**	**Products used by consumers or I&I users?**	**Tonnage of products on the market**	**1,4 DCB concentration (%)**	**Manufacture in this country?**	**Number of products on the market**	**Products used by consumers or I&I users?**	**Tonnage of products on the market**	**1,4 DCB concentration (%)**
AT	-	No data									
CY	2009	No	None found	No	-	-	No	None found	No	-	-
DK			None					None			
EE	2009		None found					None found			
FI	2009	-	-	-	-	-	No	1 (notified but possibly more on the market)	CON: ? I&I: Yes	No data	No data
DE	2009	No*	-	-	-	-	Yes	-	-	-	99%
EL	2009	No	No data								
IT		Information from the national association *Associazione Nazionale detergenti e specialità per l'industria e per la casa* suggests that the substance is not being used in Italy for some time. A similar response has been received from the Employers'									

		Association of Turin. NO other information has been collected from the authorities									
LV1	2004-2007	-	-	-	-	-	No	2	I&I: Yes CON: Probably	≥5.83	60-100
	2008	-	-	-	-	-	No	1		0.150	>60
LV2	-	No data									
LT	N/A	No data									
MT	2009	No data									
NL	2009	No	1 (but intended against moths)	No (with the exception of the 1 product)	Unknown	Unknown	No	No	No	None	0
PL	-	No data									
SE	-	Not known	Not known	Not known	Not known	Not known	Not known	Not known	Not known	Not known	Not known
SI	2009	/	Yes	Both	Not given	Not given	/	Yes	Both	Not given	Not given
	2008		1		0	95%		7		10.922 t	95%

Country	Year	Air fresheners					Toilet blocks				
		Manufacture in this country?	**(Number of) products on the market**	**Products used by consumers or I&I users?**	**Tonnage of products on the market**	**1,4 DCB concentration (%)**	**Manufacture in this country?**	**Number of products on the market**	**Products used by consumers or I&I users?**	**Tonnage of products on the market**	**1,4 DCB concentration (%)**
	2007		1		0	95%		8		11.780 t	95%
	2006		1		0	95%		8		7.761 t	95%
	2005		1		0.076 t	95%		8		7.764 t	95%
	2004		1		0.149 t	95%		6		6.454 t	95%
	2003		1		0.62 t	95%		7		2.318 t	95%
	2002		1		0.227 t	95%		7		7.589 t	95%
SK	-	No data									
IS	-	No	No				No	No			
NO	2008	No data									
CH	2009	No	No	-	-	-	Yes	1	I&I	No data	99%

*Sources: **AT**: Federal Ministry of Environment (2009); **CY**: Department of Labour Inspection (2009); **DK**: Danish EPA, Ministry of Environment (2009); **EE**: Ministry of Social Affairs (2009); **FI**: National Supervisory Authority for Welfare and Health (2009); **DE**: German Federal Institute for Occupational Safety and Health (2010); **EL**: Greek General Chemical State Laboratory (2010); **IT**: Federchimica (2010) & Unione Industriale Torino (2010); **LV1**: Latvian Environment, Geology and Meteorology Centre (2009); **LV2**: Latvian Ministry of Health, Department of Health Policy Planning (2009); **LT**: Lithuanian State Non Food Products Inspectorate (2009); **NL**: National Institute for Public Health and the Environment (2009); **MT**: Malta Standards Authority (2010); **PL**: Bureau for Chemical Substances and Preparations (2009); **SE**: Swedish Chemicals Agency (2009); **SI**: Chemicals Office of the Republic of Slovenia (2009); **SK**: Slovak Trade Inspection (2009); **IS**: Environment Agency of Iceland (2009); **NO**: Norwegian Pollution Control Authority (2009); **CH**: Swiss Federal*

*Office of Public Health (2009): There used to be 1,4 dichlorobenzene-based air-fresheners and toilet blocks on the Swiss market. Since the adaptation of the Swiss chemical regulation, there are no longer products registered in the relevant database (with the exemption of one product). This may be due to the official classification as a Carc. Cat 3 substance (harmonised with the EC), which came into force in Switzerland in 2005. The remaining product registered in the database is a professional used toilet block with 98.7% 1,4 dichlorobenzene. Note: 'No data', blank space and '-' denote no data availability. * Not the case, according to consultation with industry consultees.*

Table G54: Overview of National Legislation on 1,4 Dichlorobenzene in EU/EEA Countries

Country	Regulatory Provisions	Source
AT	No ban or restriction on 1,4 dichlorobenzene according to Austrian law	Austrian Federal Ministry of Environment (2009)
CY	No national legislation on 1,4 dichlorobenzene in Cyprus	Cypriot Department of Labour Inspection (2009)
CZ	No national legislation on 1,4 dichlorobenzene in the Czech Republic	Czech Ministry of Environment (2009)
DK	No national Danish regulation on 1,4 dichlorobenzene in air fresheners or toilet blocks	Danish Environmental Protection Agency (2009)
FI	No national legislation restricting the marketing and use of 1,4 dichlorobenzene in air fresheners or toilet blocks in Finland	Finnish National Supervisory Authority for Welfare and Health (2009)
DE	No national legislation controlling the use of 1,4 dichlorobenzene in air fresheners or toilet blocks in Germany	German Federal Institute for Occupational Safety and Health (2010)
LV	No national legislation or other non-regulatory actions, banning or otherwise controlling the marketing and use of 1,4 dichlorobenzene in air fresheners, toilet blocks or indeed other products Two regulations have been identified by Latvian authorities (Cabinet Regulation No 466 of 2002 and Cabinet Regulation No 184 of 2003) on chemical reporting and biocidal products which may be of relevance to the substance	Latvian Environment, Geology and Meteorology Centre (2009); Latvian Ministry of Health, 2009
LT	No relevant legislation is in place in Lithuania	Lithuanian State Non Food Products Inspectorate (2009)
MT	No specific national restrictions are in place in Malta	Malta Standards Authority (2009)
NL	No national legislation banning or otherwise controlling the marketing and use of 1,4 dichlorobenzene in air fresheners and toilet blocks	RIVM (2009)
NO	No national legislation restricting the marketing and use of 1,4 dichlorobenzene in air fresheners or toilet blocks in Norway	Norwegian Pollution Control Authority (2009)
PL	No national legislation banning or otherwise controlling the marketing and use of 1,4 dichlorobenzene in air fresheners and toilet blocks in Poland	Polish Bureau for Chemical Substances and Preparations (2009)

SK	The only relevant legislative measure impacting on the marketing and use of 1,4 dichlorobenzene in the Slovak Republic is Regulation of the Ministry of Health of the Slovak Republic No 480/2006 Coll. on requirements on quality, acquisition, and transport from the source to the place of treatment and loading, treatment, control of quality, packaging, labelling, and marketing of natural healing water. The Regulation includes a maximum concentration limit for dichlorobenzenes of 0.3 g/L	Slovakian Trade Inspection (2009)
SI	No national legislation restricting or otherwise controlling the use of 1,4 dichlorobenzene in Slovenia, although the Chemicals Office of the Republic of Slovenia (2009) has mentioned a series of legislative instruments that implement EU legislation and international Conventions (Seveso II Directive, the Rotterdam Convention, etc.)	Chemicals Office of the Republic of Slovenia (2009)
SE	According to the Swedish Chemical Products and Biotechnical Organisms Regulations (KIFS 2008:2, Chapter 5, Section 16; Swedish Chemicals Agency, 2008), chemical products containing 1,4 dichlorobenzene and intended to mask odours may not be may not be offered for sale, transferred or used for and by professional users. According to the EU RAR, these regulations entered into force on 1 January 1990. The Regulations were last amended in 2009 (KIFS 2009:6)	Swedish Chemicals Agency (2009)
CH	As in the EU Detergents Regulation (EC) 648/2004, there is a special labelling for cleaning products containing 1,4 dichlorobenzene in the Swiss Ordinance on Risk Reduction related to the Use of certain particularly dangerous Substances, Preparations and Articles (Ordinance on Risk Reduction related to Chemical Products (ORRChem). No other restriction is in place	Swiss Federal Office of Public Health (2009)

Table G55: Information on Accidents and Diseases from Exposure of Consumers to 1,4 Dichlorobenzene from Air Fresheners and Urinal Blocks

Country	Response	Source
Austria	No data	Austrian Federal Ministry of Environment (2009)
Cyprus	One complaint was registered in 2008 for people suffering from dizziness due to exposure to air freshener fumes. The information provided on the SDS of the air freshener stated that it contained a mixture of branch chain aliphatic hydrocarbons 20 to 90% (CAS 64742-478 and 64741-65-7). No information was provided on any 1,4 dichlorobenzene content.	Cypriot Department of Labour Inspection (2009)
Estonia	According to the Estonian National Poison Information Centre, no information has been received on possible accidents/incidents of disease in Estonia occurring as a result of consumer exposure to 1,4 dichlorobenzene from air fresheners or toilet blocks.	Estonian Ministry of Social Affairs (2009)
Finland	According to the Helsinki Poison Information Centre, there have been: one case of a 1-year-old tasting a 1,4 dichlorobenzene-containing air freshener in 2008; two cases related to 1,4 dichlorobenzene in moth balls in 2008 (product was 100% 1,4 dichlorobenzene, no longer on the market); and six cases of small children tasting 1,4 dichlorobenzene-containing air fresheners in 2007. No allergic reactions have been connected to 1,4 dichlorobenzene (Asthma and Allergy Association).	Finnish National Supervisory Authority for Welfare and Health (2009)
Germany	According to the Poison Information Ordinance (§ 16e of the German Chemicals Act), seven cases of adults in occupational context are known to the German Federal Institute for Risk Assessment (data since 1990): severity low: three cases with eye exposure, one case with dermal exposure; and severity medium: three cases with respiratory exposure (short-term impairment of health, no long term consequences). These accidents involved exposure to the pure substance rather than to the products of concern.	German Federal Institute for Occupational Safety and Health (2010)

Ireland	Between 1 January 2004 and 3 November 2009, the National Poisons Information Centre of Ireland (NPICI) had received 17 enquiries about solid/gel air fresheners. Two of these products did not contain 1,4 dichlorobenzene. The ingredients of 14 products were not known/not documented. One product contained 1,4 dichlorobenzene: The enquiry concerned a 1-year-old boy who had ingested some air freshener block. He had gagged and had been short of breath initially but this had settled by the time NPICI was contacted. NPICI received 151 enquiries about toilet blocks (including rim and cistern blocks). 76 of these products did not contain 1,4 dichlorobenzene. The ingredients of 72 products were not known/not documented. Three products contained 1,4 dichlorobenzene: these enquiries concerned ingestion by young children (one three-year old and two one-year olds) and they were all asymptomatic.	Irish Health and Safety Authority (2009)
Latvia	Latvian Competent authorities do not have any statistical information on accident/incidence of disease occurring from 1,4 dichlorobenzene containing air fresheners or toilet blocks.	Latvian Environment, Geology and Meteorology Centre (2009); Latvian Ministry of Health (2009)
Lithuania	No data on incidents with 1,4 dichlorobenzene-containing products observed.	Lithuanian State Non Food Products Inspectorate (2009)
Netherlands	A search, over the period 2004-2009, of the data base of the National Poisons Information Centre (NVIC) of the Netherlands revealed no accidents or diseases due to exposure to 1,4 dichlorobenzene from air fresheners or toilet blocks.	RIVM (2009)
Norway	During the last couple of years, the National Poisons Information Centre in Norway had 448 enquiries on air fresheners and 43 on toilet blocks. In most cases the involved persons describe intestinal irritation or irritation to the eye. These symptoms are ascribed to other substances in these products. Rash was reported in 3 of the enquiries. The product names for these cases are not available, hence it is not possible to tell whether 1,4 dichlorobenzene was involved.	Norwegian Pollution Control Authority (2009)

Poland	No information is available. There is no national poison centre in Poland; hence it is not possible to obtain such data.	Polish Bureau for Chemical Substances and Preparations (2009)
Slovakia	No data	Slovak Trade Inspection (2009)
Slovenia	The Slovenian authorities have not provided information on incidents occurring in the country although they note the "*offensive smell*" of the relevant products.	Chemicals Office of the Republic of Slovenia (2009)
Switzerland	According to the Swiss poison centre there have been 67 incidences since 1995. The products involved were moth repellents, air-fresheners and toilet blocks. Most of the cases were considered as slightly harmful and have been resolved directly on the phone with some simple measures. In six cases, health professionals were consulted and the poison centre received a feedback (5 humans and 1 dog). Three infants, one adult and one dog ingested orally a small quantity of a 1,4 dichlorobenzene containing product. In one case (an infant) slight mucosa irritation of the lower lip was observed. The breakdown of these cases among the different product types is as follows: urinal blocks: 10 cases, no feedback on progress; ir fresheners: 4 cases, 1 case with feedback (adult), asymptomatic progress; and moth repellents/other biocidal products: 53 cases, 5 cases with feedback on progress (including the 3 cases with children, all moth repellents).	Swiss Federal Office of Public Health (2009 & 2010)

Table G56: Views of Member State Competent Authorities on the Suitability of Different Risk Management Options

Question	**Possible risk management options (responses may relate to exposure to 1,4 dichlorobenzene in general and not only to exposure from use at home)**		
	No EU-wide restriction under REACH Annex XVII	**Marketing and use restriction (i.e. a ban)**	**Voluntary action by industry**
Would you support any option? (Y/N)	No: **CY**, **DK** ("*No effects on risk – cannot be* *supported*"), **LV1**, **NL**, **NO, SI**	Yes: **AT**, **CY**, **CZ** ("*we would prefer common* *regulation in the EU frame*"), **DK**, **EE**, **FI**, **FR**, **IS**, **LV, NO, PL, SI, SE, CH** Possibly: **NL** No: **LV1**	Yes: **CY**, **IS**, **LV1** (In our opinion there is not reason to determine wide restrictions under REACH, ban of marketing and use of 1,4 DCB, because available research shows, that use of air fresheners and toilets blocks is related to very low concentrations of 1,4 DCB in indoor air and a carcinogenic effect cannot arise), **NL** (In the Netherlands the manufacturers of air fresheners and toilet blocks have switched to alternatives to 1,4 DCB on a voluntary basis but moth balls containing 1,4 DCB are still available. If this application is considered a biocidal application a marketing and use restriction is not effective, because biocides are exempted in REACH. If this application is not considered as biocidal application, marketing and use restriction can be considered, the current Dutch voluntary action doesn't prevent the use of 1,4 DCB in moth balls), **SI** No: **FI**, **NO, PL**
Your views on the	**DK**: No	**AT**: Full effectiveness	**AT**: Very limited effectiveness
effectiveness of each	**NO**: Inefficient	**CY**: Most effective method	**DK**: Difficult to control

option	**SI**: Legally binding restrictions are most effective	**DK**: Most effective, best consumer protection **EE**: Positive **FI**: Good **NL**: see comments on voluntary action to the right **NO**: Effective **SI**: To stimulate use of less dangerous chemicals for humans and the environment **SE**: Effective as seen on national level	**FI**: seems to have taken place already (most products that were on the market 5 years ago have disappeared) **NO**: Inefficient **PL**: Negative **SI**: To stimulate use of less dangerous chemicals for humans and the environment

Question	**Possible risk management options (responses may relate to exposure to 1,4 dichlorobenzene in general and not only to exposure from use at home)**		
	No EU-wide restriction under REACH Annex XVII	**Marketing and use restriction (i.e. a ban)**	**Voluntary action by industry**
Your views on coherence of each option with other legislation	**NO**: Incoherent **SI**: It is counter-productive	**AT**: Full coherence with REACH and other legislation **CY**: Most coherent method **EE**: Positive **FI**: Good - substance is not an approved biocide **NL**: coherent, but consider biocidal use of 1,4 DCB **NO**: Coherent with biocides regulation **SI**: To stimulate use of less dangerous chemicals for humans and the environment **CH**: Marketing and use restrictions i.e. a ban would consolidate the current situation in Switzerland (1,4 DCB is almost phased out) and therefore is a	**AT**: None **NL**: Coherent **NO**: Incoherent **PL**: Negative **SI**: To stimulate use of less dangerous chemicals for humans and the environment

		possible option for Switzerland	
Envisaged implementation/ enforcement problems for each option	**CY**: No control **NO**: Problematic **SI**: Lack or absence of inspection control	**AT**: Enforcement possible and transparent **FI**: None **NL**: Enforcement problems are not expected **NO**: Efficient **SI**: Lack or absence of inspection control **SE**: No specific	**AT**: Enforcement not possible **CY**: No harmonised approach **DK**: Control issue. No enforcement tools **NL**: As it is a voluntary action by industry there are no implementation/enforcement problems **NO**: Problematic **PL**: Negative **SI**: Lack or absence of inspection control
Envisaged budget implications and associated administrative burden for central/local	**SI**: No	**AT**: Low (chemicals inspection already exists) **CY**: It involves administrative burden **FI**: None **NL**: Limited costs	**AT**: None **NL**: No budget implications for central/local authorities **PL**: Negative

authorities in your country		**NO**: No major budget implications or additional administrative burden **SI**: No **SE**: Very limited	**SI**: No

Question	**Possible risk management options (responses may relate to exposure to 1,4 dichlorobenzene in general and not only to exposure from use at home)**		
	No EU-wide restriction under REACH Annex XVII	**Marketing and use restriction (i.e. a ban)**	**Voluntary action by industry**
Using the space provided below, you may add any suggestions you have on other risk management	**AT, CY, CZ, FI, IS, LV1/LV2, NO, CH**: No views expressed **EE**: As there is no legal basis to restrict the use of the substance in air fresheners or toilet blocks it is also not possible to ban it on the market. From our point of view only the regulative measures can bring the successful results to reduce the risk for the consumers and give the legal ground for effective enforcement actions. **FR**: Options that could be considered include:		
options which you would	*Reducing size of packaging of 1,4 DCB-based products*: we think that modifying the size of packaging is hardy likely to reduce exposure of consumers, as this is		

like us to consider	essentially the result of the specified use, and high exposure mainly results from consumers' use of excessive quantities of air fresheners; *Limiting the concentration of 1,4 DCB in commercial preparations*: we think products would become ineffective if concentrations of their active ingredient were reduced so it is not applicable; *Restricting use of products so as to protect the most vulnerable populations*: apparently no group of individuals has been identified with a particular sensitivity to the carcinogenic effects of 1,4 DCB; *Ban on the use of 1,4 DCB products intended for the general public*: we think it is the only method likely to bring about an effective reduction in exposure of consumers. **NL**: No views expressed (but see above on issue of moth balls) **PL**: At present we cannot take the unambiguous position to support mentioned options. We do not have enough information in regard to this issue. We think that voluntary actions by industry provide minimally benefits. **SI**: Education of people to stimulate use of less dangerous chemicals for humans and the environment is needed. **SE**: We have not changed our view from supporting the risk reduction measures for consumers for 1,4 DCB of the risk evaluation and strategies for limiting the risks provided for in accordance with the opinion of the Committee set up pursuant to Article 15(1) of Regulation (EEC) No 793/93.Commission communication (2008/C 34/01)
No specific response	**DE, EL**, **LV2** ("*At this time we do not have any strong opinion do to lack of information about substance and its properties*"), **LT**, **MT**, **SK**

*Sources: **AT**: Austrian Federal Ministry of Environment (2009); **CY**: Cypriot Department of Labour Inspection (2009); **CZ**: Czech Ministry of Environment (2009); **DK**: Danish Environmental Protection Agency (2009); **EE**: Estonian Ministry of Social Affairs (2009); **FI**: Finnish National Supervisory Authority for Welfare and Health (2009); **FR**: Ministry of Ecology, Energy, Sustainable Development and Sea (2009); **DE**: German Federal Institute for Occupational Safety and Health (2010); **EL**: Greek General Chemical State Laboratory (2010); **IS**: Environment Agency of Iceland (2009); **LV1**: Latvian Ministry of Health (2009); **LV2**: Latvian Environment, Geology and Meteorology Centre (2009); **LT**: Lithuanian State Non Food Products Inspectorate (2009); **MT**: Malta Standards Authority (2009); **NL**: RIVM (2009) – we have been advised that the answers above do not represent a formal NL position, but should be considered as a first expert view based on the limited available information; **NO**: Norwegian Pollution Control Authority (2009); **PL**: Polish Bureau for Chemical Substances and Preparations (2009); **SI**: Chemicals Office of the Republic of Slovenia (2009); **SK**: Slovak Trade Inspection (2009); **SE**: Swedish Chemicals Agency (2009); **CH**: Swiss Federal Office of Public Health (2009)*

G.3 Public consultation on the Annex XV restriction report

After submission of the Annex XV restriction report, ECHA organised a six-month public consultation on the restriction dossier on 1,4-dichlorobenzene from 19 June until 19 December 2012. During the consultation, six comments were received from stakeholders, representing individuals and Member State Competent Authorities. The comments received, as well as the responses from the dossier submitter (ECHA) and from the rapporteurs of the Committees for Risk Asessment and Socio-economic Analysis are to be made available on the ECHA website.

G.3 Public consultation on SEAC draft opinion

ECHA organised a 60-day public consultation on the SEAC draft opinion, from 19 March to 17 May 2013. No comments were received during this consultation.

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Annex 1 Repeated-dose toxicity in animals

Oral exposure

Strain	Doses Number of animal	Duration of exposure	Symptoms	NOAEL (dosewithout toxiceffect) / LOAEL (lowest dose withToxic effect)	Ref

F344 Rat	Study 1: 300, 600, 900, 1,200, 1,500 mg/kg/day Study 2: 0, 37.5, 75, 150, 300, 600 mg/kg/day 10/sex/dose gavage	5 days/week 13 weeks	Study 1: - ≥ 300 in male: dose dependent nephropathy with tubular cell degeneration and necrosis, decrease in Ht and Hb level - ≥ 600 in male: ↑ kidney weight, ↓ cholestérol - ≥ 900 in 2 sexes: ↑ liver weight; in female: ↓ cholestérol - ≥1,200 in male and female: hepatocellular degeneration and necrosis, hypoplasia of the bone marrow, lymphoïd depletion of spleen and thymus, ↑ urinary porphyrins Study 2: - 600 in male: kidney cortical degeneration	Study 1: LOAEL = 300 mg/kg/day in male NOAEL = 600 mg/kg/day in Female Study 2: NOAEL: = 300 mg/kg/day in male > 600 mg/kg/day in female	US-NTP (1987)

F344 Rat	0, 75, 150, 300, 600 mg/kg/day 5/sex/dose gavage GLP +	7 days/week 4 Weeks 7 days/ week 13 weeks	Study on kidney effects: • 4 weeks - ≥ 75 in male: hyalin droplet nephropathy, ↑ urinairy LDH, proteins and epithelial cells, ↑ water consumption -≥ 150 in male: tubular cell nephropathy (necrosis, dilatated tubules) - ≥ 300 in male and female: ↑ liver weight; ↑ kidney weight in male - 600: in female ↑ kidney weight, water consumption, in male hepatocellular hypertrophy • 13 weeks : - ≥ 75 in both sexes ↑ liver weight - ≥ 150 in male ↑ kidney weight, tubular cell nephropathy (necrosis, dilatated tubules) - at 600 in female ↑ kidney weight - ≥ 300 hepatocellular hypertrophy in male	NOAEL on kidney effects: - for 4 weeks: LOAEL = 75 mg/kg/day in male NOAEL = 300 mg/kg/day in female - for 13 weeks: LOAEL = 75 mg/kg/day in male NOAEL = 300 mg/kg/day in female	Bomhard (1987, 1988a, 1988b)

F344 Rat	0, 150, 600 mg/kg/day 20/sex/dose gavage	5 days/ week 4 weeks	Study of liver cytochrome P450 dependent enzyme activities: - ≥ 150 in male and female: ↑ dose dependent cyt P450 liver enzyme induction - ≥ 150 in male, 600 both sexes: ↑ liver weight		Bomhard (1992)
Rat	0, 10, 100, 500 mg/kg/day 2 males/dose	5 days/ week 4 weeks	- at 500: oedema and centrolobular necrosis in the liver, renal tubular oedema		Hollingswo rth (1956)
Rat	0, 18.8, 188, 376 mg/kg/day 10 females/dose	5 days/week 27 weeks	Brief report - at 188: ↑ slight liver and kidney weights - at 376: cirrhosis and focal necrosis in the liver		Hollingswo rth (1956)
Rat	0, 50, 100, 200 mg/kg/day 5 females/dose gavage	1 time/day 30, 60, 90, 120 days	Brief report centered on hepatic porphyria: - ≥ 50: slight ↑ liver weight at 30 and 60 days and slight ↑ liver porphyrins at 120 days		Carlson (1977)
F344 Rat	0, 150, 300 mg/kg/day in male 0, 300, 600 mg/kg/day in female 50/sex/dose gavage	two years	- ≥ 150 in male: renal hyperplasia and mineralisation - ≥ 300 in female: nephropathy - 600 in female: transient hepatocellular proliferation, persistent liver enlargement	For non neoplasic effects LOAEL: = 150 mg/kg/day in male = 300 mg/kg/day in female	US-NTP (1987)

B6C3 F1 Mice	Study 1: 0, 85, 169, 337, 675, 900 mg/kg/day 10/sex/dose gavage Study 2: 600, 900, 1,000, 1,500, 1,800 mg/kg/day 10/sex/dose gavage	5 days/week 13 weeks	Study 1: - at 675 in male and female: hepatocellular hypertrophia Study 2: - ≥ 600 in male and female: decrease in body weight gain, hepatocellular degeneration - ≥ 900 in two sexes: ↑ liver weight; ↓ cholesterol - ≥ 600 in male, ≥ 1,000 in female: decrease of leukocytes - at 1,500 in male: ↓ triglycerides - ≥ 1,500: hypoplasia of spleen and bone marrow, lymphoïd depletion of spleen and thymus, lymphoïd necrosis of the thymus	Study 1: NOAEL: = 337 mg/kg/day in male and female Study 2: LOAEL: = 600 mg/kg/day in male and female	US-NTP (1987)
NMRI Mice	0, 300, 600, 900 mg/kg/day 8 to 10/sex/dose gavage	7 days/week 4 weeks	- ≥ 300 in male and female: ↑ liver weight - ≥ 600 in male and female: ↑ SGPT, hepatocellular hypertrophia and degeneration - at 900 in male and female: ↑ bilirubin and cholestérol	LOAEL = 300 mg/kg/day in male and female	Bomhard (1986)

B6C3 F1 Mice	0, 300, 600 mg/kg/day 50/sex/dose gavage	1/day, 5 days/week 2 years	- ≥ 300 mg/kg: slight hepatocellular degeneration, individual liver cell necrosis in both sexes, nephropathy in both sexes, renal tubular cell regeneration in female	For non neoplasic effects: LOAEL = 300 mg/kg/day in male and female	US-NTP (1987)
Beagle dog	0, 10, 50, 75 mg/kg/day 5/sex/dose gavage GLP +	5 days/week via capsule one year	- ≥ 50 mg/kg/day: in both sexes: ↑ liver weight, ↑ alkaline phosphatases (X 7), hepatocellular hypertrophy; in female: ↑ kidney weight, kidney duct vacuolisation - 75 mg/kg/day: bile duct hyperplasia in both sexes, neurological symptoms/reversible mild anemia, in female; ↑ AST and ↑ GGT (X 3)	NOAEL = 10 mg/kg/day	Naylor (1996)
Rabbit	0, 500, 1,000 mg/kg/day 5/dose gavage	5 days/week one year	- ≥ 500: focal hepatocellular oedema and necrosis	LOAEL = 500 mg/kg/day	Hollingswo rth (1956)

Inhalation exposure

Strain	Doses Number of animal	Duration of exposure	Symptoms	NOAEL/ NOEL	Ref
Rat Guinea pig Mice Rabbit Monkey	96, 158, 173, 341, 798 ppm 10/dose 96, 158, 173, 341, 798 ppm 8/dose 96, 158 ppm 10/dose 96, 158, 173, 798 ppm 1/dose 96, 158 ppm 1/dose	7 hours/day; 5 days/week; 5 to 7 months	- at 158 ppm in guinea pig and rat:↑ liver weight, oedema and minimal hepatocellular degeneration, ↑ kidney and liver weights of male rat - at 173 ppm: lung oedema and lung congestion in all animals, ↑ liver and kidney weights in rat - at 341 ppm in guinea pig: focal necrosis and slight cirrhosis in the liver - at 798 ppm in rat: letality, irritation, neurological symptoms, histological alterations severe in lung, liver and kidney	NOAEL = NOEL rat = 96 ppm NOEL guinea pig = 96 ppm NOEL mice > 158 ppm NOEL rabbit = 158 ppm NOEL monkey = 158 ppm	Hollingsworth *1956)
Wistar Rat	0, 75, 500 ppm (vapour) 76-79/sex/dose GLP +	5 hours/day 5 days/week 76 weeks	- at 75 ppm: ↑ liver weight at 26 weeks (not at 76 weeks) and liver hyperplasia at recovery (not at 76 weeks) in female - at 500 ppm: ↑ liver weight and hepatocyte hyperplasia in both sexes - at 500 ppm in male: ↑ kidney weights, ↑ urinary coproporphyrin and proteins	For non neoplasic effects NOAEL = 75 ppm	Riley (1980a)

			- No hyaline droplet nephropathy in male		
Swiss Mice	0, 75, 500 ppm 75/dose GLP +	57 weeks	increase in respiratory infections in female Limits: high incidence of infections no histopathogical examination in male		Riley (1980b)
BDF1 mice	0, 20, 75, 300 ppm (vapour) 50/sex/dose GLP +	104 weeks 6 hours/day, 5 days/week	- 300 ppm in both sexes: liver toxicity (↑ liver weight ↑ AST, ALT, LDH, alkaline phosphatase, slight local necrosis; in male hepatocellular hypertrophy - 300 ppm both sexes: ↑ kidney weight	For non neoplasic effects NOAEL = 75 ppm	JBRC (1995)
F344 rat	0, 20, 75, 300 ppm (vapour) 50/sex/dose GLP +	104 weeks 6 hours/day, 5 days/week	- 300 ppm in male: mineralisation of papilla, urothelial hyperplasia, ↑ kidney weight - 300 ppm both sexes: ↑ liver weights - 300 ppm in female: respiratory metaplasia in olfactory epithelium and eosinophilic change in respiratory epithelium	For non neoplasic effects NOAEL = 75 ppm	JBRC (1995)

Annex 2 Carcinogenicity data in animals

Oral exposure	**Dose**	**Symptoms**
F344/N Rat (NTP 1987)	0, 150, 300 mg/kg/day in male 0, 300, 600 mg/kg/day in female two years (50/sex/dose) gavage	- hyperplasia and mineralisation of kidney tubules in male at level of 150 mg/kg/day - nephropathy in female (21/49, 32/50, 41/49) - tubular cell kidney adenocarcinoma in male (1/50, 3/50, 7/50) (historical control of the laboratory = 0,4%) - parathyroid gland hyperplasia in male (4/42, 13/42, 20/38) - mononuclar leukemia in male (5/50, 7/50, 11/50) (historical control of the laboratory: 13,8 ± 8%) - No tumours in female
B6C3F1 Mice (NTP 1987)	0, 300, 600 mg/kg/day two years (50/sex/dose) gavage	- liver carcinoma in male (14/50, 11/49, 32/50) and in female (5/50, 5/48, 19/50)(historical control of the laboratory = 21.8 ± 7.7 % in male, 3.1 ± 2.3 % in female) - hepatoblastoma in male 4/50 at 600 mg/kg/day (historical controls: 1/2080) - liver adenoma in male (5/50, 13/49, 16/50); in female (10/50, 6/48, 21/50) - malignant pheochromocytoma in male (1/49) at 300 mg/kg/day and in one control female (1/49) (historical control of the laboratory: 2,2 ± 3%) - increased incidence of non neoplastic liver lesions : hepatocellular degeneration, individual liver cell necrosis in both sexes from 300 mg/kg/day
Inhalation exposure	**Dose**	**Symptoms**
Wistar rat (Loeser 1983, Riley 1980a)	0, 75, 500 ppm5 hours/day, 5 days/week, 76 weeks (+ 36 weeks unexposed)	- increase of liver weight at 26 weeks and hepatocyte hyperplasia at recovery (not at 76 weeks) at 75 ppm in female - increase of liver and kidney weight in both sexes at 500 ppm - increase in urinary proteins and urinary coproporphyrins at 500 ppm

	(76/sex/dose) GLP +	- no significant increase of tumours Limits: low level and short duration of exposure
Swiss Mice (Riley 1980b)	0, 75, 500 ppm 5 hours/day, 5 days/week, 57 weeks (+ 19 weeks unexposed) (75 females/dose)	- nasal sinus osteosarcoma at 75 ppm - increase of respiratory infections - no significant increase of tumours Limits: not valid data because of high incidence of respiratory infections
BDF1 Mice (JBRC 1995)	0, 25, 75, 300 ppm 6 hours/day, 5 days/week, 104 weeks (50/sex/dose) vapour GLP +	- hepatocellular carcinoma in male (12/49, 17/49, 16/50, 38/49) and in female (2/50, 4/50, 2/49, 41/50) (historical control of the institute = 0-4% in female, 2- 36% in male) - histiocytosarcoma of liver in male (0/49, 3/49, 1/49, 6/49) (historical control of the institute 0-8% in male) - Hepatoblastoma like feature: 300 ppm in female 6/41 and in male 2/17, 1/16 and 8/38 at 25, 75 and 300 ppm - hepatocellular adenoma in female (2/50, 10/50, 6/49, 20/50) - bronchiolar-alveolar carcinoma in female 4/50 at 300 ppm (historical control data of laboratory 0-8%) - 300 ppm in male centrolobular hepatocellular hypertrophy
F344 Rat (JBRC 1995)	0, 25, 75, 300 ppm 6 hours/day, 5 days/week, 104 weeks (50/sex/dose) Vapour GLP +	- monocellular leukemia in male (9/50, 14/50, 10/50, 13/50): (historical control data of laboratory 6-22%) non neoplasic lesions: - in the kidney (mineralisation of papilla and urothelial hyperplasia of the pelvis), increase kidney weight at 300 ppm in male - respiratory metaplasia in nasal cavity gland and eosinophilic change in respiratory epithelium at 300 ppm in female) and eosinophilic change in olfactory epithelium in both sexes and 75 ppm in female

Annex 3 Detailed description of health-related limits proposed by other authorities

A. Derivation of Minimal Risk Limit by ATSDR, 2006

To derive a point of departure for MRL derivation, BMD analysis was conducted using the incidences of the nasal lesions (moderate or greater severity) in the female rats. Data for other end points were not modeled because the effects occurred at higher concentrations (nasal lesions and hepatocellular hypertrophy in mice, kidney lesions in rats) or were not toxicologically significant (testicular mineralization in mice). All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the female rat nasal lesion incidence data. All models provided adequate fits to the data, and the quantal linear model provided the best fit to the data. Using a BMR level of 10% extra risk above the control incidence, the quantal linear model resulted in a benchmark concentration (BMC10) of 14.08 ppm and lower 95% confidence limit (BMCL10) of 9.51 ppm.

Using the BMCL10 value of 9.51 ppm for increased incidences of nasal lesions in female rats and EPA (1994) inhalation RfC methodology to determine the MRL, the BMCL10 was duration-adjusted for intermittent exposure, as follows:

BMCL10 ADJ = (BMCL10) (hours/24 hours) (days/7 days)

= (9.51 ppm) (6 hours/24 hours) (5 days/7 days)

= 1.70 ppm

For the nasal olfactory epithelium changes in female rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region for purposes of calculating the HEC. Using EPA (1988, 1994) reference values, the regional gas deposition ratio was calculated as follows (EPA 1994):

RGDRET = [(VE/SAET)A/(VE/SAET)H]

= (0.24 m3/day/15cm2)/(20 m3/day/200cm2)

= 0.16

where:

- RGDRET = regional gas deposition ratio in the extrathoracic region
- VE = minute volume in rats (VE)A or humans (VE)H
- SAET = extrathoracic surface area in rats (SAET)A or humans (SAET)H

The HEC was calculated by multiplying the rat BMCL10 ADJ by the RGDRET to yield a BMCL10 HEC of 0.27 ppm, as follows:

BMCL10 HEC = BMCL10 ADJ x RGDRET

= 1.70 ppm x 0.16

= 0.27 ppm

The BMCL10 HEC of 0.27 ppm for nasal effects in rats was divided by a total uncertainty factor of 30 to calculate the MRL. This uncertainty factor is comprised of component factors of 3 for

interspecies extrapolation and 10 for human variability. A 3-fold uncertainty factor was used instead of a default 10-fold factor to extrapolate from rats to humans, because the dosimetry adjustment (i.e., calculation of the human equivalent exposure for time and concentration [NOAELHEC]) addresses one of the two areas of uncertainty encompassed in an interspecies extrapolation factor.

B. Setting of a Tolerable Daily Intake (TDI) by Canadian authorities, 1993

The TDI was derived on the bases of the results in an inhalatory study by Loeser and Litchfield (1983 as referenced by Canadian authorities 1993) who reported increases in liver and kidney weights, urinary protein, and coproporphyrin in the high dose group of rats administered 0, 450 or 3 000 mg/m^3 1,4-dichlorobenzene 5 hrs per day, 5 days per week for 76 weeks followed by 36 weeks without exposure. The NOEL determined in rats was 450 mg/m^3.

The TDI was derived as follows:

$$TDI = \frac{450mg/m^3 x(5/24)x(5/7)x0.1444}{500x0.25}$$ = 0.078 mg/kg bw/day (78 mg/kg bw/day)

where:

- 450 mg/m^3 is the NOEL based on the Loeser and Litchfield study (1983);
- 5/24 and 5/7 is the conversion of 5 hours per day, 5 days per week of administration to continuous exposure;
- 0.144 m^3 is the assumed inhaled air volume of rats (NIOSH, 1985, as referenced by Canadian authorities 1993);
- 0.25 kg is the assumed body weight of adult rats (NIOSH, 1985, as referenced by Canadian authorities 1993);
- 500 is the uncertainty factor (× 10 for inter-species variation; × 10 for intra- species variation; × 5 for evidence of carcinogenicity, though not observed in this study).

Annex 4: Comparison of hazard profiles

Please note that the tables presented in this Annex are quoted after the RPA report (2010). Therefore, the harmonised classification is not included. There may also be some differences between classification presented in this Annex and the harmonised classification, as presented in the Regulation 1272/2008, Annex VI. Relevant sections of the Part C (C.2.2.1 and C.2.2.2), presenting the alternatives, include the current classification.

Table A5.4: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Selected Alternatives - Fragrances							
Property	**1,4 DCB**	**Fragrances and perfumes**					
		α-hexyl cinnamaldehyde	**Citronellol (3,7-dimethyl-6-octen1-ol)**	**Geraniol**	**Citral**	**d-Limonene**	**Pin-2(10)-ene**
Example proportion of product	>95%	0.25-0.5%	<5%	0-1%	<0.2%	<0.1%	5%
Identity, Classification and Labelling							
EC Number	203-400-5	202-983-3	203-375-0	203-377-1	226-394-6	227-813-5	204-872-5
CAS Number	106-46-7	101-86-0	106-22-9	106-24-1	5392-40-5	5989-27-5	127-91-3
Chemical formula	C6H4Cl2	C15H20O	C10H20O	C10H18O	C10H16O	C10H16	C10H16

Ambient state	Crystalline solid	Pale yellow to yellow clear liquid to solid	Colourless to pale yellow clear liquid	Colourless to pale yellow liquid, with an odour of roses	Liquid	Liquid	Colourless clear liquid
Vapour pressure	1.74 mm Hg; 160-170 Pa (2ºC)	0.0002 mm Hg (20oC)	0.02 mm Hg (25°C)	0.03 mmHg	0.091 mmHg; <130Pa (100°C)	2.66644 hPa (25ºC)	2.93 mm Hg (25°C)
Henry's Law constant (atm-m3/mol)	2.41 x 10-3	1.0×10-5 (estimated)		5.9 x 10-5	2.2 x 10-4	2.6 x 10-2	1.6 x 10-1
Water solubility	81.3 mg/L	Negligible		100 mg/L	590 mg/L (25°C)	Very low	4.89 mg/L (25°C)
Log Kow	3.44	5.3 (measured)	3.217 (estimated)	3.47	3.45	4.57	4.16

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Labelling **symbols**	Xi - irritant; Carc. Cat 3 – may cause concern for humans but available information is not adequate for making a satisfactory	Xi - irritant	Xi - irritant; N - dangerous for the environment	Xi -irritant	Xi -irritant	Xi - irritant; N - dangerous for the environment	Xn - harmful; N - dangerous for the environment

	assessment; N - dangerous for the environment						
Risk phrases	R36 (irritating to eyes); R40 (limited evidence of carcinogenic effect); R50 (very toxic to aquatic organisms); R53 (may cause long-term adverse effects in aquatic environment)	R 38 (irritating to skin); R 43 (may cause sensitisation by skin contact)	R 36/38 (irritating to skin and eyes); R 43 (may cause sensitisation by skin contact); R 51 (toxic to aquatic organisms); R53 (may cause long-term adverse effects in the aquatic environment)	R 36/38 (irritating to skin and eyes); R 41 (risk of serious damage to eyes); R 43 (may cause sensitisation by skin contact)	R38(irritating to skin); R43 (may cause sensitisation by skin contact)	R10 (flammable); R38 (irritating to skin); R43 (may cause sensitisation by skin contact); R50 (very toxic to aquatic organisms); R53 (may cause long-term adverse effects in the aquatic environment)	R10 (flammable); R22 (harmful if swallowed); R36/38 (irritating to skin and eyes); R50(very toxic to aquatic organisms); R53 (may cause long-term adverse effects in the aquatic environment)

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Mammalian Toxicity Profile							
Toxico-kinetics	Rapid inhalation and oral absorption; mainly excreted by urine (biphasic with rapid initial clearance)			Readily absorbed by GI tract of rats with subsequent metabolism via 2 hepatic pathways to give metabolites excreted via urine; metabolism may also occur in lung and kidney. Also readily metabolised by rabbits.	Rapidly absorbed from GI tract; Dermal exposures largely lost through extreme volatility but that remaining is fairly well absorbed; Is rapidly metabolised and excreted as metabolites (mainly via urine)	In humans pulmonary uptake is high (approx. 70%); By oral route, excretion of 75-95% and <10% in urine and faeces respectively occurs by 2-3 days in both animals and humans	Absorbed through lungs, skin and GI tract

Table A5.4: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Selected Alternatives - Fragrances

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		α-hexyl cinnamaldehyde	**Citronellol (3,7-dimethyl-6-octen1-ol)**	**Geraniol**	**Citral**	**d-Limonene**	**Pin-2(10)-ene**
Acute toxicity	Rodent LD50 oral >2000 mg/kg; LC50 inhalation >5.07 mg/L	Rat LD50 oral 3100 mg/kg; 4-hr LD50 inhalation >5 mg/L; Mouse LD50 oral 2300 mg/kg; Rabbit LD50 dermal 3000 mg/kg	Rat LD50 oral 3450 mg/kg; Rabbit LD50 dermal 2650 mg/kg; Mouse LD50 subcutaneous 880 mg/kg	Rodent LD50 oral 2100-3600 mg/kg; dermal >5000 mg/kg	Rodent LD50 oral 1670 – 6800 mg/kg; dermal >2000 Rabbit LD50 dermal 2250 mg/kg	Rat LD50 oral 5000 mg/kg; Intraperitoneal 3600 mg/kg; intravenous (male) 125 mg/kg; intravenous (female) 110 mg/kg; subcutaneous (male and female) >20200 mg/kg; Mouse LD50 oral 5600-6600 mg/kg; intraperitoneal 1300 mg/kg; subcutaneous >41500 mg/kg; Rabbit LD50 dermal (24 hr) >5000 mg/kg	Rat LD50 oral >5000 mg/kg; Rabbit LD50 dermal (24-hr) >5000 mg/kg; Moderately toxic – probable oral lethal dose in humans = 0.5-5 g/kg

Irritation	Irritant (slight)	Some evidence of irritancy (moderate-severe) in animals but not humans	In humans 6 % solution caused no irritation	Irritant (severe) to skin and eyes	Irritant (mild to severe in various experimental studies and human Patch tests)	Strongly irritant in human Patch tests	Irritant to skin and mucous membranes in animal studies; In mice, inhalation caused sensory irritation and induced sedation and signs of anaesthesia but no pulmonary irritation

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Sensitisation	Not considered a sensitiser	LLNA assay EC3 value = 2372 mg/cm2; In humans NOEL for HRIPT induction = 23622 mg/cm2; May cause sensitisation by skin contact	In humans 6 % solution caused no sensitisation	LLNA assay EC3 value = 3525 mg/cm2; In humans NOEL for HRIPT induction = 11811 mg/cm2; May cause sensitisation by skin contact	Sensitising in most Buehler and guinea pig maximisation and open epicutaneous tests and in some human Patch tests LLNA assay EC3 value = 1414 mg/cm2; In humans for HRIPT induction NOEL = 1400 mg/cm2 and LOEL = 3876 mg/cm2	Studies in animals have shown that chemical must be oxidized in air for sensitisation to occur; Sensitiser in human Patch tests	

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Repeat dose toxicity	Renal and hepatic toxin: NOAEL (dog oral) = 10 mg/kg/day. Inhalation also causes pulmonary changes with	90 day rat dermal study showed GI tract, liver, kidney, blood and bone marrow changes noted at 250 mg/kg or above; blood and GI effects noted at 125 mg/kg; NOAEL not determined		Rat 16 week oral NOAEL = 10000 ppm diet Rat 28 week oral NOAEL = 1000 ppm diet	Overall rat NOAEL for repeated dose = 200 mg/kg/day (both sexes); effects include morphological changes in nasal cavity and fore-stomach (attributed to irritation)	27 day rat oral caused dose related liver and kidney effects. Kidney effects included α2 microglobulin and chronic nephrosis; 13 week rat oral at up to 2400 mg/kg/day again showed nephropathy in	

	NOAEL (rat inhalation) = 75 ppm					male rats; Dogs given up to 6 ml/kg/d for 6 months suffered vomiting, decreased bodyweight and altered blood chemistry	

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Reproductive and develop-mental toxicity	Limited developmental toxicity: NOAEL (rat oral) = 30 mg/kg/day; NOAEC (rat inhalation) = 211 ppm	In rat 90 day dermal study, NOEL=125 mg/kg; LOEL=250 mg/kg			Rat oral NOAEL for developmental toxicity = 200 mg/kg/day; Inhalation NOAEL for teratogenicity = 68 ppm (423 mg/m3) in presence of maternal toxicity	Increase in abnormal chick embryos at single dose of 25 µM/embryo; Oral dosing on day 9-15 of gestation in rats caused maternal toxicity and developmental delays at 2869 mg/kg orally; Rabbits given 1000 mg/kg orally showed severe toxicity but 250 mg/kg without effect on dams or foetuses;	

						Oral dosing on day 7-12 of gestation in mice at 2363 mg/kg orally given to mice for 6 days from day 7-12 of gestation caused maternal toxicity and bone abnormalities in foetuses	
Genotoxicity	Not mutagenic	Negative in Ames, micronucleus and sex-linked lethal assays		Negative in Ames test and mammalian chromosomal assay	Negative in Ames and chromosomal aberstion and micronucleaus tests but positive in ister chromatid exchange assay	Negative in Ames, mouse L5178Y/TK, and chromosomal aberration and sister chromatid exchanges assays	Negative in Ames test and in sister chromatid exchange assay in Chinese hamster ovary cells

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Cancer	Animal carcinogen (possible threshold mechanism)			Negative in rodent gavage studies	Negative in male rats but equivocal findings for malignant lymphoma in females in one study; another study in same species at higher doses negative; Mouse study negative	Oral rats study at <150 mg/kg/day (males) and 600 mg/kg/day (females) showed dose-related increase in renal tubular hyperplasia and adenoma/ adenocarcinoma in males but no effect in females, or in male and female mice	
Relevant exposure standards	EU: OEL = 122 (8hour TWA); STEL = 306 mg/m3				JECFA oral ADI = <0.5 mg/kg	TLV 100 ppm (USA)	

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Ecotoxicity Profile							
Log Pow	3.37-3.39	5.33	3.91	3.28 (estimated)	2.8-3.0	4.45 (estimated)	4.16
Environ-mental partitioning at equili-brium	Air: 98.9%; Water: 0.79%; Soil: 0.15%; Sediment: 0.16%				Atmospheric releases partition to: Air 97.7%; Water 1.6%; Soil 0.7%; Sediment 0%; Aquatic releases partition to: Air 1.7%; Water 97.0%; Soil 0%; Sediment1.3%		Expect volatilisation to air from water but may be limited by absorption to suspended solids and sediments

Environ-mental half-life	33 - 50 days (air)				Aqueous – T1/2=9.54 days (pH 4), 230 days (pH 7) and 30.1 days (pH 9)	Soil – approx. 9-20 hrs (experimental); Aqueous volatilisation - river and lake of 1 hr and 5 days respectively (model); Reaction with hydroxyl radicals in air - 2.6 hrs	Vapour-phase degradation by reaction with hydroxyl radicals - half-life about 4.9 hrs; Volatilisation half-lives from river and lake = 3 hrs and 5 days respectively (modelled)
Bio-degradation (k d-1)	Surface water 0.046; Sediment 0.002; Soil 0.023	Considered readily biodegradable		Readily biodegradable (86% by 28 days in aerobic conditions; 100% by 15 days in activated sewage)	Readily biodegradable (>90% by 28 days in aerobic conditions; 90-100% by 8 days in activated sludge)	Readily biodegradable (100% by 28 days in aerobic conditions)	Biodegradation may be an important environmental fate in soil (by microorganism)

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Bio-concentration factor	Fish - 296 (reasonable worst-case)	1,028 (estimated) May have moderate bioaccumulation potential	219 (estimated)	183 (estimated)	151 (estimated)	660 (estimated)	320 (estimated for fish)
Acute toxicity - aquatic	Fish LC50 = 1.12- 14.2 mg/L; *Daphnia magna* EC50 = 0.7-2.2 mg/L (48 hour);	Fish 96-hr LC50 = 2.36 mg/L; *Daphnia* 48-hr LC50 = 0.621 mg/L (estimated); Algael 96-hr LC50 = 0.896 mg/L		Fish (*Brachydanio rerio*) 96-hr LC100 = 19.9 mg/L & LC 0 = 9.8 mg/L	Fish (*Leucuscus idus*) 96 hr LD50 = 4.6-10 mg/L; *D. magna* 24 hr EC50 = 7-11 mg/L; Algae (*S. subspicatus*)		Fish (*Pimephales promelas*) LC50 (96-hr) 0.50 mg/L; *D. magna* LC50 (48-hr) 1.25 mg/L; Algae LC50 (48-hr)

	Algae *(Scenedesmus* *capricornutum* (72-96 hr) EC50 = 3.4 mg/L	(estimated)			72 hr EC50 = 16 mg/L and 96 hr EC50 = 19 mg/L		1.44 mg/L
Acute toxicity - terrestrial							

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Repeat exposure - aquatic	Fish NOEC = 0.44 mg/L; *D. magna* NOEC (21-28 day) = 0.4-0.22 mg/L; PNEC aquatic = 20 µg/L (based on algael toxicity); PNEC sediment = 900			30 day exposure of yellow fever mosquito caused 74.4-95.8% egg-hatching inhibition	Aquatic invertebrate EC50 (21d repro) = 1.6 mg/L and NOEC of 1.0 mg/L		Fish (*Oncorhynchus mykiss*) LC50 (60 day) 930-1400 µg/L

	g/kg (dw; extrapolated)						
Repeat exposure - terrestrial	Earthworm (2 species, 2 soil types, 14-day) LC50 = 96 – 258 mg/kg dry weight; PNEC soil = 96 g/kg dw						

Source: RPA, 2010
Source: Aronson et al. (2007); Chemical Land21 (2009); Danish Environmental Protection Agency (2006); EC (2009); EC (2009b); IFRA (2009); Japanese Ministry of Foreign Affairs (2001); Oxford University (2003); NTP (2007); IFF (2007); RSC (2009); The Good Scents Company (2009); US EPA (2009 & 2009b); United States National Library of Medicine (2009) Notes: ADI: Acceptable daily intake; EC50: *Effective concentration provoking a response halfway (50%) between baseline and maximum response; EC3: Effective concentration inducing a 3fold increase in radiolabelled-thymidine incorporation in lymph node cells of treated compared to control animals; GI: Gastrointestinal; HRIPT: Human repeat insult patch test; LD50: Median lethal dose; LLNA: Local lymph node assay; NOAEC: No observed adverse effect concentration; NOAEL: No observed adverse effect level; NOEL: No observed effect level; OEL: Occupational exposure limit; STEL: Short-term exposure limit; TLV: Threshold-limit value; TWA: Time weighted average*

Table A5.5: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Surfactants, Preservatives, Dyes						
Property	**Surfactants**			**Preservatives**		**Dye**
	Sodium dodecylbenzene sulphonate	**Alcohols, C_{12-18}, ethoxylated**	**Sodium lauryl ether sulphate**	**Benzyl salicylate**	**1,2-Benzotiazoline-3(2H)-one**	**CI21095**
Example proportion of product	25-50%	<5%	1-10%	<5%	0.01-0.02%	<1%
Identity, Classification and Labelling						
EC Number	246-680-4	500-201-8	500-234-8	204-262-9	220-120-9	226-789-3
CAS Number	25155-30-0	68213-23-0	68891-38-3	118-58-1	2634-33-5	5468-75-7
Chemical formula	$C_{18}H_{30}O_3S.Na$	Not applicable (generic term is C12-18/EO7)	$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_2OSO_3Na$	$C_{14}H_{12}O_3$	C_7H_5NOS	$C_{34}H_{30}Cl_2N_6O_4$
Ambient state	White to yellow solid	Liquid paste	Light yellow liquid at 27% and yellow viscous liquid or paste at 68%	Colourless to pale yellow clear oily liquid to solid	Solid	Solid
Vapour pressure	3-17 x 10^{-13}	Low: 0.0011 – 3.3 x 10-6 hPa (25ºC; data for related alcohols)	For related C12-14 substances = 1.2 x E^{-13} to 2.1 x E^{-14} Pa (25ºC)	0.16 hPa (25ºC); 1.33 hPa (45ºC)	0.0000037 hPa (25ºC)	3.68E-25 mm Hg (25°C; estimated)

Henry's Law constant (atm-m3/mol)	6.35 x 10^{-3}					
Water solubility	20 g/100 ml (25°C)	15-35 mg/L (estimated)	For related C12-14 substances = 425 - 41 mg/L Considered soluble:	Slight	1100 mg/L (0.11%; 20ºC) 6000 mg/L (0.60%; 30ºC)	Not considered soluble
Log Kow	3.32 (calculated)	4.63 -7.87 (estimate for C12-18 alcohol ethoxylates); 5.36 - 7.19 (data for related alcohols)	For related C12-14 substances = 0.95 - 19	3.48	0.64 (calculated)	3.62 (estimated)

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Labelling symbols		One MSDS identified indicating - Xn-harmful, Xi - irritant; N - dangerous for the environment		Xi - Irritant	Xn - harmful at >25%; Xi – irritant at <25%; N – dangerous for the environment at >25%	Wassergefahrdungs-klasse (WGK) considers to be weakly water polluting

Risk phrases		One MSDS identified indicating - R22 (harmful if swallowed); R41 (risk of serious damage to eyes); R50 (very toxic to aquatic organisms)		R36 (irritating to eyes); R37 (irritating to respiratory system); R38 (irritating to skin); R43 (may cause sensitisation by skin contact)	Dependent on proportion of article composed of substance: *0.05-<5%:* R43 (may cause sensitisation by skin contact); *5-<10%:* R36 (irritant to eyes); R43 10-<20% R41 (risk of serious damage to eyes); R43 *20-<25%:* R38 (irritant to skin); R41; R43 *>25%:* R22 (harmful if swallowed); R38; R41; R43; R50 (very toxic to aquatic organisms)	

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Mammalian Toxicity Profile						
Toxicokinetics	Related substance considered to be readily absorbed from GI tract (rat - 80-90%) and rapidly eliminated (rats, within 72 hours) mainly via urine with remainder via faeces; absorption through intact skin very poor (0.1-0.6%)	Studies in rats on $C_{12}AE_3$, $C_{12}AE_6$ and $C_{12}AE_{10}$ showed extensive (>75%) GI absorption and metabolism with urinary and biliary excretion; Highest dermal penetration rate = 8.4µg/cm_2 for $C_{12}AE_3$	Related substances readily absorbed from GI-tract. Once absorbed, are extensively metabolised by beta- or omega oxidation and excreted via urine. Those with >7 to 9 EO units are excreted to increasing extent via faeces; Dermal absorption limited		Rapid complete metabolisms; excretion via urine (almost complete clearance by 24-hrs)	

Acute toxicity	Rat LD_{50} oral = 1260 mg/kg Mouse LD_{50} oral = 1330 mg/kg Mouse LD_{50} iv = 105 mg/kg Related substance showed very low inhalation toxicity (not possible to calculate LD_{50} inhalation) and dermal LD_{50} of >1000 mg/kg	Rat LCLo inhalation = 130 mg m^{-3} Related substances Rat LD_{50} oral 600-10,000 mg/kg; Dogs 1650 mg/kg; Monkeys 6700 mg/kg Rat LD_{50} inhalation (4 hr) 1.50 – 20.7 mg/L Rat LD_{50} dermal >2000->5000 mg/kg	Rat LD_{50} oral for C12-14AE2S = >2000 mg/kg and for NaC1214AE2S = >2500 mg/kg; Rat LD_{50} inhalation (1 hr) for NH_4 C12-14AE3S = >60 mg/L; Rat LD_{50} dermal for NH_4C12-14AE2S = >2000 mg/kg	Rat LD_{50} oral = 2227 mg/kg Rabbit LD_{50} dermal = 14150 mg/kg	Rat LD_{50} oral = 670 - 1450 mg/kg Mouse LD_{50} oral = 1150 mg/kg Rat LD_{50} dermal (24 hr) = >2000 - >5000 mg/kg	Rat LD_{50} oral = >16000 mg/kg

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Irritation	When tested on rabbit skin and eyes a related substance caused no irritation at up to 2.5%, moderate irritation at 5% (Draize criteria) and was irritating at higher levels. According to the EU criteria, the substance was classified as irritating to skin and also assigned R41	Related substances (undiluted): Slight to sever irritant to rabbit and rat skin; mild to severe irritant to rabbit eye	Experimentally - Skin irritancy: concentration dependent effects seen >70% = moderate to severe skin irritants; 10-30% = mild to moderate irritancy; <1% virtually non-irritant In humans skin irritation potential of aqueous solutions expected to be mild after repeated contact; - Eye irritancy: NH_4C12-14AE2S 9905) and C12-14E2S (28%) are moderate to severe eye irritants; Solutions of <10% are slight to moderate irritants; <1% are virtually non-irritant	Non irritant in Draize or 84/449/EEC B.4 skin test; Very slightly irritant in 48 hr Patch test on humans at 30% solution; Moderately irritant in Draize eye test	Moderate skin irritant in semi-occlusive skin test and severe irritant in 48 hr eye test in rabbits; Negative in human skin test	Not irritant on skin or eye of rabbit

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Sensitisation	No sensitisation potential was found for related substance in animals or humans	Related substances (C9-C21; E02-21): Weak skin sensitisation noted only for one form (C7-9AE6) in Guinea pig; other forms tested all negative	Most studies in guinea pigs or humans (Patch tests) in related substances are negative	LLNA EC_3 = 725 mg/cm_2; Human RIPT test NOEL = 17717 mg/cm_2 Not sensitising in Patch tests with 30% solution in humans Suggested as only weak sensitiser; No expected sensitisation induction level (NESIL) = 17700 µg/cm^2	Moderate contact sensitiser by Magnusson and Kligman but negative in Beuhler test; LLNA and human repeated patch tests suggest no effect level is approx 500ppm	

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Repeat dose toxicity	Oral dosing of animals with related substance has shown changes in weights of liver, caecum and other organs and minor changes in liver and kidney pathology noted: identified overall NOAEL as 85 mg/kg bw/day (9 month study) and LOAEL as 115 mg/kg bw/day	Numerous oral and limited number dermal studies of 14 - 90 days duration conducted on related substances. Carcinogenicity study data also available. Effects noted include: GI tract (mild gastric irritation), changes in organ weights (e.g. liver, spleen and heart) and for dermal route, skin irritation. Main target organ is liver, where adaptive responses occur. For 90+ days studies NOAELs = 50 - 700 mg/kg/day	Numerous rodent oral studies of up to 2 years duration and a dermal study of up to 91 days conducted on related substances. Effects noted for oral studies include: Non-glandular stomach and liver pathology; Range of organs weight effects (e.g. liver, kidney, heart, adrenal, testes and brain); NOAEL = 250 mg/kg/day; Dermal study showed clear effects.		Rat 28 & 90 day oral studies showed non-glandular stomach lesions (possibly related to irritant/corrosive effect); NOAEL (90 day) = 10 mg/kg/day (equiv to 8.42 mg active)	

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Reproductive and developmental toxicity	Series of multi-generation studies on related substance showed no reproductive effects with NOAEL = 170 mg/kg/day (highest tested); studies also showed effects in foetuses (death and deformities and decrease in pregnancy rate) only at maternal toxic doses: no effects apparent at oral dose of <780 mg/kg/day or dermal dose of <1500	Two generation dietary rat studies in C14-15AE7 and C12AE6 gave reproductive NOAELs = >250 mg/kg/day; developmental effects included liver weight changes in presence of maternal toxicity; developmental NOAEL = 50 mg/kg/day	C12AES rat multigeneration feeding study reproductive NOEL = >250 mg/kg/day; Developmental NOAEL = >1000 mg/kg bw/day; NaC12-14AE2S rat multigeneration drink water study developmental NOAEL = >750 mg/kg bw/day		Rat teratogenicity study showed slight foetotoxicity (not teratogenicity) at maternal toxic dose of 100 mg/kg/day; NOAEL = 40 mg/kg/day	

	mg/kg/day					
Genotoxicity	Related substance negative in Ames test, recombinant assay on *Bacillus subtilis and Escherichia coli* reverse mutation assay; also negative in mouse micronucleus and cytogenetic bone marrow assays and in mouse dominant lethal assay	Related substances (including C12-14AE7, C13-15AE7, C16-18AE10), negative in range of *in vitro* and *in vivo* studies	Related substances negative in range of *in vitro* and *in vivo* studies	Negative in Ames test	Marked cytoxicity in Ames test but some studies show negative response; Negative for mutagenicity but possible clastogen in Chinese hamster ovary cells; Not clastogenic in mice *in vivo;* No induction of UDS in rat hepatocytes *in vivo*	

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Cancer	Limited studies on related substance in rats were negative (mention made of mice studies but no details presented)	Several rodent oral studies available on $C_{1213}AE_{6.5}$ and $C_{14-15}AE_7$; all negative	Two 2-yr rat oral studies and a mouse dermal study conducted on C12AE3S, and an 18 month mouse dermal study on C1618AES and other mixed related substances. Although of limited design, all were negative			
Relevant exposure standards				EFSA classification - MSDI = 26 µg/day; No safety concern; CoE category B		
Ecotoxicity Profile						
Log Pow	0.45			4.01	0.4 (20ºC)	9.58 (estimated)
Environmental partitioning at equilibrium		Data on related substances suggest potential transfer from				

		aqueous to suspended solid phases and soil adsorption.				

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Environmental half-life	Related substance degraded rapidly in aerobic conditions (halflife approx. 3 hr in rivers) but not in anaerobic conditions; Also had max. half-life = 1 wk in sludge-amended soil	Readily biodegradable: theoretical oxygen demand (ThOD) 69-86% (estimated); Not expected to be abiotically degradable to appreciable degree				
Biodegradation (k d^{-1})	Related substance was readily biodegradable with: Aqueous primary half-life = 3 hr; Soil primary half-life = 7 days	Estimated half life in river 8 - 12 hrs; Sewage treatment half-life = 1 minute; Readily anaerobically biodegradable (at least 80%)	Ultimately biodegradable via intermediate steps with no recalcitrant metabolites; EUSES estimated degradation range = 87% for C12EO2.7S to 75%		QSAR suggests aerobically degradable (has low bioaccumulation potential in aquatic organisms)	Non-biodegradability according to MITI-I (OECD TG 301C) test method; Not considered a PBT or vPvB; likely to be P(and vP)

			for C18EO2.7S; Good anaerobic degradation also expected			
Bioconcentration	For related substance,	In fish *(Pimephales*		547.7 - 652.47	BCF 13.1 (calculated)	Low potential
factor	BCFs about 87 l/kg and 22 l/kg estimated for river water	*promelas)* = <5 - 135.2 (for homologues)		(depending on pH; calculated)	QSARs suggests low aquatic bioaccumulation potential	

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	Sodium dodecylbenzene sulphonate	**Alcohols, C_{12-18}, ethoxylated**	**Sodium lauryl ether sulphate**	**Benzyl salicylate**	**1,2-Benzotiazoline-3(2H)-one**	**CI21095**
Acute toxicity - aquatic	Ranges for related substance: Fish (*Pimephales promelas*) LD_{50} = 1.0439.4 & NOEC = 0.05-14 mg/L; *D. magna* EC_{50} 0.5-16.7 mg/L, NOEC = 0.1-9.8 mg/L	Fish LC_{50} = 0.4 - 100 mg/L (linear forms) and 0.25 – 40 mg/L (branched forms); *Daphnia magna* EC_{50} (48 hr) for C12-15 homolog = 0.14 – 5 mg/L; Algae (various species) for C12-15 liner forms EC_{50} = 0.28 – 50 mg/L	For related C12-14 substances = Fish (various species) LC_{50} = 0.8 to 4.1 mg/L; Invertebrate (*D. magna*) EC/LC_{50} = 0.46 to 1.30 mg/L; Algae (various species) EC_{50} (48 hr) = 0.5 to 50 mg/L		Fish (*Salmos gairdneri* and *Lepomis macrochirus*) LC_{50} (96 hr) 1.6 - 5.9 mg/L; *D. magna* EC*50* (48 hr) = 1.35 mg/L; Algae EC*50* (72 hr) = 0.1 mg/L	Fish (*Oryzias latipes*) LC_{50} (48-hr) = >200 mg/L
Acute toxicity - terrestrial	Most sensitive values for related substance are - Plant EC50 = 167-316 mg/kg dry Soil Fauna EC50 = 41>1000 mg/kg dry Microorganisms =					

	17>1000 mg/kg dry					

Table A5.5: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Surfactants, Preservatives, Dyes

Property	Surfactants			Preservatives		Dye
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Repeat exposure - aquatic	Most sensitive values for related substance are for - Aquatic species: Algae (*Microcystis spec.)* population density NOEC = 0.80 mg/L; Fish (*Tilapia mossambica*,) 0.34 mg/L; Sediment species: Worm (*Lumbriculus variegates*) survival, reproduction & growth NOEC = 81 mg/kg/day; Nematode (*Caenorhabditis elegans*) egg production NOEC = 100 mg/kg dry	Algae: 50% reduction in growth between days 2 and 4 at 0.63-4.2 mg/L for C12C15 homologs EC_{20} Approx 0.00493 - 0.000370 mM; *D. magna* calculated EC_{20} = $1.61xE_{+0}$ - $3.55xE_{-02}$ mg/L (calculated for C12-18) NOEC = 0.014-0.16 to 0.008– 0.056 (calculated for C12-15) Overall aquatic estimated PNEC = $1.61xE_{-01}$ - $3.55xE_{-03}$ mg/L; Overall sediment estimated PNEC = $3.47xE_{1}$ – $6.54xE_{1}$ mg/L (for C12-18)	No consistent difference in sensitivity between invertebrate and fish species. QSAR developed EC_{20} values = 2.7 - 0.38 mg/L; Generic PNEC aquatic for C12-14 substances in group = 0.27 – 0.038 mg/L			

Table A5.5: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Surfactants, Preservatives, Dyes

Property	Surfactants			Preservatives		Dye
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Repeat exposure - terrestrial	Most sensitive values for related substance are for - Soil ecosystem NOEC= >15 mg/kg dry; Biomass NOEC >16->27 mg/kg dry	Overall soil estimated PNEC = 31.04 – 108.35 mg/kg soil (for C12-18)				

Source: RPA, 2010

Source: Chemid plus (2009); Chemical Land21 (2009b); Dalli (2008); EC (2009 &2009 b); ECB (2005); EFSA (2007); The Good Scent company (2009); HERA (2003, 2004, 2009, 2009b and 2009c); Madson et al. (2000); NIOSH (1997); NITE (2002); Oxford University (2003b); RSC (2009); SCCNFP (2004); US National Library of Medicine (2009) and TEX (2008). Notes: ADI: Acceptable daily intake; EC20: Effective concentration provoking a response 20% between baseline and maximum response; EC50: Effective concentration provoking a response halfway (50%) between baseline and maximum response; EC3: Effective concentration inducing a 3-fold increase in radiolabelled-thymidine incorporation in lymph node cells of treated compared to control animals; GI: Gastrointestinal; HRIPT: Human repeat insult patch test; LCLo: Lowest concentration anticipated to cause death; LD50: Median lethal dose; LLNA: Local lymph node assay; MSDS Material safety data sheet; MSDI: Maximum survey derived daily intake; NOAEC: No observed adverse effect concentration; NOAEL: No observed adverse effect level; NOEL: No observed effect level; OEL: Occupational exposure limit; PNEC: Predicted no effect concentration; STEL: Short-term exposure limit; TLV: Threshold-limit value; TWA: Time weighted average

Table A5.6: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Builders, Complexing Agents, Solvents			
Property	**Builder**	**Complexing/descaling agent**	**Solvent**
	Sodium carbonate	**Citric acid, monohydrate**	**Ethanol**
Example proportion of product	25-40%	1-5%	<5%
Identity, Classification and Labelling			
EC Number	207-838-8	201-069-1	200-578-6
CAS Number	497-19-8	5949-29-1	64-17-5
Chemical formula	$CH_2O_3.2Na$	$C_6H_8O_7$	C_2H_6O
Ambient state	White crystalline hygroscopic powder	Crystalline solid	Colourless liquid
Vapour pressure	0 (20ºC)		57.3 hPa (20ºC); 280 hPa (280ºC)
Henry's Law constant (atm-m_3/mol)		2.3 x 10^{-7} P am_3/mol	0.000252
Water solubility	71 g/L (0ºC); 217 g/L (20ºC)	Freely soluble; 576–771 g/L (20°C)	High
Log Kow			-0.31
Classification	Xi – irritant; E - explosive	Xi - irritant	F -highly flammable
Labelling	R36 (irritating to eyes)	R37 (irritating to respiratory system); R38 (irritating to skin); R41 (risk of serious damage to eyes)	R11 (highly flammable)
Mammalian Toxicity Profile			
Toxicokinetics	Substance will breakdown on contact with body fluids to constitute ions that are naturally present in organisms		Readily absorbed via oral and inhalation routes; limited dermal uptake; Most absorbed ethanol (9098 %) is metabolised in liver; 2-10% excreted

			unchanged via lungs and kidneys
Acute toxicity	Rat LD_{50} oral = 4090 - 5600 mg/kg; Rat LC_{50} inhalation = 2.3 - 5755 mg/L; Mouse LC_{50} inhalation = 1.2 mg/L; Guinea pig LC_{50} inhalation = 0.8 mg/L; Mouse LC_{50}dermal = 117 2210 mg/kg	Rat oral LD_{50} = 3000 - 12000 mg/kg; Rat LD_{50} intra peritoneal = 375 mg/kg; RAT LD_{50} subcutaneous = 5500 mg/kg; Mouse oral LD_{50} = 5040 mg/kg; Rabbit oral lethal dose = 7000 mg/kg	Rodent LD_{50} oral = 1780 -16710 mg/kg Rodent inhalation LC_{50} (4hr) = 39 - 124.7 mg/L Rodent dermal LDLo = 20000 mg/kg Rodent LD_{50} intraperitoneal = 933 - 6710 mg/kg In humans signs of mild toxicity apparent at blood levels of 5-10 mg/ml

Table A5.6: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Builders, Complexing Agents, Solvents

Property	**Builder**	**Complexing/descaling agent**	**Solvent**
	Sodium carbonate	**Citric acid, monohydrate**	**Ethanol**
Irritation	Not irritating – moderately irritating to skin of rabbits; Moderately irritating to skin of rats; Not irritating to highly irritating to eyes of rabbits; Irritant to respiratory tract, eyes and skin and may cause vomiting in humans	Slightly irritant to rabbit skin at 500 mg for 24 hr; Permanent eye damage to rabbit eye from 0.5% solution for 30 minutes; Irritant to eyes respiratory system and skin in man	Not to moderate dermal: irritant Irritant to eyes
Sensitisation		Low sensitising potential; some reports of possible sensitisation in humans	Not sensitising
Repeat dose	Rat 3.5 month inhalation	Main target is reversible	Main target of repeat

toxicity	study at up to 2% showed only reduced weight gain and slight lung pathology at 0.07 mg/L; NOAEL = 0.01-0.02 mg/L	changes in blood profile and metal absorption/excretion characteristics; Rat NOAEL = 1200 mg/kg/day	exposure in humans and animals is liver, with initial steatosis and inflammatory changes, progressing to cirrhosis and potentially cancer; Long term alcohol abuse also associated with effects in GI tract, nervous system and testes; Rat chronic drinking water study showed reduced bodyweight, thyroid hyperplasia and peripheral nerve damage at 3% w/w while 4 week rat oral study showed hepatic changes at 10000 and 20000 mg/kg/day; 90 day inhalation study in rats, guinea pigs, rabbits, dogs and monkeys at 86 mg/m3 (46 ppm) showed no effect
Reproductive and developmental toxicity	Mouse fertility study – TDLo = 84,800 mg/kg; Developmental studies in rats at up to 245 mg/kg, mice at 3.4 - 340 mg/kg and rabbit at 176 mg/kg showed no effects; Effects (not specified) noted only mice given intra-uterine dose of 84 mg/kg	Not a reproductive or developmental toxin; Rat reproductive NOAEL = 2500 mg/kg/day	Long-term high level exposure results in testicular atrophy in humans; Established human foetotoxin and developmental toxin (including teratogenic effects) Rats given 22-27 mg/ml for 3-4 wks showed reduced reproductive performance; Rat 6 week inhalation study at 18.8 and 30 mg/L (10,000 and 16000 ppm) - negative

Table A5.6: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Builders, Complexing Agents, Solvents			
Property	**Builder**	**Complexing/descaling agent**	**Solvent**
	Sodium carbonate	**Citric acid, monohydrate**	**Ethanol**
Genotoxicity	Negative for primary DNA damage in *Escherichia coli*; Ames test on sodium bicarbonate and sodium sesquicarbonate negative	Not mutagenic *in vitro* or *in vivo* assays	Positive for mutagenicity and clastogenicity in *in vitro* (only with metabolic activation) and *in vivo* studies
Cancer	No data	Not carcinogenic	Established human and animal carcinogen operating via both genotoxic and non-genotoxic mechanisms (respective importance in eliciting effects uncertain)
Relevant exposure standards	UK OES 10 mg/m3 (8-hr TLV)		NL: MAC 1000 mg/m3; DE: MAK 1000 mg/m3 or 2000 mg/m3 (60 min), 1900 mg/m3, 3800 mg/m3 (1 hr, 3 times), 4000 mg/m3 (15 min, 4 times); UK: OES 1900-1920 mg/m3 (8hr); US TLV: 1000-1880 mg/m3; NO: 950 mg/m3; FR: VME 1900-9500 mg/m3
Ecotoxicity Profile			
Log Pow	ca. 0 (not applicable for an inorganic compound which dissociates)	-1.72 (20°C)	-0.32
Environmental partitioning at equilibrium	Sodium and carbonate ions do not adsorb significantly to sediment	Equilibrium state: 99.99% water; <0.01% soil; <0.01% sediment; <0.01% air	Distributes mainly to air and water (57% air, 34% water, 9% soil)

Environmental half-life		Atmospheric = 2.3 days	Tropospheric half-life = 10 – 36 hrs
Biodegradation (k d-1)	Dissociates in water to sodium and carbonate ions	Readily biodegradable – 97% (CO2 evolution); Used as metabolite in Krebs cycle by all eukaryotic cells; Dissociates readily in water into the citrate anion and representative cations	Stable to hydrolysis but readily biodegradable; 45-74% after 5 days
Bioconcentration factor			logBCF = 0.5

Table A5.6: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Builders, Complexing Agents, Solvents

Property	**Builder**	**Complexing/descaling agent**	**Solvent**
	Sodium carbonate	**Citric acid, monohydrate**	**Ethanol**
Acute toxicity - aquatic	Fish (various species) LC_{50} = 167 - 1200 mg/L; NOEC = 550 mg/L. Invertebrate (*D. Magna)* EC_{50} = 151 - 565 mg/L; (*Culex sp*.) EC_{50} = 600 Algae (various sp.) EC_{50} (120hr) = 137-1050 mg/L	Fish (various species) LD 50 (96 hr) = 440-1516 mg/L; Invertebrate (various species) EC0 = 73-1206 mg/L	Extensive – e.g. Fish (various) - LC_{50} (96 hr) = 8140-14200 mg/L; Invertebrates - *D. magna* LC_{50} (48 hr) = 9268-14221 mg/L EC_{50} (24 hr) = 10000 mg/L; *Artemia Salina* LC_{50} (24hr) = 1833 mg/L) Algae (*Chlorella vulgaris)* EC_{50} (96h) = 1000 mg/L; Microorganism EC_{50} = 1450-6500 mg/L
Acute toxicity - terrestrial			Worms: LC_{50} (48 hr) = 0.1-1 mg/cm_2 filter paper
Repeat exposure	Fish (various sp.) LC_{100} (5	Fish (*Carassius auratus*)	Fish (various sp)

- aquatic	day) = 68-110 mg/L; Invertebrate (*D. magna)* EC_{50} *(*immobilisation at4 days) = 228-297 mg/L	LC0 = 625 mg/L; LC_{100} = 849 mg/L; Invertebrate (*D. magna*) EC_0 = 80 mg/L; EC_{100} = 120 mg/L; Algae (*Scenedesmus quadricauda*) EC_0 (7 days) = 640 mg/L	EC_{50} = 14-26 mg/L; LC_{50} = 454 mg/L; Invertebrate - *(D. magna)* EC_{50} = 14-26 mg/L; *(Cerodaphnia sp)* 10 day reproduction NOEC = 9.6 mg/L
Repeat exposure - terrestrial			

Source: RPA, 2010; ACGIH (2000); Albano (2000); Baan et al. (2007); Basketter et al. (2004); EC (2006); Chemical Land21 (2009e); Cohen-Kerem & Koren (2003); EC (2009b); Ethanol HPV Challenge Consortium (2001); Gossel & Bricker (1994); HERA (2002, 2005 and 2005b); HSE (2000); IARC (1985, 1987, 1988); Kane et al. (1980); Kruhoffer (1983); Lester and Greenberg (1951); Mahan & Myers (1987); Nelson et al. (1985, 1985b, 1988); Oxford University (2005 and b); Pendlington et al. (2001); Rivier & Vale (1983); Simpson et al. (2004); Steiner et al. (1997); Swiss Agency for the Environment, Forests and Landscape (2004); Turcotte et al. (2005); US EPA (2005) Notes: ACGIH: American Conference of Industrial Hygienists; DE: Germany; EDo/LDo: Highest dose causing no effect/deaths; EDLO/LDLO: Lowest dose causing effect/deaths; ED50/LD50: Median effective/lethal dose; ED100/LD100: Dose causing effect/deaths in all organisms; FR: France; NL: Netherlands; NO: Norway; NOEL/LOEL: No/lowest observed effect level; N/LOAEL: No/lowest observed adverse effect level; MAK: Maximale Arbeitsplatz-Konzentration; TLV: Threshold-limit value; VME: Valeur Moyenne d'Exposition; UK: United Kingdom; USA: United Sates of America

Table A5.7: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Thickeners, Anti-caking Agents, Stabilisers

Property	**Thickener**	**Anti-caking agent**	**Stabiliser**
	Xanthan gum	**Sodium sulphate**	**Coconut oil monoethanolamine**
Example proportion of product	1-5%	25-50%	5-10%
Identity, Classification and Labelling			
EC Number	234-394-2	231-820-9	268-770-2
CAS Number	11138-66-2	7757-82-6	68140-00-1
Chemical formula	$(C_{35}H_{49}O_{29})_n$	$H_2O_4S.2Na$	$C_{17}H_{35}NO_2$
Ambient state	Off-white free flowing powder	White powder or crystals	Pale yellow solid
Vapour pressure		1E-06 Pa (25ºC)	
Henry's Law constant (atm-m^3/mol)			

Water solubility	Soluble	1.61 x E_{05} mg/L (20ºC)	1.40 mg/L
Log Kow		10^{-3}	
Labelling symbols		German KBwS : generally not water polluting	Fatty acid monoethanolamides: Xi – irritant German KBwS: water polluting
Risk phrases			Fatty acid monoethanolamides: R41 (risk of serious damage to eyes)
Mammalian Toxicity Profile			
Toxicokinetics	No significant absorption via oral or dermal route; Approximately 98% of oral intake eliminated via faeces unchanged and of that absorbed 15% of radio-labelled material is metabolised to CO_2 within 100 hours		
Acute toxicity	Rat LD_{50} oral = >1000 mg/kg (max. dose feasible)	Rat LD_{50} oral = 60000 - >10000 mg/kg; Mouse LD_{50} oral = 193 - 6346 mg/kg; Acute effects in humans limited to diarrhoea after single dose >300 mg/kg	Rat LD_{50} oral = >3125 - >5000 mg/kg Mouse LD_{50} oral = 3125 - >10000 mg/kg

Table A5.7: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Thickeners, Anti-caking Agents, Stabilisers

Property	**Thickener**	**Anti-caking agent**	**Stabiliser**
	Xanthan gum	**Sodium sulphate**	**Coconut oil monoethanolamine**
Irritation	Skin irritation in rabbit noted with 5% aqueous suspension; No skin irritation in rats at <2% solution; No eye irritation in rabbit with 1 % solution		No to moderate irritant in rabbit and mouse dermal tests; No to slight irritation in rabbit eye tests

Sensitisation	Negative in Guinea pig and rabbit sensitisation studies and in epidemiological investigations of exposed workers		Negative in Guinea pig maximisation tests
Repeat dose toxicity	Rat dietary studies showed increased small intestine dry weight (but not stomach, ceacum or large intestine) at >2000 mg/kg/day; Well tolerated (minor clinical pathology and GI-tract disturbance) in dogs at 2000 mg/kg/day for 12 weeks, and at 1000 mg/kg in rats and dogs for 2 years	Extensive data - Rat 6 week feeding study no effect at <2% diet; Rat inhalation studies - 3 day - no effect at 10 mg/m3; 3 month - pulmonary changes and, hepatic and spermatocyte effects at 1 mg/m3; NOEL = 0.1 mg/m3; No adverse findings in human epidemiology studies; Overall repeated dose NOAEL (for rats) considered = 320 mg/kg/day	None-dose related changes in forestomach in rat repeat dose oral studies; NOAEL 750-1500 mg/kg/day
Reproductive and developmental toxicity	Rat multi-generation study showed no effects at <500 mg/kg/day	Foetal toxicity in mice given 14 g/kg (gestation days 8-12); Negative in mouse drinking water study at up to 5000 ppm	
Genotoxicity		Negative in Ames and Escherichia coli assays	Negative in Ames tests
Cancer		Rat dietary study no effect at <630 mg/kg/day	No data (note some concerns regarding potential for nitrosamine contamination)
Relevant exposure standards	German MAK: 6 mg/m3 US TLV: 10 mg/m3 OSHA, 5 mg/m3 TWA ACGIH, 3 mg/m3 TWA	German MAK 6 mg/m3 UK OEL 10 mg/m3 (inhalable)	
Ecotoxicity Profile			
Log Pow			3.89 -4.71 (calculated)
Environmental partitioning at equilibrium			
Environmental half-life			

Table A5.7: Comparison of Hazard Profiles of 1,4 Dichlorobenzene and Substances used in Alternative Products – Thickeners, Anti-caking Agents, Stabilisers			
Property	**Thickener**	**Anti-caking agent**	**Stabiliser**
	Xanthan gum	**Sodium sulphate**	**Coconut oil monoethanolamine**
Biodegradation		Not biodegradable;	Readily biodegradable: 55
(k d^{-1})		Undergoes abiotic hydrolysis – COD = <3 mg/g; No bioaccumulation anticipated	82% after 30 days aerobic (activated sewage plant effluent); Also undergoes anaerobic biodegradation (79% in 42 days)
Bioconcentration factor		2.5 l.kg (earthworm) 13 l.kg (fish)	
Acute toxicity - aquatic	Past the US EPA (California) mysid shrimp toxicity test	Extensive data – e.g. Fish (*Gambusia affinis*) LD_{50} -24-hr = 5400 mg/L 96-hr = 120 mg/L Fish (*Morone saxatilis*) LD_{50}-24-hr = 650-1100 mg/L 48-hr = 320-1100 mg/L Crustacea (*Artemia salina*) EC_0 100-hr = 24 mg/L; 4-day = deaths at 5.4 - 7.8 mg/L; *(D magna)* EC_{50} 96 hr = 630 mg/L; Overall low acute toxicity to fish, daphnia and algae; LC_{50}/EC_{50} generally values far >1000 mg/L	Fish LD_{50}: *Brachydanio rerio,* 96-hr = 28.5 – 90 mg/L; *Leuciscus idus,* 48-hr = 13.5 – 20.7 mg/L; Crustacea EC_{50} *Crangon crangon* 48 hr = >100 mg/L *D magna* 24-hr = 10 - 135 mg/L; Algae EC_{50} (*Scenedesmus subspicatus*) (96-hr) = 0.761.1 mg/L –based on possibly contaminated material; values of 16.6-17.8 mg/l reported for algae in recent studies on pure substance
Acute toxicity - terrestrial			
Repeat exposure - aquatic		Extensive data – e.g. Fish (*Gambusia affinis*) LD_{50} 6-day = 2200 - 3200 mg/L; Algae (*Chlorella pyrenoidosa*) EC_{100} 8-day = 57700 mg/L; (*Nitscheria linearis*) EC_{50} (5day) =	

		1900 mg/L	
Repeat exposure - terrestrial			

Source: RPA, 2010
Source: Burdock Group Consultants (2006); Chemical Land21 (2009c and 2009d); EC (2009 and 2009b); US FDA (2009); The Good Scents Company (2009); HERA (2006); Madson et al. (2000); and MILLC (1998). Notes: ACGIH: American Conference of Industrial Hygienists; COD: Chemical oxygen demand; LD50: Median lethal dose; MAK: Maximale Arbeitsplatz-Konzentration (German); OSHA: Occupational Safety and Health Administration (USA); TLV: Threshold-limit value

Annex 5: Camphor's identifiers, physicochemical and availability properties

Identifier/Property	Value	Source
EC number	200-945-0	ESIS 2011
EC name	bornan-2-one	ESIS 2011; IPCS, 2011
CAS number	76-22-2	ESIS 2011; IPCS, 2011
IUPAC name	1,7,7-trimethyl-bicyclo(2,2,1)heptan-2-one	Camphor @ 3DChem.com, 2011
Synonyms	2-Bornanone; 2-Camphanone; 1,7,7-Trimethylbicyclo(2.2.1)heptan-2-one; Camphor Spirits;1,7,7-trimethylbicyclo[2.2.1]-2-heptanone (camphor);1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-on;1,7,7-trimethyl-norcamphor; 2-keto-1,77-trimethylnorcamphane; Formosa camphor, Gum camphor; Japan camphor, Laurel camphor; dl-Camphor; DL-Camphor; Synthetic camphor.	IPCS 2011 Fisher 2011, Merck Index 2006
Annex I index number	Not classified	ESIS 2011
Molecular formula	C10H16O	ESIS 2011
Molecular weight	152.3 g/mol	EU RAR 2004
Density	0.992 g/cm^3	ChemicalBoook, 2011
Vapor pressure	4 mm Hg (70 °C) 27Pa at 20°C 0.65 mmHg at 25°C	ChemicalBook, 2011
Flash Point	64 C	Fischer 2011
Water Solubility	0.12 g/100 mL (25 ºC), practically insoluble	Merck Index 2006, ChemicalBook, 2011

		Fischer, 2011
Solubility in organic solvents	1g/1ml alcohol; 1g/1ml ether; 1g/0.5ml chloroform; freely soluble in phenol	Merck Index
Physical state	colourless or white crystalline powder with strong characteristic odour and pungent aromatic taste	ChemicalBook, 2011
Melting point	180°C, the substance sublimates at room temperature	Merck Index, 2006 ChemicalBook, 2011
Boiling point	204°C	ChemicalBook, 2011
Origin	Camphor is found in wood of camphor laurel, (Cinnamonum camphora), a large evergreen tree found in Asia (particularly in Borneo, hence its alternate name); it can also be synthetically produced from oil of turpentine.	Merck Index, 2006 Camphor @ 3DChem.com, 2011

Annex 6: Parameters used in ConsExpo

Parameters, representing the worst case scenario, used in ConsExpo 4.1 for modelling of exposure to limonene and pinene:

Parameter	Limonene	Pinene	Source/Description
CAS Number			
Application temperature	25°C	25°C	RPA, 2010
Molecular weight	136.23	136.23	Merck Index, 2006
KOW	4.57	4.16	RPA, 2010
Vapour pressure	266 Pa	391 Pa	RPA, 2010 Unitarium, 2012
Exposure scenario			
Body weight	60 kg	60 kg	Guidance R.15 – female adult body weight (ECHA, 2010d)
	12.5 kg	12.5 kg	ConsExpo - 2.5 year old child, default body weight (R.15 - no value) (ECHA, 2010d)
Use frequency	365 d/y	365 d/y	Daily exposure
Exposure route - Inhalation			
Exposure duration	1 hour – toilet 23 hours – living area	1 hour – toilet 23 hours – living area	Worst case scenario based on ConsExpo
Product amount	6 ml*	6 ml*	Product information
Weight fraction compound	5%	5%	Product information
Room volume	2.5 m^3	2.5 m^3	Guidance R.15 (ECHA, 2010d) and ConsExpo – toilet
Ventilation rate	0,2 air exchanges	0,2 air exchanges per	Guidance R.15, conservative

	per hour	hour	estimation (ECHA, 2010d)
Emission duration	9 days	9 days	Product information
Mode of release	Constant rate	Constant rate	The chemical is released with a constant rate in a certain time, and it is simultaneously removed from the air by ventilation of the room. This scenario is recommended for use when details of evaporation are not exactly known, but the time period during which the compound evaporates can be estimated. It is used for calculating the steady air concentration.
Uptake			
Uptake fraction	100 %	100 %	Guidance R.8 ECHA, 2010 a
Inhalation rate	20 m^3/day	20 m^3/day	Guidance R.15 - inhalation rate for adult for a whole day exposure (ECHA, 2010d)
	7 m^3/day	7 m^3/day	Guidance R.15 – inhalation rate for 2-3 year old child (ECHA, 2010d)

* it is assumed that the density of the product is the same as for water – therefore value of 6 g is used for the modelling of exposure

Resulting calculated for 24hours exposure levels:

Activity	**Parameters**	**Exposure averaged over 24 hours**	
		mg/m^3	**mg/kg/d**
Adult exposure	25°C	0.093	0.031
Child	25°C	0.093	0.052

Annex 7: Estimation of cancer burden based on the unit risk value established by EPA

As concluded in section B we consider 1,4-dichlorobenzene a threshold carcinogenic substance, and consequently linear extrapolation models to calculate population cancer risks are not appropriate. However, based on default assumptions EPA (2006) has derived an airborne unit cancer risk value of 4 x 10^{-3} $(mg/m^3)^{-1}$, estimating the lifetime cancer risk for chronic exposure. This cancer risk assessment is only included for illustrative purposes and not further used to justify the restriction proposal.

Table AX57 presents the quantitative estimates on the cancer burden for four exposed populations:

- Domestic users exposed at homes
- Toilet attendants exposed at work for 8 hours per day, 5 days per week
- Cleaners exposed at work in average for 2 hours per day, 5 days per week
- Males exposed at public toilets in average for 2 minutes per day, 5 days per week.

Table AX57: Estimated cancer burden from using 1,4-dichlorobenzene in air fresheners and toilet blocks in the EU based on a cancer unit risk value

	Exposure (mg/m3) averaged over 24 hours	**Unit risk (mg/m3)-1 (U.S. EPA, 2006)**	**Exposed population**	**Cancer burden in 70 years**	**Cancer burden per year**
Domestic use	0.33	0.004	164,836	217.58	3.11
Toilet attendant (8 hours)	4.6		512	9.43	0.13
Cleaning personnel (2 hours)	1		21,351	85.40	1.22
Consumer in public toilet (2 minutes)	0.000717		14,497,658	41.58	0.59
Total				**354**	**5.1**

The model suggests that domestic use results in 3 cancer cases per year, and the public use in less than 2 cases. It is not realistic to assume that all these cases would be avoided already in the first year after the entry into force of the restriction. However, the exposure to 1,4-dichlorobenzene of most of the exposed persons is almost completely removed after the existing stock of products is used, and the impact can be considered to occur relatively fast. It is not realistic to assume either, that people would die immediately to cancer. However, for the majority of the cases, death would be likely to occur within 5 years of diagnosis if it is presumed that the induced tumours are primary hepatic cancers (RPA, 2010).

Our results are in line with other studies deriving indicative estimations of the cancer burden based on unit risk values. These studies have used the unit risk value of the Californian EPA established in 1996 of 11 x 10^{-3} $(mg/m^3)^{-1}$. Both Sax *et al*. (2006) and McCarthy *et al*. (2009) concluded that there was an increased risk for cancer cases based on measured ambient concentrations of 1,4-dichlorobenzene (see also section B.10.1.1.2.). No information on exposure sources were identified in these studies. In addition, Aronson *et al*. (2007) concluded that domestic use of 1,4-dichlorobenzene products for over six months would be considered "unsafe" based on an estimated lifetime cancer risk of 3.9 x 10^{-3} and a daily exposure of 0.1 mg/kg. RPA (2010) followed the same approach as Aronson *et al*. for cancer burden related to the use of 1,4-dichlorobenzene urinal blocks in the public toilets and modelled a cancer burden of 1 case per year in the EU.

Annex 8: Quantitative impact assessment based on decrease in lung functioning due to 1,4-dichlorobenzene exposure

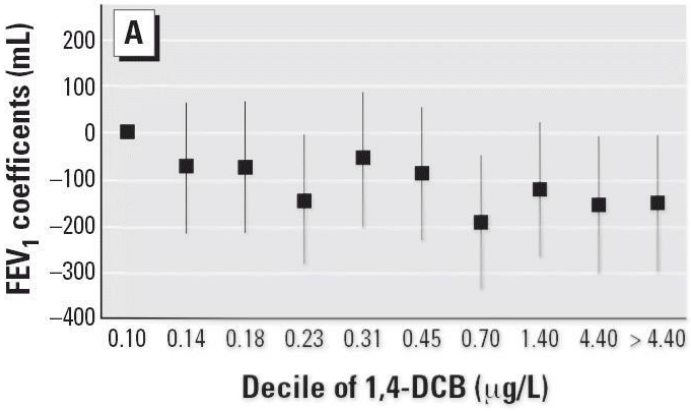
This quantitative impact assessment was included in the original Annex XV report submitted by ECHA. However, as RAC did not find the scientific basis for the assessment solid enough the information was not used by SEAC. The assessment is included into this Annex as it remains a valid example of an methodological approach which could be useful for other restriction cases.

Information on health impacts of 1,4-dichlorobenzene in humans is scarce. One of the few studies of sufficient size and quality is a report by Elliott *et al*. (2006) addressing lung functioning in relation to exposure. As lung volume is a reliable indicator for mortality over-risks we carried out a quantitative impact assessment based on the results of Elliott *et al.* (2006). It should however be noted that the study by Elliot *et al*. is the only human study addressing and indicating a correlation between exposure to 1,4-dichlorobenzene and decreased lung volume. Even if adverse effects on lung functioning has been reported after exposure to other volatile organic compounds (VOCs; see for example Yoon *et al*. 2010), and the findings from experimental studies with 1,4-dichlorobenzene in terms of irritation and lesions of the nasal epithelium also support a causal relationship, a confirming study demonstrating the link between 1,4-dichlorobenzene exposure and lung function would clearly have increased the validity of the present impact assessment.

Exposure to 1,4-dichlorobenzene and FEV_1

Elliott *et al.* (2006) examined if concentrations of 11 VOCs were associated with changes in lung functioning. They tested the lung function in 953 adults who participated in the Third National Health and Nutrition Examination Survey (NHANES III) which was carried out in 1988-1994 in the US. The study also provided measured concentrations of 1,4-dichlorobenzene in blood.

Figure AX2 shows the changes in forced expiratory volume in 1 second (FEV_1) for each decile of 1,4-dichlorobenzene concentrations compared with the corresponding blood levels of the lowest decile. The individuals in the highest decile had a mean decrement of -153 ml in FEV_1 (95% Confidence Interval, -297 to -8). The measured blood concentrations of 1,4-dichlorobenzene of the 90th percentile were 3.89 µg/l for males and 4.83 µg/l for females. Similar decrements seem to occur already starting from the 7th decile with blood concentrations of 0.7 µg/l (see Figure AX2). However, it should be noted that there was no dose response relationship between increasing 1,4-dichlorobenzene concentrations in blood and reductions in lung function.



Source: Elliott et al. (2006)

Figure AX2: Changes in the FEV1 (with 95% CIs) for each decile of 1,4-dichlorobenzene concentrations in blood

Elliot *et al.* (2006) did not convert blood levels to inhalation exposure of 1,4-dichlorobenzene. To use their data for an impact assessment we used data from Sexton *et al*. (2005) who studied e.g. the relationship between air and blood concentrations of 1,4-dichlorobenzene. Their report is based on the School Health Initiative: Environment, Learning, Disease (SHIELD) that examined the exposure of more than 150 children to environmental agents over two years. For 1,4-dichlorobenzene blood concentrations between 12 and 27 µg/l at the 95th percentile and 24 and 470 µg/l at the 99^{th} percentile were reported.

As far as we know this is the only report available on which a conversion of blood levels into the corresponding air levels could be easily based. Even if it addresses children, who might differ from adults in terms of toxicokinetics, we found it appropriate for our purposes. It should however be acknowledged that the lack of information regarding inhalation exposure and corresponding blood level in adults is adding uncertainty to this part of the impact assessment.

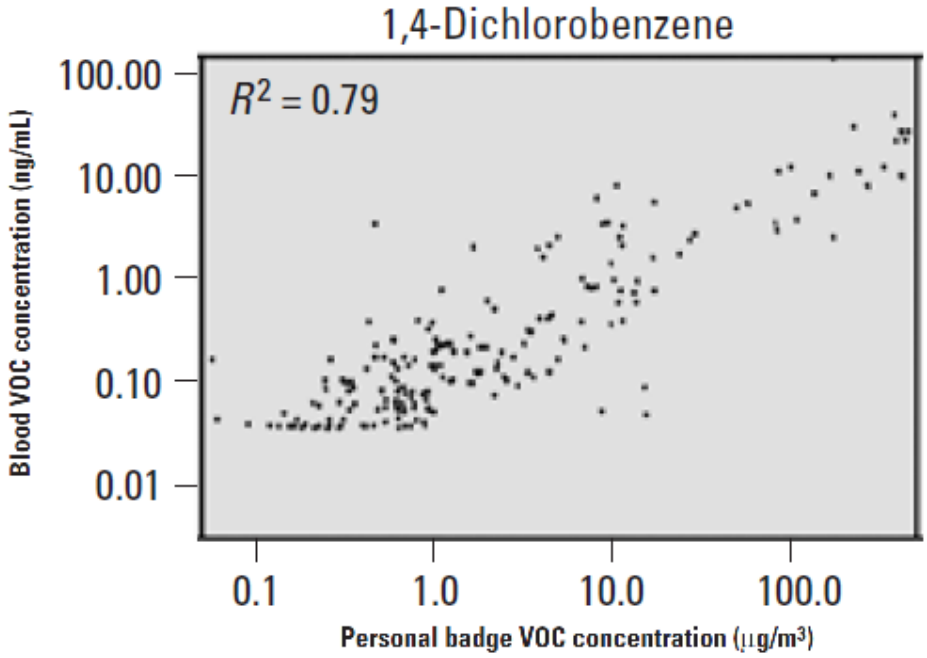
Figure AX3 gives details on blood concentrations versus air concentrations. Given the rapid metabolism of 1,4-dichlorobenzene blood levels are expected to reflect recent exposures.

The blood concentration of the highest decile in the study by Elliot *et al.* (4.4 µg/l) were used to assess the impact of 1,4-dichlorobenzene exposure on the identified populations in this report. Based on the study of Sexton *et al*. (2005) a blood concentration of 4.4 µg/l could be estimated to result from an inhalation exposure of 0.044 mg/m^3. In our report the estimated exposures in the realistic scenarios were 4.6 mg/m^3 for toilet attendants, 1 mg/m^3 for professional cleaners and 0.33 mg/m^3 for consumers exposed at homes (Table F45). The estimated exposure for users of public toilets was significantly lower (0.000717 mg/m^3).

Box AX2: Blood concentrations of 1,4-dichlorobenzene versus inhalation exposure

Sexton *et al*. (2005) reported both blood concentrations and corresponding air concentration measured with monitoring batches. The figure below presents the blood concentrations of 1,4-dichlorobenzene versus personal exposure concentrations. It can be seen from the figure that 10 µg/l (10 ng/mL) corresponds to a personal inhalation exposure of around 100 µg/m^3 (0.1 mg/m^3) or more.

Figure AX3: Blood concentrations of 1,4-dichlorobenzene versus personal exposure concentration



Source: Modified from Sexton et al. (2005) (Similar figures for other substances removed)

It can be concluded that the decrease in lung function demonstrated by Elliot *et al.* (2006) occurred at considerably lower exposure levels than those estimated in this report for domestic users and for professionals working in public toilets. Thus, it seems plausible that this lung functioning decrease would also occur in our study populations. This conclusion is in line with the assumptions made by Elliott *et al.* (2006) that the exposure to 1,4-dichlorobenzene in their study population was related to the use of air fresheners, toilet bowl blocks and moth balls and their suggestion that the exposure levels to 1,4-dichlorobenzene found in the U.S. population may result in reduced pulmonary function. However, the authors aired uncertainties and reservations in their paper in concluding on the link between exposure to 1,4-dichlorobenzene and decreased lung function stating that it was not possible to determine if 1,4-dichlorobenzene exposure preceded pulmonary function decline due to the cross-sectional nature of the study and also that the inverse association between 1,4-dichlorobenzene concentration and pulmonary function may have been affected by unmeasured confounders. They stated that they had no data to address the possibility that those who are exposed to toilet bowl, air fresheners or other room deodorisers may also be exposed to cleaning products that impair pulmonary function. They concluded that larger and longitudinal studies (measuring exposure and function at various time points) would be necessary to properly evaluate the effects on respiratory symptoms and disease.

FEV_1 as a risk factor

Pulmonary function has been identified as a risk factor for cardiovascular disease, stroke, and lung cancer, as well as an important predictor of all-cause mortality (Hole *et al*., 1996). For deaths in cancers other than lung cancer no correlation with lung function was found by Hole *et al.* (1996). They analysed data from 7058 men and 8353 women aged 45-64 at the time of the baseline screening in 1972-1976. During 15 years of follow up 2575 men and 1894 women died. It was concluded that impaired lung function is a major clinical indicator of mortality risk.

The decrease in lung functioning is also connected to chronic obstructive pulmonary disease (COPD). Baughman *et al*. (2011) used data from the Copenhagen City Heart Study of 23,000 participants who conducted four clinical examinations and a self-administered questionnaire conducted over a 28-year period. Lung function decline was associated with increased risk of COPD morbidity and mortality. The median decline in FEV_1 during the five-year period between the first and second examinations was reported to be 60 ml per year, and at 75^{th} percentile 118 ml per year. The decrease in lung functioning (in FEV_1) was a significant predictor of COPD morbidity for males and females starting from the second quartile. For COPD mortality a significant correlation was seen already for the second and third quartiles. The decrease in FEV_1 values reported in Elliot *et al*. (2006) due to exposure to 1,4-dichlorobenzene is in the same order of magnitude as the changes in FEV_1 values reported by Baughman *et al*. (2011).

Based on Elliott *et al*. (2006) and Hole *et al*. (1996) it was estimated that the hazard ratio (over-risk) for mortality from all causes increases by 12% in our study populations (excluding users of public toilets). The details of this estimation are given in Box AX3.

Box AX3: Deriving the hazard ratio from the estimated decrease in FEV_1

The decrease in FEV_1 of 150 ml corresponded to a percentage of about 4.4 of the mean FEV_1 in the report by Elliot *et al.* (2006). This was derived by dividing the decrease in FEV_1 by the mean FEV_1.

$$\frac{150ml}{3440ml} \approx 4.4$$

A decrease of 1 percentage in FEV_1 resulted in an increase of 0.028 (or 2.8%) of the hazard ratio in the report by Hole *et al*. (1996). This was calculated by dividing the difference in the relative hazard ratio between the 1^{st} and the 5^{th} quintiles with the difference between the upper bond of the 1^{st} quintile and the lower bond of the 5^{th} quintile for relative FEV_1 (averages for males and females).

$$\left[(1.92-1.00)/2+(1.89-1.00)/2\right] \div \frac{\left[(107-73)+(111-75)\right]/2}{(107+111)/2} \approx 2.8$$

Multiplying the estimated change of 4.4 percentages in the FEV_1 with the factor of 0.028 gives an increase in mortality (over-risk) of 0.124 or 12.4%.

All cause mortality

Calculations have been conducted to estimate the impact of exposure to 1,4-dichlorobenzene on mortality based on the hazard ratios reported by Hole *et al*. (1996). Table AX58 gives data and the results. The calculation did not consider the declining trend in the use of 1,4-dichlorobenzene. The following formula was used:

$$Mortality\_burden\_(cases/year) = q \times a \times b$$

$where:$
$q = Exposed\_population$
$a = Mortality\_rate$
$b = Increase\_in\_mortality$

Table AX58: Estimated all cause mortality related to decreased lung functioning in 2012

	Exposed population	Mortality rate in EU27 in 2010	Increase in mortality (%)	Mortality burden per year
Domestic use	164,836	0.97%	12.40%	198
Toilet attendant (8 hours)	512			1
Cleaning personnel (2 hours)	21,351			26
Total	186,699			**225**

Based on the exposure estimate of realistic scenarios presented in this report it is estimated that around 225 people would die each year in the EU earlier than expected due to exposure to 1,4-dichlorobenzene and its adverse effect on lung functioning. The model suggests that domestic use would result in 198 cases per year, and the public use in 27 cases.

Characteristics of the lung function decrease induced by 1,4-dichlorobenzene based on comparisons with smoking

The health impacts presented in Table AX58 represent an estimate of the increase in mortality in 2012 associated with exposure to 1,4-dichlorobenzene through the use of air fresheners and toilet blocks by the population at risk. Estimating the benefits of restricting this use requires understanding of two aspects of the relationship:

- The time profile describing how reductions in exposure to 1,4-dichlorobenzene translate into reductions in annual mortality;
- The characteristics (and specifically, the life expectancy) of those individuals affected.

Due to the lack of information related to 1,4-dichlorobenzene exposure we have for the purpose of this report used information on smoking to extrapolate estimates needed for the health impact assessment. This is justified by the fact that smoking is a chronic inhalation exposure which influences lung function (for example it decreases the FEV_1), partly by exposure to VOCs, and that smoking is correlated to decreased life expectancy due to mortality (amongst others) in cardiovascular disease, chronic obstructive pulmonary disease (COPD) and lung cancer. It should however be noted that the assumptions for health impacts of 1,4-dichlorobenzene based on information on smoking adds uncertainty to the benefit analysis.

Estimated reductions in annual mortality after reduction of exposure. Recovery after smoking cessation has been extensively studied and is well understood. According to the US

Department and Health and Human Services, Centre for Disease Control and Prevention (1990) lung functioning has recovered after 1 month to 1 year. After this time period the risk for heart infarction has decreased by 50%, while the risk for stroke decreases to 50% after 5 to 7 years. Based on this information we assume that the mortality over-risk due to exposure to 1,4-dichlorobenzene decreases by 50% per year after the onset of a restriction, and that the over-risk is totally reduced 10 years after the onset of the restriction.

Expected loss of life-years due to exposure to 1,4-dichlorobenzene. Based on a large prospective epidemiological study of 34 439 British doctors the average loss in life expectancy for smokers has been estimated at 10 years (Doll *et al*. 2004). Due to the lack of corresponding information for 1,4-dichlorobenzene we decided to use a rather cautious assumption of an average loss of 1 year for exposed individuals.

Valuation of the health impacts of restricting the use of 1,4-dichlorobenzene-based products

Based on the discussion above the following assumptions were used for the health valuation:

- Time profile of benefit realisation: It is assumed that full benefits would be realised after 10 years and that the impact declines by 50% per year during these 10 years;

- Life expectancy: It is assumed that the effect of 1,4-dichlorobenzene exposure would be to reduce life expectancy by one year;

- Value of changes in life expectancy: The value of a lost life-year is valued at either €50,000 or €120,000.

The conservatice assumption of a reduction of one year in life expectancy was based on Doll *et al.* (2004) (see above) and implies that a valuation approach based on the 'value of a lost life-year' is more appropriate than one based on the value of statistical life, which implies a loss of life-expectancy of around 40 years. The values of changes in life expectancy are those recommended in Guidance on Socio-Economic Analysis - Restrictions (ECHA, 2008).

The approach adopted was to estimate the number of life years saved each year assuming that it would take 10 years to achieve full benefit from the restriction. These quantities were then multiplied by the respective unit values to give an estimate of the value of the benefits in each year. This permitted the calculation of a present and annualised value of these benefits based on a 20-year time horizon and a discount rate of four per cent (ECHA, 2008). The annualised benefit can then be compared with estimates of the annual costs (section F.2) to examine under what assumptions the benefits might justify those costs. This provides an indication of how likely it is that the benefits of the proposed restriction would justify the costs in practice.

The formula for the present value is given by the following:

$$PV = \sum_{t=1}^{n} \frac{B_t}{(1+i)^t}$$

where *PV* is present value, *n* is the number of years (20), B_t is the benefit in year *t*, and *i* is the discount rate (0.04). The annualised value is simply the constant benefit value *B* which sets PV equal to the same present value as is calculated when annual benefits are allowed to vary (B_t).

Table AX59: Yearly distribution of health benefits over 20-year period

		Value of health benefits (€m)	
Year	**Reduction in fatalities**	**VoLYL* €50,000****	**VoLYL* €120,000****
1	112	5.6	13.5
2	169	8.4	20.2
3	197	9.8	23.6
4	211	10.5	25.3
5	218	10.9	26.2
6	221	11.1	26.6
7	223	11.2	26.8
8	224	11.2	26.9
9	224	11.2	26.9
10	225	11.2	27.0
11-20	225	11.2	27.0

* VoLYL = Value of a life year lost
** €50,000 is the median value and €120,000 is the mean value (New Ext, 2004; ECHA, 2008)

Table AX60: Value of health benefits over 20-year period (€m)

	VoLYL €50,000	**VoLYL €120,000**
Present Value	148.1	355.5
Annualised value	10.9	26.2

The tables above present the results of this sensitivity exercise and estimates of the annualised value of health benefits under different assumptions for the value of a life-year lost (VoLYL). It can be seen that the annualised value of benefits ranges from €10.9 million to €26.2 million. This range reflects the effect of assuming that a single life-year is valued at €50,000 or at €120,000. The domestic use of the products counts for 88% of the health benefits (from €9.6 million to €23.1 million) and the use by professionals 12% (from €1.3 to €3.1 million)[32].

[32] 198/225=0.88; 27/225=0.12

Table AX61: Ranges of estimated health benefits for the 3 Restriction options (annualised values)

Restriction option	Estimated health benefit range (€m per year)
1	9.6 – 23.1
2	1.3 – 3.1
3	10.9 – 26.2

Uncertainties

Annex 8 presented quantified health impacts related to the use of 1,4-dichlorobenzene in air fresheners and toilet blocks and compared them with the benefits of having in place a restriction prohibiting these uses.

This comparison was based on the following steps:

- The amount of 1,4-dichlorobenzene placed on the market was used to estimate the number of use locations. Assuming a number of exposed persons per use location permitted to quantify the size of the population at risk (Table F45).
- The population at risk was combined with an estimated increase in mortality (%) due to decreased lung functioning. This permitted to estimate the mortality burden per year (Table AX58).
- The mortality burden per year was monetised using assumptions for the value of a life-year lost (Table AX60).
- The amount of 1,4-dichlorobenzene placed on the market was used to estimate the change in consumer surplus for the three restriction options under examination (see Table F48 and Table F49).

Finally, the monetised mortality burden was compared to the change in consumer surplus. This led to the conclusion that the benefits from the restriction (expressed in monetised mortality burden) outweigh the costs (calculated as loss in consumer surplus).

Each of the above steps is associated with uncertainties, and where pertinent these were discussed in the relevant sub-sections of section F. The starting point of the quantification is the amount of 1,4-dichlorobenzene placed on the market. Even if this amount was estimated for 2012 from market information (AMEC, 2012), the amount to be placed on the market in the future in the absence of a restriction is unknown, but estimated to decline moderately (to 90% of the current value). If we assume, as a simple scenario analysis that this amount would decline by e.g. 50%, this would result in reducing all the estimations presented above by the same percentage. These estimations are given in Table AX62 for Restriction option 3 (Restriction on both professional and consumer uses), for illustrative purposes. A comparison of the present value of the benefits to the change in consumer surplus shows that, as expected, the benefits of this option outweigh the costs.

Table AX62: Costs and benefits of Restriction option 3 from assuming a reduction of 50% in the amount of 1,4-dichlorobenzene placed on the market

		Calculated from:
1,4-dichlorobenzene placed on the market (t)	404	50% of amount placed on the market in 2012
Use locations	290,548	Table F45
Population at risk	7,342,178	Table F45
Mortality burden per year	112	Table AX58
Present value (M€)	5.4 – 13.0	Table AX60
Change in consumer surplus (M€)	1.9 – 2.6	Table F48 Table F49