SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

3a,4,7,7a-tetrahydro-4,7-methanoindene (DCDP)

EC No 201-052-9

CAS RN 77-73-6

Evaluating Member State(s): France

Dated: May 2022

Evaluating Member State Competent Authority

French Agency for Food, Environmental and Occupational Health Safety (ANSES) on behalf of French Ministry of Environment
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France
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Year of evaluation in CoRAP: 2016

Before concluding the substance evaluation a (draft) Decision to request further information was issued on: 10 March 2017

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the Registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the Substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the Substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, 3a,4,7,7a-tetrahydro-4,7-methanoindene (DCDP; EC number 201-052-9) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected reprotoxic
- Exposure of workers
- High RCR
- High (aggregated) tonnage

During the evaluation other concerns were identified:

- Substance identity
- Exposure of consumers
- Exposure during the service-life of articles
- Possible endocrine disruption properties

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Dossier evaluation ongoing.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	x
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures OEL Enforcement/Article 36 notification	x
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

A CLH dossier should be considered in order to establish the classification for acute toxicity (revision of the classification), reprotoxicity and repeated dose toxicity. Classification for reprotoxicity and repeated dose toxicity will be considered following the completion of the ongoing data generation required in compliance check (CCH; 90-day repeated dose toxicity study and two pre-natal developmental toxicity (PNDT) studies, followed by an extended one-generation reproductive toxicity study (EOGRTS).

Nevertheless, it can already be concluded that the Substance already meets the criteria to be classified for environment as:

- Aquatic Acute 1 – H400: Very toxic to aquatic life
- Aquatic Chronic 2 – H411: Toxic to aquatic life with long-lasting effects

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not relevant at this stage

4.1.3. Restriction

Not relevant at this stage

4.1.4. Other EU-wide regulatory risk management measures

OEL: currently numerous OELs exist in many Member States but are not harmonised. Considering the Substance is used in occupational settings, presents hazardous properties and that the existing OELs are not aligned, it seems relevant to establish a common binding OEL at EU level.

Enforcement/Article 36 notification: France invites the National Enforcement Authorities of the Member States where DCPD is registered, to check whether the full composition of the Substance is available (if appropriate via an Article 36 notification), and most importantly if the classification of the substance takes into account any relevant impurities (see also section 7.3 and 7.6.2 below and confidential annex).

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not relevant

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLH	tbd	FR MSCA
Possible RMOA	tbd	FR MSCA

The Forum will be informed as soon as possible that enforcement is needed for the Substance in relation to substance identity and associated classifications.

A harmonised classification proposal will be submitted once the ongoing data generation is available.
A RMOA will be conducted by France to consider risk management options to reduce environmental and (if needed) human exposure.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, 3a,4,7,7a-tetrahydro-4,7-methanoindene (DCDP; EC number 201-052-9) was originally selected for substance evaluation in order to clarify concerns about:

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- Exposure of workers
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During the evaluation other concerns were identified:
- Substance identity
- Exposure of consumers
- Exposure during the service-life of articles
- Possible endocrine disruption properties

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Reproductive toxicity, including endocrine disruption properties	**Concern unresolved** Relevant data currently generated under CCH. To be reconsidered in a follow-up action when data requested is submitted.
Exposure	**Concern unresolved** Registrants are strongly encouraged to update their registration dossiers on the following points: - Exposure in downstream and end-uses of mixtures and articles containing polymers to be clarified. - Combined inhalation exposure estimations and risk characterisation for workers over a day to be clarified. - Acute inhalation exposure and risk characterisation for systemic effects for workers to be assessed. - Risk related to skin irritation of workers to be assessed. Description of PPE to be added.
Substance identity	**Concern unresolved** DCPD is a mono-constituent which exists under two stereoisomer forms (endo and exo). The Substance covers both stereoisomers. Three ranges of purity exist for this substance: UPR grade (80-95%), high purity (>95%) and Resin grade (73 – 83%). This last range of purity is disregarded as it is not covered by the boundary composition. The specifications of the substance proposed by the lead registrant do not cover all compositions registered. Indeed some significant and relevant impurities (2-methylbut-2-ene (EC: 208-156-3), toluene (EC: 203-625-9), mixed xylenes (EC: 292-694-9 and EC: 215-535- 7), 4-vinylcyclohexene (EC: 2O2-B4B-9) and isoprene (CAS RN 78-79-5)) are not reported in the boundary composition although they could be present in all DCPD sources as manufacturing processes are similar. Additionally, uncertainties remain for several compositions as unknown impurities have been specified until 5% w/w.
Additional endpoints	

Acute toxicity	Oral route: harmonised C&L process to be initiated: Acute Tox 3 - H301 Inhalation route: harmonised C&L process to be initiated: Acute Tox 2 - H330 No acute toxicity by dermal route. No further action for this route.
Irritation	Existing harmonised classification as Skin Irrit 2 - H315 and Eye Irrit 2 – H319. No further action.
Sensitisation	No concern for skin and respiratory sensitisation. No further action.
Repeated-dose toxicity	Lowest NOAEL (oral) = 4 mg/kg bw/day (rats, in a combined repeated dose and reproduction/ developmental screening test) Lowest NOAEC (inhalation) = 27.6 mg/m^3 (mice, 90-day study) NOAEL may need revision when new studies under CCH will be available.
Mutagenicity	Presence of mutagenic impurities to be clarified by enforcement. One chromosomal aberration test shows slightly positive results but micronucleus test performed in the same study with the same conditions and using a purified sample is negative. Other studies are negative. No further study requested.
Carcinogenicity	No data. Presence of carcinogenic impurities to be clarified by enforcement.
PBT vPvB	Based on the assessment described in the subsections of Part B, the Substance is not a PBT / vPvB substance.

7.2. Procedure

The evaluation of the Substance was comprehensive, all hazard endpoints for human health, environment and all uses were evaluated.

The aggregated dataset and the literature available were used for the evaluation. The literature search was performed in May 2016. Relevant information after this date had not been identified up to August 2021.
The eMSCA had informal contact with the Registrants regarding substance identity, uses and access to full study reports.
The eMSCA considered that information was still missing to clarify the concerns identified and a draft decision was issued at the end of the first round of evaluation (March 2016-March 2017) to request data on impurities, physico-chemical properties of the solid and liquid forms, human exposure and reproductive toxicity studies.
The draft decision was sent to the registrants which provided comments on the requests.
It was decided after exchanges with ECHA that all the requests will be transferred in a Compliance check (CCH). A termination letter was therefore sent by ECHA on the 19 April 2019 to the registrants.
A CCH was issued by ECHA on 26 April 2019. Only requests related to human health were included, with a specific request regarding the test material, its purity and the impurities present in the test material. The CCH decision requires the Registrant(s) to perform a 90-day study by oral route and a pre-natal developmental toxicity (PNDT) study in a first species by oral route. The studies are expected by the deadline of 31 August 2022.
In parallel, a PNDT by oral route in a 2nd species PNDT is on-going further to a testing proposal (TP) and is expected by 31 August 2022.
Information requirements under Section 8.7.3. of Annex IX/X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) is not addressed yet in the ongoing CCH

because the information from the 90-day study is relevant to choose the proper design of the EOGRTS.
As the need to request further data under SEv is not identified, a conclusion document is issued by the eMSCA.

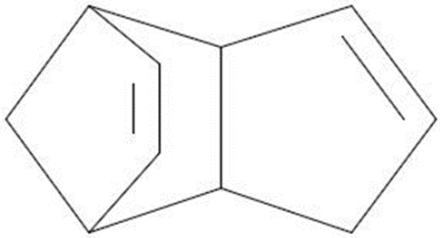
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Dicyclopentadiene (OECD name) 3a,4,7,7a-tetrahydro-4,7-methanoindene (*IUPAC* name)
EC number:	201-052-9
CAS RN:	77-73-6
Index number in Annex VI of the CLP Regulation:	601-044-00-9
Molecular formula:	$C_{10}H_{12}$
Molecular weight range:	132.202 g/mol
Synonyms:	4,7-Methano-1H-indene, 3a,4,7,7a-tetrahydro- Bicyclopentadiene DCPD

Type of substance ☒Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Purity of the substance: > 80% w/w.

The composition submitted by the registrants is a monoconstituent according to REACH guidance for identification and naming of substances.

DCPD is available in three different grades: DCPD resin grade, DCPD UPR grade[2], and DCPD high purity grade. This substance boundary composition is only applicable to DCPD UPR (> 80% - 95%) and high purity grade (>95%).

The details of registered compositions including impurities are given in a confidential annex.
The boundary composition specifies 16 impurities including 2 relevant impurities (Benzene and 1,3-butadiene).

Thirty-two (32) impurities are not included in the boundary composition including 9 that are not identified and 5 (2-methylbut-2-ene (EC No 208-156-3), toluene (EC No 203-625-9), mixed xylenes (EC No 292-694-9 and EC No 215-535- 7), 4-vinylcyclohexene (EC No

[2] UPR grade: developed for use in unsaturated polyester resins.

202-848-9) and Isoprene (EC No 201-143-3)) that are classified as CMR and are expected to impact the hazard profile and the classification of the Substance.

Table 5

Constituents	Typical concentration	Concentration range	Remarks
Dicyclopentadiene / 77-73-6	90% (w/w)	80 - < 99% (w/w)	Solid form (purity > 95%) Liquid form (range purity 80-95%)

Analytical information is provided (UV/VIS, IR, NMR, MS spectra and GC, HPLC chromatograms) but for some registrants analytical data are insufficient to confirm the composition and the structure of the Substance.

7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES		
Property	**Value**	
	UPR grade (liquid) **Purity [80 – 95%]**	**High purity DCPD (solid)** **Purity > 95%**
Physical state at 20°C and 101.3 kPa	DCPD (purity 83 - 88%) is a colourless liquid with characteristic odour (Camphor like odour) at ambient temperature and pressure. Visual description of the substance by registrants.	High purity DCPD is colourless crystalline solid with characteristic odour (Camphor like odour) at ambient temperature and pressure. [NIOSH handbook (2005)]
Melting / freezing point	**Value used for SEV:** 10.6°C at 94% of purity Melting point was measured with method ASTM 1493 a	**Value used for SEV:** 32°C NIOSH, 2005, Pocked Guide to Chemical Hazards. *Other literature data (WHO ICSC, 2005) gives consistent value between 32 and 34°C.*
Boiling point	**Value used for SEV:** between 80-190°C at purity > 80% No information is available on the method used, GLP status and purity of test substance	**Value used for SEV:** Decomposition: 170°C [NIOSH, 2005, Pocked Guide to Chemical Hazards] *Other literature data (WHO ICSC, 2005) gives consistent temperature of decomposition between 170 and 172.5°C.*
Relative density	**Value used for SEV:** 0,975–0,989 g/cm^3 at 20°C 0,965-0,980 g/cm^3 at 30°C for a purity of 94%. Relative density was measured with method ASTM D4052	**Value used for SEV:** 0.93 g/cm^3 at 35°C [NIOSH, 2005, Pocked Guide to Chemical Hazards] *Other literature data (WHO ICSC, 2005) gives consistent value of 0.98 g/cm^3*
Viscosity	**Value used for SEV**:	Viscosity is not relevant for solid.

	4,384 mm^2/s at 20°C 2,811mm^2 at 40°C, for a purity of 94%. Viscosity was measured with method ASTM 445 DCPD liquid is self-classified Asp. Tox. 1 - H304.	
Vapour pressure	No information is available on the vapour pressure of liquid DCPD. The vapour pressure results are presented for high purity (solid) DCPD but as data was generated at temperatures above the melting point, DCPD would be in liquid form. Thus vapour pressure of liquid DCPD is expected to be similar to the high purity DCPD in its melted (liquid) form.	**Value used for SEV:** 1.4mmHg (186Pa) at 20°C NIOSH handbook (2005) DCPD is volatile at 20°C.
Water solubility	No information is available on water solubility of liquid DCPD. This information cannot be requested under Substance evaluation.	**Value used for SEV:** 0.02 g/L at 25°C and pH 7, which is classified as slightly soluble, WHO ICSC, 2005. *Other supportive data:* *Water solubility was determined to be 20 mg/l at 25°C according to the test procedure OECD TG 105 but no information is available on the GLP status and purity of test substance*
Surface tension	Not relevant The surface tension study does not need to be conducted as, based on the structure of this substance, surface activity is not expected or predicted	Not relevant The surface tension study does not need to be conducted as, based on the structure of this substance, surface activity is not expected or predicted
Henry's law constant	No information is available on Henry's law constant of liquid DCPD. This information cannot be requested under Substance evaluation.	**Value used for SEV:** The calculated Henry's Law Constant for DCPD is 1229.6 Pa.m3/mol. The value has been calculated based on the physico-chemical characteristics of the substance (Vapour pressure, water solubility and molecular weight) and the equation
Partition coefficient n-octanol/water (Log Kow)	No information is available on Log Kow of liquid form. This information cannot be requested under Substance evaluation.	**Value used for SEV**: 2.78 at 25°C [WHO ICSC (2005)] *Other supportive data:* *Log Kow was determined to be 2.78 according to the test procedure OECD TG 107 (GLP status) but no information is available on the purity of test substance*

Flammability	**Value used for SEV:** Flash Point typically 25°C - 32°C No information on the primary source of the data or the methods used is available. However, this information is taken from WHO ICSC (2005) and so can be considered reliable and suitable for use as the supporting study for this endpoint **Classification**: Flam. Liquid 3 (Hazard statement: H226 flammable liquid and vapour) Available data are in agreement with classification proposed by registrants. However, it was not possible to verify on which basis the harmonized classification Flam. Liq. 2 (translated from the classification under DSD, R11) was chosen. The harmonized classification should be revised.	**Value used for SEV:** The flashpoint of high purity DCPD is 32.2°C. No information on the primary source of the data or the methods used is available. However, this information is taken from NIOSH (2005) and so can be considered reliable and suitable for use as the supporting study for this endpoint **Self-Classification** (Worst case scenario): Flam. Solid 2 (Hazard statement: H228 flammable Solid).
Autoflammability / self-ignition temperature	**Value used for SEV:** not autoflammable at ambient temperature. The auto-flammability temperature of the test substance is 503°C. No information is available on the method used or on the purity/form of DCPD. However, this information is taken from a reliable peer reviewed database and so can be considered reliable and suitable for use as the key study for this endpoint (WHO ICSC 2005).	
Explosive properties	**Value used for SEV:** non explosive Based on theoretical considerations and on chemical structure (no chemical groups associated with explosive properties present in the molecule), DCPD has no explosive properties.	**Value used for SEV:** non explosive Based on theoretical considerations and on chemical structure (no chemical groups associated with explosive properties present in the molecule), DCPD has no explosive properties.
Oxidising properties	**Value used for SEV:** non oxidizing properties Based on theoretical considerations and on chemical structure, DCPD liquid has no oxidizing properties.	**Value used for SEV:** non oxidizing properties Based on theoretical considerations and on chemical structure, DCPD solid has no oxidizing properties.
Granulometry	Not relevant for liquid.	Not relevant as high purity DCPD is a waxy solid at ambient temperature.
Stability in organic solvents and identity of relevant degradation products	Not required as the stability of the substance is not considered as critical.	Not required as the stability of the substance is not considered as critical.
Dissociation constant	The dissociation constant study does not need to be conducted as the substance does not contain any functional groups that dissociate. No significant dissociation is expected.	The dissociation constant study does not need to be conducted as the substance does not contain any functional groups that dissociate. No significant dissociation is expected.

7.5. Manufacture and uses

7.5.1. Quantities

Table 7

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☐ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☒ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

The Substance is manufactured and/or imported in the European Economic Area in the range of 100 000 - 1 000 000 tonnes per year.

Based on the registration information accessed on 23 July 2020, there are 44 active registrants and 1 inactive registrant.

7.5.2. Overview of uses

DCPD is used as a monomer intermediate to manufacture polymers and as a non-monomer intermediate to manufacture other substances. Since it is an intermediate, it is consumed during the production of new substances. The registration dossier does not include any exhaustive description of the substances manufactured from DCPD (polymers and non polymers) nor on the mixtures and articles where the polymers are used. The information available in the registration dossier is that the Substance is used to produce a wide range of resins (aromatic hydrocarbons, unsaturated polyesters, phenolics and epoxies) used in many mixtures and articles (including, but not limited to, high quality optical lenses, flame retardants for plastics, hot melt adhesives); it is also used as an intermediate to produce insecticides, as hardener and dryer in linseed and soybean oil, and in the production of EPDM (ethylene propylene diene monomer) elastomers, metallocenes, resins, varnishes, paints.

The scope of the registration and the chemical safety assessment depends on the function of the Substance (monomer or not monomer). The reduced registration conditions set up in Article 18 do not apply to monomers according to Article 6(2). According to Article 2(9), polymers are not registered and thus downstream and end-uses of polymers formed from DCPD must be addressed in the registration dossier of DCPD. However, no information is currently available in the registration dossiers to link downstream and end-uses of polymers to uses of DCPD as monomer or non-monomer intermediate.

The available registration dossiers does not generally include information on the end-uses of the polymers (type of mixtures where polymers are incorporated, articles made from polymers, and sectors of use of these mixtures and articles).

Information below is provided as available in the disseminated registration dossier on 23 July 2020.

Table 8

USES	
	Use(s)
Manufacture	ERC 1, 2, 3, 4, 5, 6a, 6b, 6c, 6d, 7 PROC 1, 2, 3, 4, 8a, 8b, 9, 15, 28

Uses as intermediate	All registrations were made as full registrations, but for 7 of them the tonnage indicated in the dossiers refers to the use as transported isolated intermediate. Industrial use as monomer and non-monomer, resulting in manufacture of another substances (including, but not limited to, polymers) See below (use at industrial sites)
Formulation	**Distribution** ERC 1, 2, 3, 4, 5, 6a, 6b, 6c, 6d, 7 PROC 1, 2, 3, 4, 8a, 8b, 9, 15 Use of the substance as such PC 15, 19, 21, 32
Uses at industrial sites	**Use as intermediate** ERC 6a, 6d PROC 1, 2, 3, 4, 8a, 8b, 9, 15, 28 PC 19, 21, 32 SU 8, 9, 10 Use of the substance as such or in a mixture Subsequent service life is not considered relevant for this use **Polymer production** ERC 4, 6a, 6b, 6c PROC 1, 2, 3, 4, 5, 6, 8a, 8b, 9, 14, 21, 28 PC 32 SU 8, 9, 11, 12 Subsequent service life is or is not considered relevant for this use depending on the registrant Use of the substance as such or in a mixture **Polymer processing** ERC 4, 6d PROC 1, 2, 3, 4, 5, 6, 8a, 8b, 9, 13, 14, 21, 28 PC 32 SU 10, 11, 12 Subsequent service life is or is not considered relevant for this use depending on the registrant Use of the substance as such or in a mixture **Distribution** ERC 1, 2, 3, 4, 5, 6a, 6b, 6c, 6d, 7 PROC 1, 2, 3, 4, 8a, 8b, 9, 15, 28 PC 1, 18, 32 SU 8, 9 Use of the substance as such or in a mixture Subsequent service life is or is not considered relevant for this use depending on the registrant
Uses by professional workers	**Polymer processing** ERC 8a, 8c, 8d, 8f PROC 1, 2, 6, 8a, 8b, 14, 21, 28 PC 15, 21, 32 SU 11, 12 Use of the substance as such or in a mixture Subsequent service life is or is not considered relevant for this use depending on the registrant
Consumer Uses	**Use only as polymer** ERC 8a, 8d PC 1, 4, 9a, 9b, 9c, 15, 18, 23, 24, 31, 34
Article service life	**Polymer components** Articles used by workers, consumers ERC 10a PROC 14, 24 AC 1, 10

	The substance is not intended to be released by the article
Uses advised against	None

- **Environmental release categories:**
  - ERC 1: Manufacture of the substance
  - ERC 2: Formulation into mixture
  - ERC 3: Formulation into solid matrix
  - ERC 4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
  - ERC 5: Use at industrial site leading to inclusion into/onto article
  - ERC 6a: Use of intermediate
  - ERC 6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)
  - ERC 6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article)
  - ERC 6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)
  - ERC 7: Use of functional fluid at industrial site
  - ERC 8a: Widespread use of non-reactive processing aid (no inclusion into or onto article, indoor)
  - ERC 8c: Widespread use leading to inclusion into/onto article (indoor)
  - ERC 8d: Widespread use of non-reactive processing aid (no inclusion into or onto article, outdoor)
  - ERC 8f: Widespread use leading to inclusion into/onto article (outdoor)
  - ERC 10a: Widespread use of articles with low release (outdoor)

- **Process categories:**
  - PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions
  - PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions
  - PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment condition
  - PROC 4: Chemical production where opportunity for exposure arises
  - PROC 5: Mixing or blending in batch processes
  - PROC 6: Calendering operations
  - PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities
  - PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities
  - PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing)
  - PROC 13: Treatment of articles by dipping and pouring
  - PROC 14: Tabletting, compression, extrusion, pelletisation, granulation
  - PROC 15: Use as laboratory reagent
  - PROC 21: Low energy manipulation and handling of substances bound in/on materials or articles
  - PROC 24: High (mechanical) energy work-up of substances bound in/on materials and/or articles
  - PROC 28: Manual maintenance (cleaning and repair) of machinery

- **Sectors of end-use:**
  - SU 8: Manufacture of bulk, large scale chemicals (including petroleum products)
  - SU 9: Manufacture of fine chemicals
  - SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) *replaced with the Life Cycle Stage "Formulation or repacking (F)" in the most recent R12 guidance*[3]
  - SU 11: Manufacture of rubber products
  - SU 12: Manufacture of plastics products, including compounding and conversion

- **Product categories:**
  - PC 1: Adhesives, sealants

[3] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.12: Use description. Version 3.0, December 2015.

- PC 4: Anti-Freeze and de-icing products
- PC 9a: Coatings and paints, thinners, paint removers
- PC 9b: Fillers, putties, plasters, modelling clay
- PC 9c: Finger paints
- PC 15: Non-metal-surface treatment products
- PC 18: Ink and toners
- PC 19: Intermediate *replaced with the Technical Function "Intermediate" in the most recent R12 guidance*
- PC 21: Laboratory chemicals
- PC 23: Leather treatment products
- PC 31: Polishes and wax blends
- PC 32: Polymer preparations and compounds
- PC 34: Textile dyes, and impregnating products

- **Article categories:**
  - AC 1: Vehicles
  - AC 10: Rubber articles (includes foam materials)

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 9: Harmonised classification

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS RN**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
601-044-00-9	3a,4,7,7a-tetrahydro-4,7-methanoindene	201-052-9	77-73-6	Flam. Liq. 2	H225	-	-
				Acute Tox. 4 *	H302		
				Skin Irrit. 2	H315		
				Eye Irrit. 2	H319		
				Acute Tox. 4 *	H332		
				STOT SE 3	H335		
				Aquatic Chronic 2	H411		

The asterisk (*) indicates a minimum classification (article 1.2.1 of the CLP regulation).

- Liquid form: a harmonised classification as Flam. Liq. 2 is available.
  However based on the data available a classification as Flam. Liquid 3 (Hazard statement: H226 flammable liquid and vapour) is warranted. It was not possible to verify on which basis the harmonized classification Flam. Liq. 2 was chosen. It has been translated from the classification under DSD, R11.

- Solid form: should be classified as Flam. Solid 2 (Hazard statement: H228 flammable solid).

7.6.2. Self-classification

- In the registration(s):

The Registrant(s) present two different classifications depending on the purity (as reported in the Chemical Safety Report of 8 May 2018).

Table 10: Self-classifications in the registration dossiers

Hazard Class and Category Code(s)	Hazard statement code(s)	High Purity DCPD (> 95%)	Commercial DCPD (>80% but <95%)
Flam. Liq. 3	H226: Flammable liquid and vapour.		X
Flam. Sol. 1	H228: Flammable solid.	X	
Acute Tox. 4	H302: Harmful if swallowed.	X	X
Asp Tox. 1	H304: May be fatal if swallowed and enters airways.		X
Acute Tox. 2	H330: Fatal if inhaled.	X	X
Skin Irrit. 2	H315: Causes skin irritation.	X	X
Eye Irrit. 2	H319: Causes serious eye irritation.	X	X
Repr. 2 - Specific effect: foetotoxic effects such as reduced pup body weight, increased pup mortality, and decreased pup survival. Route of exposure: Oral	H361: Suspected of damaging fertility or the unborn child.	X	X
STOT SE 3 - Affected organs: respiratory tract Route of exposure: Inhalation	H335: May cause respiratory irritation.	X	X
Aquatic Acute 1	H400: Very toxic to aquatic life.	X	X M factor = 1
Aquatic Chronic 2	H411: Toxic to aquatic life with long lasting effects.	X	X

- The following hazard classes are notified among the aggregated self-classifications in the C&L Inventory (accessed 24 July 2020):

- Flam. Liq. 2 - H225
- Flam. Liq. 3 - H226
- Flam. Sol. 1 - H228
- Acute Tox. 4 - H302
- Asp. Tox. 1 - H304
- Skin Irrit. 2 - H315
- Eye Irrit. 2 - H319
- Eye Irrit. 2B - H320
- Acute Tox. 2 - H330
- Acute Tox. 3 - H331
- Acute Tox. 4 - H332
- STOT SE 3 - H335 (respiratory tract, lungs, eyes, central nervous system, skin, kidney)
- STOT SE 3 - H336 (narcotic effect)
- Repr. 2 – H361 (oral)
- STOT SE 1 - H370 (respiratory organ system, liver, kidney)
- STOT RE 1 - H372 (kidney)
- STOT RE 2 - H373 (circulatory organ, liver, lungs)
- Aquatic Acute 1 - H400
- Aquatic Chronic 2 - H411

The eMSCA highlights that several compositions of DCPD, registered by different Registrants contain CMR impurities at concentrations above the classification limits that would lead to classification of the registered substance as CMR. However, the concerned Registrants did not classify their substances accordingly.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

No data are available. The Substance is not expected to undergo hydrolysis in the environment due to a lack of hydrolysable functional groups.

7.7.1.1.2. Phototransformation in air

Table 11: Study on phototransformation in air

Method	Results	Remarks	Reference
(Q)SAR	Reaction with hydroxyl radicals at 25°C: Overall OH Rate Constant: = 119 x 10^{-12}cm^3/molecule-sec Half Life: = 1.077 h (12 hour day; 1.5 x10^6 OH/cm^3)	*2 (reliable with restrictions)* weight of evidence *(Q)SAR* *Test material (common name): DCPD*	AOPWIN v1.92 model

Based on the data on photochemical degradation in the air, DCPD is considered to rapidly degrade in the atmosphere *via* photo oxidation process. The eMSCA can support this conclusion.

7.7.1.1.3. Phototransformation in water

No data are available.

7.7.1.1.4. Phototransformation in soil

No data are available.

7.7.1.2. Biodegradation

7.7.1.2.1. Biodegradation in water

7.7.1.2.1.1. Screening tests

Table 12: Screening tests for biodegradation in water

Method	Results	Remarks	Reference
Test type: ready biodegradability Activated Sludge supernatant OECD TG 301 F (Ready Biodegradability: Manometric Respirometry Test) (with the exception of	Not readily biodegradable % Degradation of test substance: 0 after 28 d (O2 consumption)	2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate)	Unpublished study report, 2004,

the inoculum preparation which was performed ASTM D5864)		**Test material (CAS name): DCPD/ co-dimer Concentrate** (See endpoint summary for justification of read-across)	
QSAR	Biowin2 (Non-Linear Model) = 0.7561 Biowin3 (Ultimate Survey Model) = 2.9070 (weeks) MITI Biodegradation Probability: Biowin5 (MITI Linear Model) = 0.4328 Biowin6 (MITI Non-Linear Model) = 0.2276	2 (reliable with restrictions) Weight of evidence Test material: DCPD	BIOWIN v4.10
Test type: ready biodegradability Not specified OECD TG 301 C (Ready Biodegradability: Modified MITI Test (I))	Not readily biodegradable % Degradation of test substance: 0 after 2 weeks	4 (not assignable) Weight of evidence experimental result Test material: DCPD	MITI Japan 1997

The study (Unpublished study report, 2004) presents the biotic degradation of DCPD/Codimer Concentrate (CAS 68478-10-4) following the OECD TG 301F (Ready Biodegradability: Manometric Respirometry Test). No biodegradation after 28 days is shown. Each test system was sealed immediately after addition of the test substance to minimize loss due to volatilization. The DCPD/Codimer Concentrate consists of DCPD along with lower concentrations of other codimers of cyclopentadiene which have similar structures to DCPD and are expected to have similar biodegradation properties. Therefore, read across of this conservative result to DCPD is considered robust.

From this study, it can be concluded that the **DCPD is not readily biodegradable**.

However, as described in Section R.7.9 of Chapter R.7b of the ECHA Guidance, a negative result in a test for ready biodegradability does not necessarily mean that the Substance will not be degraded under relevant environmental conditions and persist in the environment.

Others information is available:

- Screening information by BIOWIN shows results not completely consistent. The combined results of the three freely available estimation models BIOWIN 2,6 and 3 in the EPI suite (USEPA,2000) may be used:
    - Non-linear model prediction (BIOWIN 2): does not biodegrade fast if probability < 0.5 – DCPD = 0.7561 => **criteria not met**
    - Ultimate biodegradation timeframe prediction (BIOWIN 3): ≥ months if value < 2.25 – DCPD = 2.9070 => **weeks => criteria not met**
    - MITI non-linear model prediction (BIOWIN 6): does not biodegrade fast if probability < 0.5 – DCPD = 0.2276 => **criteria met**
- Ready biodegradability test provided by MITI Japan indicates that the substance was not readily biodegradable. Nevertheless the study report is unavailable for review.

The eMSCA concludes based on the OECD 310F study, that **DCPD is not readily biodegradable.** This result is in **contradiction with QSAR predictions. Nevertheless and as DCPD does not meet the B criteria, it is not necessary to conclude on the P criteria.**

7.7.1.2.1.2. Simulation tests (water and sediments)

No available data

7.7.1.2.1.3. Biodegradation in soil

No available data.

7.7.2. Environmental distribution

7.7.2.1. Adsorption/desorption

Table 13: Studies on adsorption/desorption

Method	Results	Remarks	Reference
Study type: Calculation method QSAR estimation	Adsorption coefficient: log Koc: 2.47 Koc: 292 (estimated data from log Kow = 2.78, non-hydrophobics))	2 (reliable with restrictions) weight of evidence (Q)SAR Test material: DCPD	EUSES 2.1.2 model Technical Guidance Document (ECB, 2003)
Study type: QSAR model KOWIN KOCWIN v.2.00 QSAR estimation	Adsorption coefficient: log Koc: 3.18 Koc: 1513 (estimated data (from MCI)) log Koc: 2.41 Koc: 258.4 (estimated data (from log Kow = 2.78))	2 (reliable with restrictions) weight of evidence (Q)SAR Test material: DCPD	KOCWIN v.2.00

According to REACH, Annex VIII, adsorption/desorption study does not need to be conducted if the substance shows by its physicochemical properties a low potential for adsorption. Unfortunately, the main property to characterise the adsorption potential is the Log Kow, for which a measured data is not available.

Based on QSAR predictions provided by the registrant, the eMSCA concludes that DCPD does not bind strongly on soil. In the current assessment, a Koc value of 1513 from MCI method has been used. QSAR models estimate Koc using the Molecular Connectivity Index (MCI) or a log Kow-based method. According to the P2 Framework Manual 2012 of US EPA, the MCI method is more robust and been in use longer. Moreover in the case of the DCPD, no robust Log Kow by measured data is provided.

7.7.2.2. Volatilisation

A vapour pressure of 186 Pa at 20°C (NIOSH handbook (2005)) and a Henry's law constant of 1229.6 $Pa.m^3.mole^{-1}$ at 25°C indicate that DCPD has a strong potential to volatilization.

7.7.3. Distribution modelling

Please see environmental exposure assessment section.

7.7.4. Bioaccumulation

7.7.5. Aquatic bioaccumulation

Table 14: Studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
Lepomis macrochirus aqueous (freshwater) flow-through Total uptake duration: 14 d Total depuration duration: 7 d Radiometric analyses for water and for fish. equivalent or similar to OECD TG 305 (before 2012)	BCF = 53 (edible fraction) Time of plateau: 2d Concentration in water = 0.98 mg/l Elimination = 7 days	2 (reliable with restrictions) supporting study experimental result Test material: DCPD	Unpublished report (1976)
QSAR	Log BCF =1.501 BCF = 31.71 L/kg wet wt (regression-based estimate) Biotransformation half-life = 1.838 days (normalized to 10 g fish) Log BCF =1.775 BCF = 59.61 L/kg wet-wt (Arnot-Gobas upper trophic) Log BCF =1.814 BCF = 65.21 L/kg wet-wt (Arnot-Gobas upper trophic, zero biotransformation)	2 (reliable with restrictions) weight of evidence (Q)SAR Test material: DCPD	EPI Suite v4.11 BCFBAF v3.01
Cyprinus carpio Mode of exposure aqueous flow-through Media type: not specified Total exposure / uptake duration: Total depuration duration: Details on estimation of bioconcentration: not reported according to OECD TG 305 C (Bioaccumulation: Test for the Degree of Bioconcentration in Fish) [before 14 June 1996]	BCF: 112 - 330 not reported (not specified) (not reported) (Conc.:0.3 mg/l) BCF: 58.9 - 384 not reported (not specified) (not reported) (Conc.:0.03 mg/l)	4 (not assignable) weight of evidence experimental result Test material: DCPD	MITI JAPAN 1997

In the study (Unpublished study report 1976), bluegill were exposed to ^{14}C radiolabelled DCPD during 14d in a flow-through system. The mean measured concentration of the DCPD in water during the test was 0.98 ± 0.25 µg/mL. The log BCF values for the test material were determined to be 53 (edible fraction) for the period of apparent equilibrium (days 2-4). Between this period and the end of the exposure (day 14), the mean measured ^{14}C residues in the muscle portion appeared to generally decrease. During the depuration phase (after 24H), the mean measured concentration of DCPD in the edible fraction of bluegill decreased to below the minimum detectable limit of 5.00 mg/kg. Based on those results the lead registrant considered that the test material is not bioaccumulative.

A study limitation is the measurement of the substance DCPD only in the edible fraction and not in the whole fish. From the low concentrations in muscles (edible fraction), and even if no measure is made in non edible fractions (e.g. excretion organs), a rapid potential of detoxification of excretion of DCPD in fish could be expected.

Nevertheless, this study cannot be considered as sufficient to definitively conclude that the substance is not bioaccumulative. A weight of evidence approach is needed:

- A low Bioconcentration Factor (BCF) values (31.71 – 65.21 L/kg $_{wet\ wt}$) was estimated by QSAR;

- In a MITI study (report not available), an estimated BCF between 58.9 and 384 is reported.

The eMSCA concludes, based on this weight of evidence approach, **DCPD is not likely to bioaccumulate in aquatic organisms.**

7.7.6. Terrestrial bioaccumulation

No data available.

7.7.7. Secondary poisoning

Based on the available information, there is no indication of a bioaccumulation potential and, hence, secondary poisoning is not considered relevant.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

Table 15: Short-term effects on fish

Method	Results	Remarks	Reference
Ictalurus punctatus freshwater static method : Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, Environmental Protection Agency, Ecological Research Series EPA 660/3-75009, April 1975. Method is similar to OECD 203	LC50 (96 h): 15.7 mg/L test mat. (nominal) based on: mortality (95% CL: 13.8 – 18 mg/l)	2 (reliable with restrictions) Key study experimental result Test material: DCPD	Unpublished report (1976)
Lepomis macrochirus freshwater static method : Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, Environmental Protection Agency, Ecological Research Series EPA 660/3-75009, April 1975. Method is similar to OECD 203	LC50 (96 h): 23.3 mg/L test mat. (nominal) based on: mortality (95% CL: 17.6 – 30.1 mg/l)	2 (reliable with restrictions) Supporting study experimental result Test material: DCPD	Unpublished report (1976)
Pimephales promelas freshwater static method : Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, Environmental Protection Agency, Ecological Research Series EPA 660/3-75009, April 1975. Method is similar to OECD 203	LC50 (96 h): 31.1 mg/L test mat. (nominal) based on: mortality (95% CL: 23 – 42 mg/l)	2 (reliable with restrictions) Supporting study experimental result Test material: DCPD	Unpublished report (1976)
Oncorhynchus mykiss (reported as Salmo gairdneri) freshwater	LC50 (96 h): 15.9 mg/L test mat. (nominal) based on: mortality	2 (reliable with restrictions) Supporting study	Unpublished report (1976)

static method : Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, Environmental Protection Agency, Ecological Research Series EPA 660/3-75009, April 1975. Method is similar to OECD 203	(95% CL: 13 – 19.5 mg/l)	experimental result Test material: DCPD	
Pimephales promelas QSAR	LC50 (96 h): 10.25 mg/L	2 (reliable with restrictions) Weight of evidence QSAR Test material: DCPD	SciQSAR DTU develop model, Danish (Q)SAR Database
Fish QSAR	LC50 (96 h): 9.76 mg/L	2 (reliable with restrictions) Weight of evidence QSAR Test material: DCPD	ECOSAR v1.11
Oryzias latipes semi-static according to OECD TG 203 (Fish, Acute Toxicity Test)	LC50 (96 h): 4.3 mg/L nominal based on: not specified (95% CL: 3.1 – 5.8 mg/l)	4 (not assignable) Weight of evidence experimental result Test material: DCPD	MITI JAPAN, (1997)

Unpublished study report (1976) tested the toxicity of DCPD to four species of fish. The range of LC_{50} values reported within the paper was between 15.7 -31.1 mg/L. The study followed a method similar to standard guidelines (OECD TG 203) but did not include analytical confirmation of the exposure concentrations. Considering the potential volatility of DCPD and that the study was carried out in static condition, endpoint values based on nominal concentration can be overestimated. On this point and taking into account the percentage of the theoretical concentration of 69% refound in the prolonged fish Toxicity Test (described below), the LC50 values reported here could be considered underestimated.

The toxicity levels for fish reported in the previous study are supported by the following data:

- An Environmental Agency Japan test following OECD TG guideline 203, using semi-static conditions without analytical confirmation of exposure concentrations showed the 96 hour LC_{50} to be 4.3 mg/L. Nevertheless, this study report was unavailable for review.
- QSAR results have also been included as part of the weight of evidence, which used the SciQSAR program, Danish (Q)SAR Database to derive a 96 hour LC_{50} of 10.25 mg/L and ECOSAR to derive a 96-hour LC_{50} of 9.76 mg/L.

In a weight of evidence approach, the **96 hour-LC_{50} of 15.7 mg**/L has been selected.

7.8.1.1.2. Long-term toxicity to fish

Table 16: Long-term effects on fish

Method	Results	Remarks	Reference
Lepomis macrochirus Freshwater flow-through adult fish equivalent or similar to OECD TG 204 (Fish, Prolonged Toxicity Test: 14-day Study) [not valid for new testing from 2 April 2014]	NOEC (14d): 0.98 mg/L (meas. (not specified)) based on: mortality (0.98±0.25)	2 (reliable with restrictions) Key study experimental study	Unpublished report (1976)
QSAR	NOEC (30d): 0.767 mg/L (not specified) (Calculated from ChV) ChV* (30d): 1.084 mg/L (not specified) based on: not specified (Standard duration assumed) * geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC)	2 (reliable with restrictions) Weight of evidence QSAR Test material: DCPD	ECOSAR v1.00

The unpublished study report (1976) indicates the results of the bioaccumulation study with DCPD (only one dose tested, flow-through system)): DCPD is radiolabelled using ^{14}C. The mean specific activity was measured to be 6.46 disintegrations per minute per microgram equivalent to 69% of the theoretical concentration.

At the mean measured concentration of 0.98 mg/L ^{14}C-DCPD in the water through 14 days of exposure, no mortality or change in behaviour was observed. The exposure takes place only over 14 days, sufficient for the determination of longer term lethal effects but potentially inadequate to determine sub lethal effects. Although this study does not fully comply with standard guidelines, it is considered to be adequate in a weight of evidence approach.

The ECOSAR model predicted a 30-day NOEC of 0.767 mg/L.

For predicting toxicity mode of action (MOA) for fish, DCPD was put into class 2 (less inert compounds) by the Verhaar scheme (modified), available in Toxtree v2.6. The scheme utilises 2D chemical structure to classify potential environmental pollutants into one of four categories representing one, or more, mechanisms of action. According to the study Kienzler et al. 2016, there were highly significant relationships between acute and chronic toxicity for each MOA class. Results show that an acute to chronic ratio (ACR) of 100 when applied to acute fish toxicity data for substances with MOA 2, as defined by the Verhaar classification scheme, will protect against the chronic effects of industrial substances in 90% of the cases.

A chronic value of 0.157 mg/L can be extrapolated from the lowest LC50 (96 h) of 15.7 mg/L and an ACR of 100. This value is in the same range that the experimental endpoint of 0.98 mg/L for which no mortality was observed.

From this weight of evidence approach, the **chronic value of 0.157 mg/L** has been selected.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

Table 17: Short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater semi-static OECD 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h): 0.823 mg/L (meas. (geom. Mean)), based on mobility	1 (reliable without restrictions) Key study experimental result Test material: DCPD	Unpublished study report, 2016,
Daphnia magna freshwater static OECD 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h): 0.62 mg/L test mat. (nominal) based on mobility (95% CL: 0.53 – 0.72 mg/l)	2 (reliable with restrictions) supporting study experimental result Test material: DCPD	Unpublished study report, 1995,
Daphnia magna freshwater semi-static OECD 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h): 8 mg/L test mat. (nominal) based on mobility (95% CL: 6.8 – 9.5 mg/l)	4 (not assignable) supporting study experimental result Test material: DCPD	MITI JAPAN, (1997)

The acute toxicity of DCPD to Daphnia magna was determined in a GLP-compliant study following OECD TG202 (Unpublished study report, 2016). Based on geometric mean measured concentrations, the 48 hour EC_{50} was 0.823 mg/L, with 95% confidence limits of 0.740 to 0.909 mg/L. The study was conducted in a closed system under semi-static conditions (to avoid possible losses of the test item due to volatilization) with a saturated solution of the test item and diluted to give test concentrations of 6.25, 12.5, 25, 50 and 100% saturated solution (nominal concentration of 10 mg/L for 100% solution saturated). After completion of stirring, the saturated solution was allowed to stand for 0.5 hours for separation of any undissolved test item. The saturated solution was prepared one day prior to the start of the test and the 24 h exposure intervals (at -24 and 0 hours) in a sealed glass.

At the start of the exposure, the measured concentrations for the saturated solution at 100% were 6.29 mg/L. (at 0 hours) and 6.92 mg/L (at 24 hours) representing approximatively 65% of the nominal concentration. During the test, the geometric mean measured concentrations from all measuring points from 0 h to 48 h were determined to be 0.3, 0.57, 1.11, 2.39 and 5.09 mg/L for 6.25, 12.5, 25, 50 and 100% saturated solution respectively.

Table 18: Analytical control of saturated solution throughout the test

Dilution level of the saturated solution (%)	0 hours Start of the exposure interval Measured conc. [mg/L]	24 hours End of the exposure interval Measured conc. [mg/L]	%	24 hours Start of the exposure interval Measured conc. [mg/L]	48 hours End of the exposure interval Measured conc. [mg/L]	%	Geometric mean measured conc. of the test item (mg/L)
100	6.29	4.12	66	6.92[1]	-[1]		5.09
50	3.08	1.86	60	-[1]	-[1]		2.39
25	1.41	0.72	51	1.27	1.16	91	1.11

12.5	0.7	0.426	61	0.649	0.545	84	0.570
6.25	0.346	0.19	55	0.369	0.333	90	0.3
Control	<LOQ	<LOQ		<LOQ	<LOQ		

[1] Not analysed and/or not taken into account for geometric mean due to 100% mortality after 24 hours

The analysis of the measured exposure concentrations indicate that the toxicity endpoint value could be underestimated by the use of nominal concentrations. Nevertheless, it seems difficult to quantify the loss due to the volatilization considering the variability observed in the measured concentrations.

In an Unpublished study report (1995), a 48 hour-EC_{50} to Daphnia magna of 0.62 mg/L is estimated based on nominal values. The concentration and stability of the test item was not determined throughout the test. The study followed a static design. Therefore, we could have expect a lower EC_{50} value if based an analytical value because of the volatilisation. This value will have been nevertheless below the 48 hour EC_{50} of 0.823 mg/L of the first study, based on geometric mean measured concentrations.

An Environmental Agency Japan test following OECD TG 202, using semi-static conditions without analytical confirmation of exposure concentrations showed the 48 hour EC_{50} to be 8 mg/L. Nevertheless, this study report was unavailable for review.

In a weight of evidence approach, the lowest result, **48 hour-LC_{50} of 0.62 mg**/L has been selected.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

Table 19 : Long-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Invertebrates QSAR	NOEC (21 d): 0.574 mg/L test mat. (estimated) based on: not specified.	2 (reliable with restrictions) Weight of evidence QSAR Test material: DCPD	ECOSARv1.00
Daphnia magna Not specified	NOEC (21d): 3.2 mg/L not specified (not specified) based on: reproduction	4 (not assignable) Supporting study experimental result Test material: DCPD	MITI Japan, (1997)

The toxicity data by the Environmental Agency of Japan (1997) were unavailable for review. The study of chronic toxicity to Daphnia magna from DCPD over 21 days following OECD TG 202 (1984) showed a NOEC 3.2 mg/L.

A QSAR estimate has been included to provide additional data for this endpoint. The estimated 21 day NOEC is 0.574 mg/L. The use of a QSAR model is only considered as part of a weight of evidence approach. No experimental study is available to estimate the chronic toxicity for invertebrates, moreover, acute toxicity values are in the same range than proposed chronic values. It give rise to uncertainties about the potential chronic toxicity value. DCPD is manufactured and/or imported in the European Economic Area in 100000 - 1 000 000 tonnes per year. Consequently and according to the Annex IX of REACH, long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.

Consequently and considering the unacceptable risk for aquatic compartment demonstrated by the environmental risk assessment, **a long-term study on aquatic invertebrates should be conducted.**

No endpoint value is considered for long-term effects on aquatic invertebrates.

7.8.1.3. Algae and aquatic plants

The results are summarised in the following table:

Table 20: Effects on algae and aquatic plants

Method	Results	Remarks	Reference
Algae QSAR	NOEC (96h): 1.688 mg/L (estimated)	2 (reliable with restrictions) Weight of evidence QSAR Test material: DCPD	ECOSAR v1.00
Microcystis aeruginosa (cyanobacteria) Algal Assay Procedure: Bottle Test (US EA 1971).	EC50 (96h): 31 mg/L	2 (reliable with restrictions) weight of evidence experimental study Test material: DCPD	Unpublished study report (1976)
Anabaena flos-aquae (Cyanobacteria) Algal Assay Procedure: Bottle Test (US EA 1971).	EC50 (96h): 22 mg/L	2 (reliable with restrictions) weight of evidence experimental study Test material: DCPD	Unpublished study report (1976)
Pseudokirchneriella subcapitata (algae) Algal Assay Procedure: Bottle Test (US EA 1971).	EC50 (96h)> 100 mg/L	2 (reliable with restrictions) weight of evidence experimental study Test material: DCPD	Unpublished study report (1976)
Pseudokirchneriella subcapitata (algae) Not specified	EC50 (72h): 27 mg/L (meas. (not specified)) based on: not specified NOEC (72h): 18 mg/L (meas. (not specified)) based on: not specified	4 (not assignable) Supporting study experimental result Test material: DCPD	MITI Japan., (1997)

The unpublished study report (1976) tested the toxicity of DCPD to three species of algae. The range of EC_{50} values reported within the paper was between 22 ->100 mg/L. The study followed a method similar to standard guidelines but did not include analytical confirmation of the exposure concentrations.

The toxicity data by the Environmental Agency of Japan (1997) was unavailable for review. The study of chronic toxicity to algae from DCPD showed a NOEC (72h) of 18 mg/L.

A QSAR estimate has been included to provide additional data for this endpoint. The estimated 96h-NOEC is 1.7 mg/L.

Even if no reliable endpoint value is available, algae appears not to be the most sensitive trophic level.

7.8.1.4. Sediment organisms

No relevant information available.

7.8.1.5. Other aquatic organisms

No relevant information available.

7.8.2. Terrestrial compartment

7.8.2.1. Toxicity to soil macro-organisms

Table 21: Effects on terrestrial plants

Method	Results	Remarks	Reference
Eisenia fetida Substrate: artificial soil according to OECD TG 222 (Earthworm Reproduction Test (Eisenia fetida/Eisenia andrei))	NOEC (56d): 125 mg/kg soil dw test mat. (nominal) based on: reproduction EC50 (56d): 250 mg/kg soil dw test mat. (nominal) based on: reproduction	1 (reliable without restriction) key study experimental result Test material: DCPD	Unpublished study report, 2016a,

The effect of DCPD on earthworm reproduction was determined in a GLP-compliant study following OECD TG 222. Earthworms were exposed to 6 concentrations of DCPD alongside a control in artificial soil. There were no statistically significant differences in earthworm reproduction rates in the treatment groups from 15.6 to 125 mg DCPD/kg_{SDW} compared to the control. However, at the test item concentration of 250 mg DCPD/kg, the earthworm reproduction was statistically significantly reduced and, at the test item concentration 500 mg DCPD/kg_{SDW}, no juveniles were found. Overall, the NOEC of the test item concerning mortality, biomass and reproduction was determined to be 125 mg DCPD/kg_{SDW} and based on reproduction.
The EC_{50}value for reproduction was determined to be 250 mg DCPD/kg_{SDW}.

7.8.2.2. Toxicity to soil micro-organisms

Table 22: Effects on soil micro-organisms

Method	Results	Remarks	Reference
Species/ Inoculum: Soil Microorganisms: Nitrogen Transformation Test (OECD TG 216)	NOEC (29d): >=1000 mg/$kg_{soil\ dw}$ test mat. (nominal) based on: nitrate formation rate	1 (reliable without restriction) key study experimental result Test material: DCPD	Unpublished study report, 2016b

The effect of DCPD on the nitrification of soil microorganisms was determined in a GLP-compliant study following OECD TGTG 216. No inhibiting effect on the nitrification potential was observed up to a concentration of 1000 mg/kg_{SDW}, the highest concentration tested. The NOEC is therefore considered to be ≥ 1000 mg/kg_{SDW}.

7.8.2.3. Toxicity to terrestrial plants

No data available.

7.8.3. Microbiological activity in sewage treatment systems

Table 23: Effects on micro-organisms

Method	Results	Remarks	Reference
Pseudomonas putida Freshwater not specified according to Standard Test Method 172-07	Minimum inhibitory concentration 2 ppm expressed as Total Organic Carbon Total Organic Carbon (meas. (not specified)) based on: growth inhibition (mean concentration of the test material which began to inhibit growth of the test organism was 17% WAF - corresponding to about 2 ppm expressed as Total Organic Carbon)	2 (reliable with restrictions) key study experimental study Test material: DCPD	Unpublished study report, 1993

Discussion

The mean concentration of the test material which began to inhibit growth of the test organism was 17% WAF. This corresponds to about 2ppm expressed as Total Organic Carbon, which in turn corresponds to 2.2 mg DCPD/L.

One study was available for review for toxicity to microorganisms. This is a WAF, GLP compliant study which followed a standard method and is considered adequate for assessment.

7.8.4. Non compartment specific effects relevant for the food chain (secondary poisoning)

No relevant information available.

7.8.5. PNEC derivation and other hazard conclusions

Table 24: Environmental PNEC values

Table PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.00157mg/L	Assessment factor: 100 Extrapolation method: assessment factor PNEC aqua (freshwater) The PNECfreshwater was derived by applying an assessment factor of 100 to the lowest long term result (NOEC of 0.157 mg/L). An assessment factor of 100 was applied as one long-term is available.
Marine water	PNEC aqua (marine water): 0.000157mg/L	Assessment factor: 1000 Extrapolation method: assessment factor PNEC aqua (marine water) The PNEC marine water was derived by applying an assessment factor of 1000 to the lowest long term result (NOEC of 0.157 mg/L). An assessment factor of 1000 was applied as one long-term result is available.
Sediments (freshwater)	PNEC sediment (freshwater): 1.69E-02 mg/kg_{ww}	According to the guidance on information requirements and chemical safety assessment-chapter R10: characterisation of dose-response for environment (ECHA 2008), in the absence of any ecotoxicological data for sediment-dwelling organisms, the PNEC sed may be provisionally calculated using the equilibrium partitioning method (EPM), following the chapter R16. PNEC aqua=0.00157 mg/L; Koc=460 L/kg; PNEC sed = 1.69E-03 mg/kg_{ww}
Sediments (marine water)	PNEC sediment (marine water): 1.69E-03 mg/kg_{ww}	According to the guidance on information requirements and chemical safety assessment-chapter R10: characterisation of dose-response for environment (ECHA 2008), in the absence of any ecotoxicological data for sediment-dwelling organisms, the PNEC sed may be provisionally calculated using the equilibrium partitioning method (EPM), following the chapter R16. PNEC aqua=0.000157 mg/L; Koc=460 L/kg; PNEC sed = 1.69E-04 mg/kg_{ww}
Sewage treatment plant	PNEC STP: 2.2 mg/L	Assessment factor: 1 Extrapolation method: assessment factor PNEC STP The PNEC was derived by applying an assessment factor of 1 to the NOEC of 2.2 mg/L determined in the growth inhibition study with Pseudomonas putida.

Soil	PNEC soil: 2.83 mg/kg_{ww}	Assessment factor: 50 Extrapolation method: assessment factor PNEC soil The soil PNEC has been derived using the experimental data available on terrestrial invertebrates (56 day NOEC of 125 mg/kg SDW) and micro-organisms (29 d NOEC of 1000 mg/kg SDW). The microorganisms result been normalised from an organic carbon content of 0.63% to 3.4%, giving NOEC of 5397 mg/kg SDW. An assessment factor of 50 has been applied to the lowest result as there are two long-term toxicity test available for different trophic levels. The soil PNEC is therefore 2.5 mg/kg dw, equivalent to 2.83 mg/kg $_{soil}$ ww.
Air	No hazard identified	DPCD is not expected to contribute to ozone depletion, ozone formation, global warming or acidification. Therefore, the evaluation of atmospheric risk is not required.
Secondary poisoning	No potential for bioaccumulation	Considering that DCPD is not expected to bioaccumulate, secondary poisoning issues to birds following chronic exposure is considered as negligible. As a consequence, no PNEC for birds is determined for the environmental risk assessment of the DCPD.

7.8.6. Conclusions for classification and labelling

Environmental classification justification

Based on the available data on DCPD:
- The most acute sensitive aquatic species are invertebrates, with EC_{50} = 0.62 $mg.L^{-1}$;
- The most chronic sensitive aquatic species are fish, with NOEC = 0.157 $mg.L^{-1}$;
- DCPD is not readily biodegradable;
- DCPD is not bioaccumulative.

Thus, DCPD warrants to be classified as Aquatic Acute 1 - H400: Very toxic to aquatic life according to the CLP regulation criteria.

As the Substance is not readily biodegradable, the lowest chronic key value indicates that DCPD meets the criteria for classification as **Aquatic Chronic 2** under CLP, with the hazard phrase **H411: "Toxic to aquatic life with long lasting effects"**.

7.9. Human Health hazard assessment

The human health hazard assessment focused on reprotoxicity which was the reason for inclusion of the Substance in the CoRAP, but all endpoints were reviewed.

The eMSCA faced a major challenge due to the composition of the registered and the tested substances. Indeed, some instances of registered and tested DCPD contain hazardous impurities (the substance being defined as in Article 3 (1) as a chemical elements and its compounds including additives and impurities).

In particular, several compositions of DCPD registered by different Registrants contain CMR impurities at concentrations above the classification limits that would lead to classification of the registered substances as CMR. However, the concerned Registrants did not classify their substances accordingly.

In addition, the composition of the substance used in the toxicological studies is not available in the study reports. When it is given, it appears that some tested substances contain hazardous impurities including CMR impurities. The eMSCA could not find any

correlation between the toxicity profile and the purity since even "pure" DCPD contains CMR impurities.

Further details on registered and tested compositions are given in a confidential annex.

The eMSCA intended to request information on impurities so as to clarify the composition of the registered substance. However, neither Substance Evaluation nor Dossier Evaluation were considered as an appropriate way to clarify this concern. **Accordingly, eMSCA invites the National Enforcement Authorities of the Member States where DCPD is registered to check whether the full composition of the registered substance is available (if appropriate via an Article 36 notification), and most importantly if the classification of the Substance takes into account any relevant impurities.**

7.9.1. Toxicokinetics

Three studies performed by gavage in rats, mice and dogs (Unpublished report, 1976a) and one study performed in a lactating cow (Ivie and Oehler , 1980) are available.

In addition, one study investigated the liver enzyme induction in rats by intraperitoneal injection of hexobarbital in DCPD-treated and control rats (Unpublished report, 1976j).

Table 25: Data on toxicokinetics

Method	Results	Remarks	Reference
Toxicokinetics and metabolism in rats Rates of absorption, tissue distribution, metabolism and rate of excretion Rats (Sprague-Dawley) male 12 animals Oral: gavage Exposure regime: single dose Dose: 110 mg/kg bw (^{14}C labelled DCPD) Vehicle: corn oil Sacrifice at 2, 4, 6, 24, 48, 72h.	Rapidly absorbed (Cpmax in plasma: 23.28 µg/mL at 6h) Concentration in plasma is slightly higher than in blood cells in the first 48h (ratio blood cells/plasma is between 0.83 and 0.93) Half-life in plasma ~10.5h Distribution (examined: abdominal muscle, adrenals, blood, brain, empty urinary bladder, eyes, fat, femur, heart, kidneys, liver, lungs, plasma, skin, spleen, testes): - radioactivity was distributed in all organs/tissues/fluids: highest concentrations in fat (366 µg/g at 6h), adrenals (154 µg/g at 6h), empty urinary bladder (127 µg/g at 6h), kidneys (80 µg/g at 6h), liver (75 µg/g at 2h) - Cmax at 6h for all, except for liver for which it occurred at 2h - radioactivity declined rapidly (<10% of Cmax) by 24h in fat, by 48h in adrenals, blood, brain, eyes, fat, femur, heart, lungs, plasma, skin, spleen, testes and by 72h in abdominal muscle, empty urinary bladder, kidneys, liver; and was still detectable in all tissues after 72h. Excretion (examined: urine, faeces, carcass, gastrointestinal tract, expired air): DCPD was mostly excreted in urine then to a lesser extent in faeces and expired air. Excretion was maximal at 72h. Recovery was low due to DCPD volatility according to the author. Metabolites (analysed in urine 0-24h): 7 different components were detected in urine but were not characterised (none seem to be non-metabolised DCPD and some are likely to be conjugates).	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity > 97%)	Unpublished report (1976a)
Toxicokinetics and metabolism in mice Rates of absorption, tissue distribution, metabolism and rate of excretion Mice (Swiss Webster) male 24 animals Oral: gavage Exposure regime: single dose	Rapidly absorbed (Cpmax in plasma: 11.36 µg/mL at 2h) Concentration in plasma is higher than in blood cells in the first 24h (ratio blood cells/plasma is between 0.43 and 0.67) Half-life in plasma ~6h Distribution (examined: abdominal muscle, adrenals, blood, brain, empty gall bladder, empty urinary bladder, eyes, fat, femur, heart, kidneys, liver, lungs, plasma, skin, spinal cord, spleen, testes): - radioactivity was distributed in all organs/tissues/fluids: highest concentrations in empty urinary bladder (248 µg/g at 1h), empty gall bladder (79 µg/g at 1h), fat (70 µg/g at 1h), kidneys (36.5 µg/g at 2h)	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity > 97%)	Unpublished report (1976a)

Method	Results	Remarks	Reference
Dose: 40 mg/kg bw (^{14}C labelled DCPD) Vehicle: corn oil Sacrifice at 0.25, 1, 2, 4, 6, 24, 48, 72h.	- overall Cmax at 1-2h (Cmax at 1h in abdominal muscle, adrenals, blood, brain, empty gall bladder, empty urinary bladder, fat, femur, heart, lungs, skin, spinal cord, spleen, testes; Cmax at 2h in kidneys, liver, plasma; Cmax at 4h in eyes) - radioactivity declined rapidly by 24h (<10% of Cmax for all, except gall bladder for which this occurred at 6h) but was still detectable after 72h in all tissues. Excretion (examined: urine, faeces, carcass, gastrointestinal tract, expired air): DCPD was mostly excreted in urine then to a minor extent in faeces and expired air. Excretion was maximal at 24h. Recovery was low due to DCPD volatility according to the author. Metabolites (analysed in urine 0-24h): 7 different components were detected in urine but were not characterised (none seem to be non-metabolised DCPD and some are likely to be conjugates).		
Toxicokinetics and metabolism in dogs Rates of absorption, tissue distribution, metabolism and rate of excretion Dogs (Beagle) male 5 animals Oral: unspecified Exposure regime: single dose Dose: 100 mg/kg bw (^{14}C labelled DCPD) Vehicle: corn oil Sacrifice at 4, 24, 48, 72h, 7 days.	Rapidly absorbed (Cpmax in plasma: 39.9 µg/mL at 2h) Concentration in plasma is higher than in blood cells (ratio blood cells/plasma is between 0.15 and 0.43) Half-life in plasma ~13.5h Distribution (examined: abdominal muscle, adrenals, bile, blood, bone marrow, cerebellum, cerebrum, empty cecum, empty large intestine, empty small intestine, empty stomach, empty urinary bladder, eyes, fat, femur, gall bladder, heart, kidneys, liver, lungs, lymph nodes, medulla, pancreas, plasma, skin, spinal cord, spleen, testes, thyroid): - radioactivity was distributed in all organs/tissues/fluids: highest concentrations in bile (933 µg/mL at 4h), gall bladder (338 µg/g at 4h), empty urinary bladder (171.5 µg/g at 4h), empty stomach (158 µg/g at 4h) - Cmax at 4h for all, except for cerebrum, fat, lungs, skin, spinal cord for which it occurred at 24h - radioactivity declined rapidly (<10% of Cmax) by 24h in bile, empty caecum, empty small intestine, empty stomach, gall bladder; by 48h in abdominal muscle, empty large intestine, kidneys, pancreas, plasma; by 72h in blood, empty urinary bladder, heart, liver, lymph nodes, spleen, thyroid, testes; by 7 days in adrenals, bone marrow, cerebellum, cerebrum, eyes, fat, lungs, medulla, skin; it was still > 10% Cmax after 7 days in femur and spinal cord and still detectable after 7 days in all tissues except large intestine and caecum.	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity > 97%)	Unpublished report (1976a)

Method	Results	Remarks	Reference
	Excretion (examined: urine, faeces, gastrointestinal tract, excised organs, bile, blood, muscle): DCPD was mostly excreted in urine then to a far less extent in faeces. Excretion was maximal at 48h. Recovery was low due to DCPD volatility according to the author. Metabolites (analysed in urine 0-24h): 6 different components were detected in urine but were not characterised (none seem to be non-metabolised DCPD and some are likely to be conjugates).		
Fate of DCPD in a lactating cow Cow (Jersey) female 1 animal Oral: capsule Exposure regime: 5 daily doses of unlabelled DCPD, then 24h later a single dose of ^{14}C labelled DCPD Dose:10 mg/kg bw/day Sacrifice 96h after dosing with ^{14}C labelled DCPD.	Rapidly absorbed (Cpmax in whole blood: 290 dpm/g at 2h post dosing) Radioactivity declined rapidly in blood (not detectable 24h after treatment). No detectable radioactivity in tissues collected 96h after treatment (brain, fat, gall bladder, heart, kidneys, liver, muscle, ovary, lung, adrenals, skin, spleen, urinary bladder, udder). Excretion (examined: urine, faeces, milk): rapid excretion (~75% by 24h, total excretion ~86% by 96h), about 81% in urine, 4% in the faeces and < 0.1% in milk. The authors suggest that due to the volatility of DCPD, the remaining may have been lost through gases eructated from the rumen or expired air or during samples collection. Metabolites (analysed in urine at 4, 8 and 12h after treatment): 14 different components were detected in urine but could not be characterised. At least 65% of the radioactivity was in the form of glucuronides conjugates (possibly formed by epoxidation of the double bond(s) and hydrolysis to diols, epoxy diols or tetraols, and ultimate conjugation with glucuronic acid) . 1 component (different from DCPD) was detected in faeces but could not be characterised. Collected: whole blood, urine, feces, milk Radioactivity measured in milk, urine, blood, tissues samples, feces	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity not specified)	Ivie and Oehler (1980)
Test for liver enzyme induction in rats Rats (Sprague-Dawley) male/female 10 animals/sex/group Oral: dietary administration Exposure for 4 days; on day 5 intraperitoneal injection of 100 mg/kg hexobarbital	Duration of sleeping time (based on inability of the rat to right itself when placed on its side) was measured following IP injection of hexobarbital in DCPD-treated and control rats Necropsy: no treatment related finding DCPD was judged not to be a liver enzyme inducing agent in rats.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976j)

Method	Results	Remarks	Reference
Dose: 0 and 750 ppm Vehicle: corn oil			

7.9.2. Acute toxicity and Corrosion/Irritation

7.9.2.1. Acute toxicity

7.9.2.1.1. *Oral route*

Originally the Registrant(s) concluded that the Substance is acutely toxic by oral route and shall be classified as Acute Tox 4, H302 (harmful if swallowed) based on the LD_{50} for male/female rats (Unpublished report, 1989a) of 590 mg/kg bw. However, a study performed in mice (Unpublished report, 1976b) gave a LD_{50} of 190 mg/kg bw for females. Although this study is of lower quality (RI=2), there is no sound reason to consider its results as not reliable. Furthermore, the study on rats (Unpublished report, 1989a) was performed using a mixture containing 72% of DCPD, which is less relevant. The current harmonised classification is Acute Tox 4*, H302 (harmful if swallowed) is a minimal classification established under the Directive 67/548/EEC, and due to a change in the classification thresholds in the Regulation UE 1272/2008, therefore the hazard class may not be adequate. Overall, the eMSCA considers that the LD50 value of 190 mg/kg bw for females mice should have been used and would lead to a classification of DCPD as **Acute Tox 3-H301 (toxic if swallowed).**

In addition, the eMSCA notes adverse effects to organs and in particular to the lungs (haemorrhage, hyperemia, congestion in rats, mice, calves) and to the central nervous system (ptosis in rats, tremors and convulsions in rats, ataxia in rats and calves, incoordination, falling, tonic and clonic spasms in calves, brain lesions in calves).

Table 26: Data on acute toxicity by oral route

Method	Results	Remarks	Reference
Acute oral toxicity test in the rat Rats (Sprague-Dawley) male/female 5 animals/sex/dose Oral: gavage Vehicle: unchanged (no vehicle) Doses: 500, 794, 1260, 2000 mg/kg bw OECD TG 401	LD50: 590 mg/kg bw (male/female) LD50: 512 mg/kg bw (male) LD50: 676 mg/kg bw (female) Death occurred on day 1 or 2 Clinical signs: after dosing, hunched posture, pilo-erection, lethargy and decreased respiratory rate at all doses, occasional ptosis at 794 and 1260 mg/kg, ptosis and occasional ataxia at 2000 mg/kg; on day 1, incidents of red/brown staining around the snout at 500 and 794 mg/kg. Necropsy: in decedents haemorrhagic lungs, dark liver, sloughing of non-glandular gastric epithelium; survivors were normal.	1 (reliable without restriction) key study experimental result Test material: DCPD **(purity 72%)**	Unpublished report (1989a)
Acute oral toxicity study in mice Mice (Swiss Webster) male/female 10 animals/sex/dose Oral: gavage Vehicle: corn oil Doses: 167, 215, 278, 360, 464, 600 mg/kg bw Similar to OECD TG 401	LD50: 220 mg/kg bw (male/female) LD50: 190 mg/kg bw (male) LD50: 250 mg/kg bw (female) Death occurred on day 1 or 2 Clinical signs: decreased activity, prostration. Necropsy: in decedents, hyperemia of lungs, yellow fluid in stomach and small intestine, distension of bladder with pinkish-orange fluid, black discoloration of portions of liver and spleen (some findings may be due to post-mortem degeneration); survivors were normal.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976b)
Acute oral toxicity study in rats Rats (Sprague-Dawley) male/female 10 animals/sex/dose Oral: gavage Vehicle: corn oil Doses: 278, 360, 646, 600, 793 mg/kg bw Similar to OECD TG 401	LD50: 449 mg/kg bw (male/female) LD50: 520 mg/kg bw (male) LD50: 378 mg/kg bw (female) Death occurred on day 2 Clinical signs: red stains around nose and mouth, decreased activity, occasional ataxia, prostration after dosing; some instances of tremors and convulsions. Necropsy: most decedents showed no abnormalities, but some had hyperemia in lungs.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976c)

Method	Results	Remarks	Reference
14-day toxicity study in dogs Dogs (Beagles) male/female 1 animal/sex/dose Oral: dietary administration, exposure for 14 days Vehicle: corn oil Doses: 0, 40, 125, 375 ppm corresponding to 8, 25, 59 mg/kg/day	No animal died No information on statistical significance Dose-dependent increase of the body weight at all time points for all treated males (up to +23% after 14 days at 375 ppm) Dose-dependent decrease of the body weight at all time points for all treated females (up to -15% after 14 days at 375 ppm) Clinical signs: none reported Necropsy: no effect in thyroid, lung, heart, liver, spleen, stomach, small intestine, large intestine, kidneys, adrenals, bone marrow, brain. Effects were observed in mesenteric lymph nodes: hemorrhage and erythrophagocytosis in males (control and high dose), hemorrhage in female (high dose), reddening of the medullary area in all treated males and in females exposed to 40 and 375 ppm. Organ weight: *observations detailed in section 7.9.7.* Blood chemistry: increase of urea nitrogen in males at all doses, increase of glucose in male at 375 ppm and decrease in female at 375 ppm, increase of alkaline phosphatase in males at all doses and decrease in female at 375 ppm, increase of GOT in male at 125 ppm, increase of GPT in males at 125 and 375 ppm and in female at 40 ppm, decrease of bilirubin in female at 375 ppm. Haematology: slight decrease of the cell volume in female at 375 ppm (-8%), no effect on haemoglobin, increase of red blood cells in males at all doses and decrease in females, increase of the white blood cells in male at 40 ppm (+17%) and in females ((+24% and +12% at 40 and 375 ppm), decreased neutrophiles and increased lymphocytes in males and the opposite in females, at all doses	3 (not reliable) supporting study experimental result DCPD (purity 98 to 99%)	Unpublished report (1976h)
Acute toxicity study (oral) Rats Oral: gavage	LD50: 0,353 ml/kg corresponding to ~ 346 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
Acute toxicity study in cattle Calves, male/female 2 animals/sex/dose Oral: gavage Doses: 250, 500, 1000, 2000 mg/kg bw	LD50 between 1000 (1/4 died) and 2000 mg/kg bw (4/4 died) Death occurred on days 2 to 6 Clinical signs: anorexia, ataxia and excess salivation from 250 mg/kg; at higher doses, incoordination, falling, prostation with running movements and tonic, clonic spasms. 1 calf in 250 mg/kg group developed severe pneumonia. Necropsy: 2 calves (on 4) of the 500 mg/kg group had brain lesions (small foci of gliosis in one, few small scattered hemorrhages in the other). One surviving calf of the 1000 mg/kg group had mild cerebral edema (increase in the perivascular space in both the gray and white matter) and mild gliosis in the fiber tracts of the thalamus. Meningeal congestion was observed in dead calves of the 2000 mg/kg group (congestion of meningeal and cerebral vessels confirmed by microscopy). At 1000 and 2000 mg/kg, congestion of the lungs, small intestine, rumen and abomasum were reported. At 2000 mg/kg renal congestion and epicardial bleeding were observed.	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Cysewski *et al.* (1981) *Only abstract available* *Assessment available in the executive summary of safety and toxicity information on dicyclopentadiene, National Toxicology Program, November 30, 1990 (Arthur D. Little, Inc.)*
Acute toxicity study in rats (range finding) Rat (Carworth-Wistar) male Oral: gavage Vehicle: unchanged (no vehicle)	LD50: 0,41 mL/kg corresponding to ~402 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1962)

7.9.2.1.2. *Inhalation route*

Based on the available information, the Registrant(s) concluded that the Substance is acutely toxic by inhalation and shall be classified as **Acute Tox 2, H330 (fatal if inhaled)** instead of the current harmonised minimal classification (Acute Tox 4* H332). This conclusion is supported by the eMSCA.

The eMSCA notes that the Registrant(s) based its conclusion on the LC_{50} (4h) for male/female rats of 1972 mg/m^3 (Unpublished report, 1981). The value was recalculated from a 6h LC_{50} using Haber's rule with n=3. However the LC_{50} (4h) for female mice (Unpublished report, 1981), recalculated using the same method, is lower (805 mg/m^3) and should have been used instead. The conclusions regarding the hazard classes are unchanged.

In addition, the eMSCA notes adverse effects to organs and in particular to the lungs (congestion of lungs in rats, irregular/labored respiration in rats and mice, dyspnea in rats) and to the central nervous system (narcosis, hypersensitivity in rats, impared gait, stereotypic behavior in rats and mice, clonic/tonic convulsions in rats, mice, dogs, loss of coordination in rats, mice, rabbits, dogs, guinea pigs).

Table 27: Data on acute toxicity by inhalation route

Method	Results	Remarks	Reference
Acute inhalation toxicity study in rats (range-finding) Rats (Fischer 344) male/female 6 animals/sex/dose Inhalation: vapour (whole body), 6 hours exposure Vehicle: unchanged (no vehicle) Doses: 46, 130, 260 or 557 ppm (analytical) corresponding to 249, 703, 1407, 3013 mg/m^3	LC50 (6 h): 284 ppm (male) corresponding to 1536 mg/m^3 (analytical) LC50 (6 h): 353 ppm (female) corresponding to 1910 mg/m^3 (analytical) Death occurred on day 1 or 2 Clinical signs: irregular/labored respiration, impared gait, stereotypic behavior from 260 ppm; loss of coordination, clonic/tonic convulsions at 557 ppm. Necropsy: not investigated. NOAEC for irregular breathing and stereotypic behavior: 46 ppm (248.74 mg/m^3).	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
Acute inhalation toxicity study in mice (range-finding) Mice (B6C3F1) male/female 6 animals/sex/dose Inhalation: vapour (whole body), 6 hours exposure Vehicle: unchanged (no vehicle) Doses: 46, 130, 260 or 557 ppm (analytical) corresponding to 249, 703, 1407, 3013 mg/m^3	LC50 (6 h): 143 ppm (male) corresponding to 774 mg/m^3 (analytical) LC50 (6 h): 130 ppm (female) corresponding to 703 mg/m^3 (analytical) Death occurred on day 1 or 2 Clinical signs: from 130 ppm, irregular breathing, labored respiration, stereotypic behavior, coordination loss, tremors; from 260 ppm: convulsions. Necropsy: not investigated. NOAEC for irregular breathing and stereotypic behavior: 46 ppm (248.74 mg/m^3).	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
9-day inhalation study in rats Rats (Fischer 344) male/female 10 animals/sex/dose Inhalation: 9 days, 6h/day (exposure for 5 days, then 2 days of rest, then exposure for 4 days) Vehicle: unchanged (no vehicle) Doses: 0, 5.1, 33, 99.9 ppm (analytical) corresponding to 0, 28, 179, 541 mg/m^3	No death but significant decrease of body weight at 100 ppm; for females significant decrease of the food consumption at 100 ppm after 4 days Clinical signs: occasional audible respiration and gasping before and after exposure (females); occasional alopecia (females); at 100 ppm occasional wetness in nares and red/black crusty nasal discharge; Functional observations (Irwin screen test), 5 animals tested/sex: 1 male had impaired righting reflex on day 1 after exposure to 100 ppm Necropsy (all animals examined, only gross necropsy): in females exposed to 5 ppm : 1 necrosis of the tip of tail, 1 small nodule on the parietal surface of the medial lobe of liver (normal liver tissue), 1 small clear spot on the right apial lobe of lung. In males exposed to 100 ppm: 1 small lesion on one lobe of lung, 1 dome-shaped nodule in the parietal surface of the medial lobe of liver. In males exposed to 33 ppm: 1 small clear shiny area on the top of left lung (likely pneumonia). Organs of the nervous system were not examined.	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)

Method	Results	Remarks	Reference
	Organ weight: significant increase of kidneys weight for males at all doses. Organs of the nervous system were not weighed.		
9-day inhalation study in mice Mice (B6C3F1) male/female females: 10 animals/dose males: 9/8/9/9 animals/respective doses Inhalation: 9 days, 6h/day (exposure for 5 days, then 2 days of rest, then exposure for 4 days) Vehicle: unchanged (no vehicle) Doses: 0, 5.1, 33, 99.9 ppm (analytical) corresponding to 0, 28, 179, 541 mg/m^3	All mice exposed to 100 ppm died within 5 days No significant effect on body weight and food consumption Clinical signs: occasional alopecia Functional observations (Irwin screen test), 5 animals tested/sex: 1 male exposed to 5 ppm had decreased response to provoking situations or stimuli and 2 had abnormal tail and/or toe pinch reflex; 2 males and 4 females exposed to 33 ppm had decreased response to provoking situations or stimuli; 1 female exposed to 33 ppm had abnormal tail pinch reflex; in animals exposed to 100 ppm observations are occasional stereotypic behavior, abnormal coordination, reduced locomotor activity, (slight) tremors, abnormal tail and toe pinch reflex, abnormal gait (in additions in males: decreased response to provoking situations or stimuli; in addition in females: abnormal righting reflex, convulsions). Necropsy (all animals examined, only gross necropsy): in decendents, red discoloration and red patches in lungs, mottled liver, red/watery fluid in intestine; signs of pneumonia observed in 3, 1 and 2 males (respectively in control, 5 ppm and 33 ppm groups). Organs of the nervous system were not examined. Organ weights: for surviving males, non statistically significant decrease of the kidney weight (~-12% and -17%), and lungs weight (~-25% and ~-20%) respectively at 5 and 33 ppm as absolute weight and relative to body weight. Organs of the nervous system were not weighed.	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
Acute toxicity study (inhalation) in rabbits Rabbits male 4 animals/dose Inhalation: vapour (whole body), 4 hours exposure	LC50 (4 h): 771 ppm corresponding to 4171 mg/m^3 (analytical) Clinical signs: poor coordination.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)
Acute toxicity study (inhalation) in mice Mice male 6 animals/dose Inhalation: vapour (whole body), 4 hours exposure	LC50 (4 h): 145.5 ppm corresponding to 787 mg/m³ (analytical) Death occurred on day 1 Clinical signs: poor coordination, in 1 mouse exposed to 272 ppm, tonic convulsions.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
Acute toxicity study (inhalation) in dogs Dogs (Beagle) female 1 animal/dose Inhalation: vapour (whole body), 4 hours exposure (1h for the highest dose because the animal died) Dose: 368, 1472, 2478 and 4182 mg/m^3	LC50 (4 h): between 2478 and 4181 mg/m^3 Death occurred 1h after start of exposure for the highest dose Clinical signs: poor coordination, tremors from 1472 mg/m^3; eye and nose irritation from 2478 mg/m^3; tonic and clonic convulsions at 4182 mg/m^3 before death.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)
Acute toxicity study (inhalation) in rats Rats (albino) male/female 6 animals/sex/dose Inhalation: vapour (whole body), 4 hours exposure	LC50 (4 h): 359.4 ppm (male) corresponding to 1943 mg/m^3 LC50 (4 h): 385.2 ppm (female) corresponding to 2083 mg/m^3 Clinical signs: from 272 ppm, irritation of extremities, eye irritation, poor coordination and convulsions prior to death.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)
Acute toxicity study (inhalation) in guinea pigs Guinea pigs male 6 animals/dose Inhalation: vapour (whole body), 4 hours exposure	LC50 (4h): 770,5 ppm corresponding to 4168 mg/m^3 Clinical signs: slight loss of coordination at 458 ppm	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971) *Not included in the registration dossier.*
10-day inhalation toxicity study in rats Rats (Harlan-Wistar) male/female 6 animals/sex/dose Inhalation: exposure for 10 days, 7h/day, 5 day/week Doses: 0, 72, 146, 332 ppm (analytical) corresponding to 390, 790, 1792 mg/m^3	All animals died at 332 ppm (1792 mg/m^3) within 3 days (females) and 4 days (males). One male had convulsions during and after the 2nd exposure. Dead animals had hemorrhage in lungs, blood in the intestines. In addition females had hemorrhage in thymus. Animals exposed to lower doses survived, gained weight normally, displayed no adverse clinical signs and no lesions were found at necropsy.	3 (not reliable) supporting study experimental result Test material: DCPD (purity assumed 96.7%)	Kinkead *et al.* (1971)
10-day inhalation toxicity study in mice Mice (albino) male/female	All mice exposed to 146 ppm (790 mg/m^3) died on day 1 and had convulsions before death. 5 on 6 animals/sex exposed to 72 ppm (390 mg/m^3) also died but had no convulsions. Survivors gained weight normally.	3 (not reliable) supporting study	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
6 animals/sex/dose Inhalation: exposure for 10 days, 7h/day, 5 day/week Doses: 0, 47, 72, 146 ppm (analytical) corresponding to 254, 390, 790 mg/m^3	No gross lesions were found at necropsy.	experimental result Test material: DCPD (purity assumed 96.7%)	
10-day inhalation toxicity study in dogs Dogs (Beagles) male 1 animal/dose Inhalation: exposure for 10 days, 7h/day, 5 day/week Doses: 0, 20, 47, 72 ppm corresponding to 108, 254, 390 mg/m^3	Animals gained weight normally. The dog exposed to 47 ppm (254 mg/m^3) had diarrhea, excessive salivation on day 2, lack of control of hindquarters on day 9. The dog exposed to 20ppm had diarrhea on day 3.	3 (not reliable) supporting study experimental result Test material: DCPD (purity assumed 96.7%)	Kinkead *et al.* (1971)
Acute toxicity study (inhalation) in rats Rats Inhalation, 4 hours exposure	LC50 (4h): 660 ppm corresponding to 3564 mg/m^3	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Kinkead *et al.* (1971)
Subcute toxicity study (inhalation) in rats Rats (Alderley Park) male/female Acute and repeated toxicity study 2 animals/sex/dose (250, 1000, 2500 ppm); 4 animals/sex/dose (100 ppm) Inhalation Doses: 1h at 2500 ppm; 4h at 1000ppm; 10 days at 250 ppm (6h/day); 15 days at 100 ppm (6h/day)	1h at 2500 ppm: 1/4 died; clinical signs: eye and nose irritation, dyspnoea, narcosis; necropsy: for decedents, congestion of lungs, liver and kidneys 4h at 1000ppm:4/4 died; clinical signs: eye and nose irritation, dyspnoea, muscular incoordination, tremors, hypersensitivity At 250 ppm 1/4 died after the 2nd exposure; survivors lost weight; clinical signs: nose irritation, dyspnoea, lethargic, tremors, hypersensitivity.	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Gage (1970)

7.9.2.1.3. *Dermal route*

Based on the available information it can be concluded that the substance is not acutely toxic by dermal route (LD50 > 2000 mg/kg bw).

Table 28: Data on acute toxicity by dermal route

Method	Results	Remarks	Reference
Acute dermal toxicity (limit test) in the rat Rats (Sprague-Dawley) male/female 5 animals/sex Intact skin; coverage: occlusive Vehicle: unchanged (no vehicle) Dose: 2000 mg/kg OECD TG 402	LD50: > 2000 mg/kg bw (male/female) Clinical signs: vocalisation for 30 minutes after dosing, on days 1 and 2: hunched posture, on day 1: lethargy, piloerection, erythema and oedema, ptosis in 2 females, red/brown staining of snout in 2 males; on day 2: reduced respiratory rate in 1 male; from day 2: eschar until day 10 (8 rats) or day 12 (2 rats)	1 (reliable without restriction) key study experimental result Test material: DCPD **(purity 72%)**	Unpublished report (1989b)
Acute toxicity study in rats (range finding) Rabbits (New Zealand White) male 4 animals Coverage: occlusive Vehicle: unchanged (no vehicle)	LD50: 4.46 mL/kg bw (male) corresponding to 4460 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1962)
Acute toxicity study in rats (range finding) Rabbits (New Zealand White) male 4 animals Coverage: occlusive	LD50: 6.72 mL/kg bw (male) corresponding to 6720 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1954)
Acute toxicity study by dermal route in rabbits Rabbits	LD50: 5,08 mL/kg corresponding to ~ 4978 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Kinkead *et al.* (1971)

7.9.2.1.4. *Other routes*

Table 29Data on acute toxicity by other routes

Method	Results	Remarks	Reference
Acute toxicity study in rats Rats Intraperitoneal	LD50: 0,31 mL/kg corresponding to ~ 304 mg/kg bw	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Kinkead *et al.* (1971) .

7.9.2.2. Corrosion/irritation

7.9.2.2.1. *Skin*

The Registrant(s) concluded that the substance is irritant to skin and should be classified as **Skin Irrit 2, H315 (causes skin irritation)**. Based on the available information, the eMSCA supports this conclusion.

Table 30: Data on skin irritation

Method	Results	Remarks	Reference
Acute dermal irritation test in the rabbit Rabbits (New Zealand White) 3 animals Clipped intact skin; coverage: semiocclusive Vehicle: unchanged (no vehicle) Dose: 0.5 mL of undiluted test substance OECD TG 404	moderately irritating (scoring according to Draize scale) erythema score: 2 of 4 at time point 24, 48 and 72h. Fully reversible within 7 days (possible hyperkeratinisation at 7 days in all animals) edema score: 3.7 of 4 at 24h; 1.6 of 4 at 48 and 72h. Fully reversible within 7 days. Primary irritation index: 4.7	1 (reliable without restriction) key study experimental result Test material: DCPD **(purity 72%)**	Unpublished report (1989c)
Skin irritation study in rats Rabbits (albino) 5 animals Clipped intact skin; coverage: open Dose: 0,01 mL of undiluted test substance	moderately irritating Overall irritation score: 5 of 10 at 24 h	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1962)
Acute dermal irritation study in rabbits Rabbits (New Zealand White), male 4 animals Clipped intact skin for 2 animals and abraded skin for 2 animals; coverage: occlusive Dose: 2 g/kg bw of undiluted test substance	minimal skin irritation No edema or eschar 3/4 had slight erythema, which persisted 7 to 9 days Skin stained yellow in 2/4 adter day 8 Necropsy: ¼ had some pitting and dark areas of the spleen	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976i) *Not included in the registration dossier.*
Acute dermal toxicity (limit test) in the rat Rats (Sprague-Dawley) male/female 5 animals/sex Intact skin; coverage: occlusive Vehicle: unchanged (no vehicle) Dose: 2000 mg/kg OECD TG 402	*refer to* ***Table 28*** erythema and oedema on day 1 eschar from day 2 to day 10 in 8 rats and to day 12 in 2 rats	1 (reliable without restriction) key study experimental result Test material: DCPD **(purity 72%)**	Unpublished report (1989b)
Modified 9 -induction Buehler contact sensitization study Guinea pig (Dunkin-Hartley) female 12 test animals and 12 controls	refer to ***Table 33*** At the induction sites: scaterred mild redness, fissuring, dry, thickened, straw coloured skin (possible hyperkeratinisation), loss of skin suppleness,	1 (reliable without restriction) key study experimental result Test material: DCPD (purity 96.7%)	Unpublished report (1989e)

Method	Results	Remarks	Reference
Induction: epicutaneous, occlusive; 0.5mL of undiluted substance; 9x6h on days 0, 2, 4, 7, 9, 11, 14, 16, 18	superficial cracking of the skin, small superficial scattered scabs.		

7.9.2.2.2. *Eyes*

The Registrant(s) concluded that the mixture containing 72% of the substance was not irritating but that the Substance with a higher purity was slightly irritating to the eyes. The Registrant(s) considered that the harmonised classification as **Eye Irrit 2, H319 (causes serious eye irritation)** should be maintained. Based on the available information, the eMSCA supports this conclusion.

Table 31: Data on eye irritation

Method	Results	Remarks	Reference
Animal data			
Acute eye irritation test in the rabbit Rabbits (New Zealand White) Instillation into the conjunctival sac Vehicle: unchanged (no vehicle) Dose: 0.1 mL OECD TG 405	moderately irritating Cornea score: 0 (only dulling at 1h in 2 rabbits) Iris score: 1 (on 2) at 1h in all 3 rabbits Conjunctivae redness score: 2.3 (on 3) at 1h, 0.6 at 24h, 0.3 at 48 and 72h Conjunctivae chemosis score: 2 (on 4) at 1h, 0.3 at 24h	1 (reliable without restriction) key study experimental result Test material: DCPD **(purity 72%)**	Unpublished report (1989d)
Primary eye irritation study in rabbits Rabbits (albino) 9 animals: for 3 the eyes were washed 2 seconds after application, for 3 the eyes were washed 4 seconds after application, for 3 the eyes were left unwashed Vehicle: unchanged (no vehicle) Dose: 0.1 mL	irritating to the conjunctivae scoring system: Draize conjunctival irritation was present in 7 out of 9 rabbits in day 1 and 2. 4 animals out of 9 had conjunctival score of 2.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976d)
Eye irritation study in rabbits Rabbits	grade 2 (on 10) for corneal necrosis	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1962) *Not included in the registration dossier.*
Eye irritation study in rabbits Rabbits	irritating	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Smyth *et al.* (1954) *Cited in OECD SIDS*
Rabbits	moderately irritating	4 (not assignable) supporting study experimental result	RTECS Database (Prehled Prumyslove

Method	Results	Remarks	Reference
		Test material: DCPD (purity not specified)	Toxikologie, 50 (1986)
Acute toxicity study (inhalation) in dogs Dogs (Beagle) female 1 animal/dose Inhalation: vapour (whole body), 4 hours exposure (1h for the highest dose because the animal died) Dose: 368, 1472, 2478 and 4182 mg/m^3	*refer to* ***Table 27*** eye and nose irritation from 2478 mg/m^3	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)
Acute toxicity study (inhalation) in rats Rats (albino) male/female 6 animals/sex/dose Inhalation: vapour (whole body), 4 hours exposure	*refer to* ***Table 27*** irritation of extremities, eye irritation	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)
Subcute toxicity study (inhalation) in rats Rats (Alderley Park) male/female 2 animals/sex/dose (250, 1000, 2500 ppm); 4 animals/sex/dose (100 ppm) Inhalation Doses: 1h at 2500 ppm; 4h at 1000ppm; 10 days at 250 ppm (6h/day); 15 days at 100 ppm (6h/day)	*refer to* ***Table 27*** 1h at 2500 ppm (1/4 died): eye and nose irritation, lungs congestion in decedents 4h at 1000ppm (4/4 died): eye and nose irritation At 250 ppm (1/4 died after the 2nd exposure): nose irritation and weight loss	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Gage (1970)
Human data			
Human sensory response test Human volunteers 2 subjects (each exposed to both doses) Doses: 1 and 5.5 ppm	Irritating to the eyes Slight eye irritation after 7 min for 1 subject at 1 ppm; eye irritation after 10 min for 1 subject at 5.5ppm.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 96.7%)	Kinkead *et al.* (1971)

7.9.2.2.3. *Respiratory tract*

The Registrant(s) concluded that the Substance is irritant to the respiratory tract and should be classified as **STOT SE 3 (affected organs: respiratory tract; route of exposure: inhalation), H335 (may cause respiratory irritation)**. Based on the available information, the eMSCA supports this conclusion.

Table 32: Data on respiratory tract irritation

Method	Results	Remarks	Reference
Animal data			
Acute inhalation toxicity study in rats (range-finding) Rats (Fischer 344) male/female 6 animals/sex/dose	*refer to* ***Table 27*** irregular/labored respiration NOAEC for irregular breathing and stereotypic behavior: 46 ppm (248.74 mg/m^3).	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)

Method	Results	Remarks	Reference
Inhalation: vapour (whole body), 6 hours exposure Vehicle: unchanged (no vehicle) Doses: 46, 130, 260 or 557 ppm (analytical) corresponding to 249, 703, 1407, 3013 mg/m^3			
Acute inhalation toxicity study in mice (range-finding) Mice (B6C3F1) male/female 6 animals/sex/dose Inhalation: vapour (whole body), 6 hours exposure Vehicle: unchanged (no vehicle) Doses: 46, 130, 260 or 557 ppm (analytical) corresponding to 249, 703, 1407, 3013 mg/m^3	*refer to* ***Table 27*** irregular breathing, labored respiration from 150 ppm (LC50 (6 h): 143 ppm) NOAEC for irregular breathing and stereotypic behavior: 46 ppm (248.74 mg/m^3).	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
9-day inhalation study in rats Rats (Fischer 344) male/female 10 animals/sex/dose Inhalation: 9 days, 6h/day (exposure for 5 days, then 2 days of rest, then exposure for 4 days) Vehicle: unchanged (no vehicle) Doses: 0, 5.1, 33, 99.9 ppm (analytical) corresponding to 0, 28, 179, 541 mg/m^3	*refer to* ***Table 27*** no death but significant decrease of body weight at 100 ppm occasional audible respiration, mouth breathing, gasping before and after exposure	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
9-day inhalation study in mice Mice (B6C3F1) male/female females: 10 animals/dose males: 9/8/9/9 animals/respective doses Inhalation: 9 days, 6h/day (exposure for 5 days, then 2 days of rest, then exposure for 4 days) Vehicle: unchanged (no vehicle) Doses: 0, 5.1, 33, 99.9 ppm (analytical) corresponding to 0, 28, 179, 541 mg/m^3	*refer to* ***Table 27*** all mice exposed to 100 ppm died within 5 days in decendents: red discoloration and red patches in lungs non statistically significant decrease of the lungs weight for surviving males (~-25% at 5 ppm and ~-20% at 33 ppm as absolute weight and relative to body weight)	2 (reliable with restrictions) key study experimental result Test material: DCPD (purity 97%)	Unpublished report (1981)
Acute toxicity study (inhalation) in dogs Dogs (Beagle) female 1 animal/dose Inhalation: vapour (whole body), 4 hours exposure	*refer to* ***Table 27*** eye and nose irritation from 2478 mg/m^3 (LC50 (4 h): between 2478 and 4181 mg/m³)	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98.3 %)	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
(1h for the highest dose because the animal died) Dose: 368, 1472, 2478 and 4182 mg/m^3			
10-day inhalation toxicity study in rats Rats (Harlan-Wistar) male/female 6 animals/sex/dose Inhalation, 10 days (7h/day, 5 day/week) Doses: 0, 72, 146, 332 ppm (analytical) corresponding to 390, 790, 1792 mg/m^3	*refer to* ***Table 27*** All rats exposed to 332 ppm died within 4 days (all victims had hemorrhage in lungs)	3 (not reliable) supporting study experimental result Test material: DCPD (purity assumed 96.7 %)	Kinkead *et al.* (1971)
90-day inhalation toxicity study in rats Rats (Wistar) male/female 12 animals/sex/dose Inhalation: vapour (whole body), 90 days, 7h/day, 5 days/week Vehicle: unchanged (no vehicle) Doses: 0, 19.7, 35.2, 73.8 ppm (analytical) corresponding to 0, 107, 190 and 399 mg/m^3	3 males exposed to 73.8ppm had chronic pneumonia and bronchiectasis	3 (not reliable) supporting study experimental result Test material: DCPD (purity 96.7 %)	Kinkead *et al.* (1971)
Subcute toxicity study (inhalation) in rats Rats (Alderley Park) male/female 2 animals/sex/dose (250, 1000, 2500 ppm); 4 animals/sex/dose (100 ppm) Inhalation Doses: 1h at 2500 ppm; 4h at 1000ppm; 10 days at 250 ppm (6h/day); 15 days at 100 ppm (6h/day)	*refer to* ***Table 27*** 1h at 2500 ppm (1/4 died): eye and nose irritation, lungs congestion in decedents 4h at 1000ppm (4/4 died): eye and nose irritation At 250 ppm (1/4 died after the 2nd exposure): nose irritation and weight loss	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Gage (1970) *Not included in the registration dossier.*
Human data			
Human sensory response test and odour threshold test Human volunteers Human sensory response test: 2 subjects (each exposed to both doses) Odour threshold: 3 subjects Doses: 1 and 5.5 ppm (sensory response), 0.0006, 0.003 and 0.006 ppm (odour threshold)	Irritating to the respiratory tract Slight throat irritation after 7 min for 1 subject at 1 ppm. 1 subject could taste dicyclopentadiene for 1h after the 5.5 ppm exposure. The odour threshold appears to be slightly below 0.003 ppm.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 96.7%)	Kinkead *et al.* (1971)
Odour threshold Human (literature review)	Air odor threshold: 0.0057 ppm (v/v) (standard error 1.9) Threshold limit value (TLV, ACGIH), defined as a time-	2 (reliable with restrictions) supporting study experimental result	Amoore & Hautala (1983)

Method	Results	Remarks	Reference
	weighted average concentration for a normal 8h work-day and a 40h work-week: 5 ppm (v/v) Safe dilution factor (volatility divided by TLV): 720 Odor safety factor (TLV divided by threshold factor): 870 Odor safety class: A (more than 90% of distracted persons perceive warning of TLV concentration in air)	DCPD (purity not specified, solid at 20°C)	

7.9.3. Sensitisation

7.9.3.1.1. *Skin sensitisation*

The Registrant(s) concluded that the Substance should not be classified for skin sensitisation under CLP. Based on the available data, the eMSCA can support this conclusion.

Table 33: Data on skin sensitisation

Method	Results	Remarks	Reference
Modified 9 -induction Buehler contact sensitization study Guinea pig (Dunkin-Hartley) female 12 test animals and 12 controls Induction: epicutaneous, occlusive; 0.5mL of undiluted substance; 9x6h on days 0, 2, 4, 7, 9, 11, 14, 16, 18 Challenge: epicutaneous, occlusive; 0.2mL of undiluted substance; day 28	Not sensitizing. One animal of test group killed due to ill health on day 12. At the induction sites: scaterred mild redness, fissuring, dry, thickened, straw coloured skin (possible hyperkeratinisation), loss of skin suppleness, superficial cracking of the skin, small superficial scattered scabs. Challenge reactions: score of 0 (on 3) for all animals	1 (reliable without restriction) key study experimental result Test material: DCPD (purity 96.7%)	Unpublished report (1989e)
Guinea pig sensitization (Draize test) Guinea pig 8 test animals and 4 positive controls (2,4-dinitro-1-chlorobenzene) Induction: intracutaneous injection (0.05 mL at 0.1% w/v); 3 times per week (10 injections total) Challenge: intracutaneous injection (0.05 mL) Vehicle: saline solution for positive control and corn oil for DCPD	Not sensitizing Mild erythema	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 98-99%)	Unpublished report (1976e)

7.9.3.1.2. *Respiratory sensitisation*

No specific data.

None of the effects observed in inhalation studies were related to respiratory sensitisation.

7.9.4. Repeated dose toxicity

7.9.4.1.1. *Oral route*

The studies available to investigate repeated dose toxicity by oral route are summarised below.

Table 34: Data on repeated dose toxicity by oral route

Method	Results	Remarks	Reference
Combined repeated dose and reproduction/ developmental screening test by oral administration in rats Rats (Sprague-Dawley) male/female 10 animals/sex/dose Oral: gavage Males exposed for 44 days; females exposed from 14 days before mating through gestation and parturition until day 3 of lactation; 1/day Vehicle: olive oil Doses: 0, 4, 20 or 100 mg/kg/day (nominal) OECD TG 422	NOAEL (male): 4 mg/kg bw/day due to histological changes in kidneys and adrenals at 20 mg/kg/day NOAEL (female): 20 mg/kg bw/day due to mortality (2/10), lower body weight and lower food consumption at 100 mg/kg/day. Mortality: 2 females in the highest dose group died (probably one before and one during mating). Both showed bilateral adrenals enlargement with congestion and unilateral necrosis with hemorrhage in fascicular zone, hemorrhage of thymus with karyorrhexis of lymphocytes, liver congestion and dark reddish lungs with congestive pulmonary edema. In addition, one had hemorrhage of the stomach mucosa, atrophy and karyorrhexis of lymphocytes in spleen. Body weight: in the highest dose group (100 mg/kg/day), slight suppression of body weight gain was observed in males (~-10%) and females (-56% after 7 days; -14% during gestation; -30% at PND4). Food consumption: statistically significant decrease in the 100 mg/kg/day group after 7 days (-16% for males / -30% for females); for females the food consumption was decreased in a dose-dependent manner (but not statistically significant) at PND4 (-21% at 100 mg/kg/day, -15% at 20 mg/kg/day). Clinical signs: the only reported clinical signs are salivation from day 8. Necropsy/histopathology, organs weight: organs examined: liver, kidney and adrenals (all groups); thymus, testes, epididymis, brain, heart, spleen, ovaries (controls and 100 mg/kg groups only); organs weighed: thymus, liver, kidneys, adrenals, testes, epididymis. - liver: effects were observed only in males: ○ enlargement (1/10 at 20 mg/kg/day, 3/10 at 100 mg/kg/day) ○ statistically significant increased weight (as absolute weight and relative to the body weight) in the 100 mg/kg/day group (+14% and + 20% respectively ○ single cell necrosis (7/10 at 100 mg/kg/d) and multilocular biliary cyst (1/10 at 20 mg/kg/day) - kidneys: effects were observed only in males: ○ increased weight (as absolute weight and relative to the body weight) in the 4 mg/kg/day group (+12%), 20 mg/kg/day group (+20%) and 100 mg/kg/day group (+17% and +22% respectively), statistically significant in 20 and 100 mg/kg/day groups	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 94,65%)	Unpublished report (1993b), *Study in Japanese (translation provided by the Registrant(s). Due to limitations in the protocol, a Klimisch score of 2 was attributed by the eMSCA, although the Registrant(s) gave it a score of 1 and considered it as the key study)*

Method	Results	Remarks	Reference
	○ increase of hyaline droplets in tubular epithelium for all exposed males at all doses; basophilic change in tubular epithelium (3/10 at 20 mg/kg/day, 2/10 at 100 mg/kg/day), discoloration and withish dots (1/10 at 100 mg/kg/day); enlargement and multiple cysts (1/10 at 20 mg/kg/day) - adrenals: slight increase of adrenals weight in males (up to +6% as absolute weight and +12% relative to body weight), enlargement, and increase of fatty droplets in fascicular zone (3 males/10 at 20 mg/kg/day, 8 males/10 at 100 mg/kg/day; 1 female/10 at 100 mg/kg/day) - spleen: enlargement for 1 male/10 at 20 mg/kg/day (histopathology not examined) - thymus: increase of the thymus weight (non statistically significant) in the 4 mg/kg/day group (+18%/+8% as absolute weight in males/females, +20%/+9% relative to body weight in males/females) - testes: atrophy of seminiferous tubules (1/10 control, 2/10 at 20 mg/kg/day, 1/10 at 100 mg/kg/day) - mammary gland: mammary adenoma (1/10 at 20 mg/kg/day showing nodule at necropsy) Blood chemistry: *only investigated in males* (GOT[4], GPT[5], ALP, gamma-GTP, urea nitrogen, glucose, total cholesterol, triglycerides, creatinine, total bilirubin, total protein, albumin, A/G ratio, calcium, inorganic phosphorus, sodium, potassium, chloride): statistically significant increase of GOT (+40%) and GPT (+88%) in the 100 mg/kg/day group; statistically significant decrease of calcium in the 4 mg/kg/day group. Haematology: *only investigated in males* (red blood cell (RBC), white blood cell (WBC), platelets, haemoglobin, haematocrit, differential white cell count, reticulocyte, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration): the Registrant(s) considered that there were no effects, but the following were observed: statistically significant decrease of the RBC and hematocrit in the 20 and 100 mg/kg/day groups, statistically significant decrease of hemoglobin concentration in the 100 mg/kg/day group, slight increase of platelets and WBC (neutrophils) in the 20 and 100 mg/kg/day groups Reproductive parameters: *detailed in section 7.9.7.*		

[4] Glutamate oxaloacétictransaminase or aspartate aminotransférase.
[5] Glutamate pyruvate transaminase or alanine aminotransferase.

Method	Results	Remarks	Reference
28-day repeated dose toxicity test Rats (Fischer 344) male/female 6 animals/sex/dose Oral: gavage Exposure for 28 days; 1/day; satellite groups for a 14 day recovery Vehicle: no information Doses: 0, 8, 40, 80 mg/kg/day	NOAEL : 8 mg/kg/day Mortality: no information Body weight: inhibition of body weight gain observed in the 200 mg/kg/day groups in both sexes and the 40 mg/kg/day group in males, but in females this inhibition was recovered at day 17 of the treatment. Food consumption: no information. Clinical signs: no information. Organ weight: increases in liver and adrenal gland weights, and decrease in thymus weight observed in the 200 mg/kg/day groups in both sexes, and increase in kidney weight was also observed in the 200 and 40 mg/kg/day groups in male Necropsy/histopathology: hypertrophy of the adrenal cortex, and foamy cytoplasm in hepatocytes observed in the 200 mg/kg/day groups of both sexes. Repair of histopathological lesions occurred within 14 days resting period.	4 (not assignable) supporting study experimental result Test material: DCPD (purity not specified)	Satoh *et al.* (1990) *Only abstract available.*
3-month subchronic toxicity in dogs Dogs (Beagles) male/female 4 animals/sex/dose Oral: dietary administration Exposure for 90 days; 1/day Vehicle: corn oil Doses: 0, 100, 300 and 1000 ppm (nominal in diet) corresponding to ~ 0, 2.5, 7.5, 25 mg/kg bw/day	NOAEL: 1000 ppm (male/female) No significant toxicity was seen at any dose level. Minor indications of intestinal distress (vomiting and soft stools) seen at the highest dose (1000 ppm) were considered to be of no toxicological significance by the author Mortality: none Body weight: no effects Food consumption: overall slightly lower in exposed animals than in control Clinical signs (difficult to interpret, because there is no tabular report and several pages are illegible in the observation reports of individual dogs): slightly higher frequency of vomiting and soft stools in the males and females of the highest dose group. Necropsy/histopathology: organs examined (control and highest dose groups only): adrenals, brain, caecum, colon, epididymes, eyes, gall bladder, kidneys, lungs, mesenteric lymph node, ovaries, pancreas, pituitary gland, sciatic nerve, prostate, rib junction, muscle, small intestine, spinal cord, spleen, sternum, stomach, testes, thyroids, urinary bladder, uterus. Organs weighed: adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes, thyroids: no statistically significant change of organ weights. - adrenals: in males and females, decreased adrenals weight was observed at all doses, in a non-dose dependent manner (up to -6% for males and -13% for females as absolute weight, -12% for males and -25% for females as percentage of body	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98-99%) Due to the low number of animals per group, the significance of any statistical analysis is questionable. Inconsistencies were found in the report.	Unpublished report (1980a)

Method	Results	Remarks	Reference
	weight, -17% for males and females as percentage of brain weight). No lesion was seen at necropsy. - brain: 1 female/4 of the 1000 ppm group had mild hydrocephalus and minimal focal periarteriolar mineralisation in brain. For all exposed females, a slight decrease of the brain weight (relative to body weight) was observed (-9 to -12%). - heart: in males slight decrease of the heart weight as absolute weight (-5% in the 300 ppm group and -7% in the 1000 ppm group) and relative to brain weight at all doses (-7% to -12%); in females decrease of the heart weight relative to body weight (up to -19%) at all doses. - kidneys: in males, decreased weight was observed at all doses (non dose-dependent) as absolute weight (up to -13% in the 300 ppm group) and relative to body weight (-4% to -9%) and brain weight (-10 to -20%); in females, increased absolute kidney weight (+5% to +9%) was observed. 1 female/4 of the 1000 ppm group had moderate interstitial fibrosis and moderate nonsuppurative inflammation. - liver: in males, decreased weight was observed at all doses (non dose-dependent) as absolute weight (up to -16% in the 300 ppm group) and relative to body weight (up to -12% in the 100 ppm group) and brain weights (up to -22% in the 300 ppm group); in females, increased weight was observed at all doses as absolute weight (up to +18% in the 100 ppm group) and relative to brain weight (up to +12% in the 300 and 1000 ppm groups). - lungs: 1 male/4 in the 1000 ppm group had minimal mineralised granulosa; in addition interstitial inflammation was observed in 2 males/4 in the control group, 1 male/4 in the 1000 ppm group, all females in the control and 1000 ppm groups. - mesenteric lymph node: 1 male/4 in the control group and 1 male/4 in the 1000 ppm group had minimal eosinophilic leukocyte infiltrate. - ovaries: increased weight was observed at all doses in a non-dose dependent manner, when expressed as absolute weight (up to +222%), percentage of body weight (up to +183%) and percentage of brain weight (up to +220%). No lesion was seen at necropsy. - pituitary gland: cysts were found in 2 males/4 in the 1000 ppm group, 3 females/4 in the control group and 1 female/4 in the 1000 ppm group. - small intestine: 1 male/4 in the 1000 ppm group had minimal eosinophilic leukocyte infiltrate.		

Method	Results	Remarks	Reference
	- spleen: in males, increased weight at all doses as absolute weight (up to +25% in the 1000 ppm group) and relative to body weight(dose-dependent, up to +31% in the 1000 ppm group) and brain weight (up to +24% in the 1000 ppm group). - thyroid: increase of the thyroid weight was observed for females and decrease for males, at all doses, in a non-dose dependent manner (for females : up to + 41%, +21% and +34% as absolute weight, percentage of body weight and percentage of brain weight respectively, and for males up to -29%, -23% and -34% respectively). 1 female/4 in the 1000 ppm group had minimal cystic remnant of ultimobranchial duct; another female of this group had the same lesion on parathyroids. - testes: decreased testes weight relative to brain weight was observed (-9%, -13% and -9% for the 100, 300 and 1000 ppm groups respectively); effects on absolute testes weight and testes weight relative to body weight are less clear (respectively +3%, -6%, -8% and 3-%, +5% et -4% at 100, 300 and 1000 ppm); no effect was seen at necropsy. - urinary bladder: 1 female/4 of the 1000 ppm group had moderate mild acute hemorrhage, mild nonsuppurative inflammation and mild mucosal hyperplasia. Blood chemistry: no effect observed in the concentrations of bilirubin, albumin, total protein, uric acid, calcium, glucose, cholesterol. An overall increase of the concentrations of urea nitrogen, phosphorus and alkaline phosphatase was observed in females, an overall decrease of the concentrations of phosphorus and lactic deshydrogenase was observed in males. The data on the content of GOT and GPT is illegible in the report. Haematology: - leukocyte count: increase at weeks 0 and 14 in males of the 100 ppm group (+18-19%), at week 0 in males of the 1000 ppm group (+14%), at weeks 4 and 8 in all exposed females (+12-42%), at week 14 in females of the 300 ppm group (+24%). - erythrocyte count, hematocrit: overall slight increase in males; overall slight decrease in females. - hemoglobin: overall slight increase in males. Urinalysis: no effect. Ophtalmic evaluation: minor effects observed in 5 dogs (3/8 animals in the 100 ppm group and 2/8 animals in the 1000 ppm group).		
90-day toxicity study in rats Rats (Sprague-Dawley) male/female	The author concludes that there was no evidence of toxicity following dietary administration to rats for 90 days.	3 (not reliable) supporting study experimental result	Unpublished report (1976f)

Method	Results	Remarks	Reference
30 animals/sex/dose Oral: dietary administration Exposure for 90 days Vehicle: corn oil Doses: 0, 80, 250, 750 ppm corresponding to ~ 6, 20, 62 mg/kg/day	No information on statistical significance of the findings except for body weight and food consumption (Student test) Mortality: 8% died, equally distributed in all doses (16 males and 4 females). Body weight: occasional significant differences were scattered and not dose-dependent. The range of body weights of control males and females was much wider than of exposed animals. For males, first a decrease was observed in the 750 ppm grup (weeks 4-7) then an increase at all doses from week 9. For females there was a slight increase on weeks 9-11 at all doses and from week 13 in the 250 ppm group. Food consumption: for males, a statistically significant decrease was observed on weeks 2-5 in the 750 ppm group, and a statistically significant increase on week 9 at all doses. For females, an overall decrease was observed in the 750 ppm group. Clinical signs: none Necropsy/histopathology and organs weight: organs examined (5 animals/sex examined in control and highest dose groups): adrenals, bone marrow, brain, eye, heart, kidneys, large interstine, liver, lungs, mesenteric lymph node, nerve with muscle ovaries, pancreas, pituitary, prostate, rib junction, seminal vesicles, small intestine, spleen , stomach, testes with epididymis, thoracic spinal cord, thyroid, urinary bladder, uterus. Organs weighed: adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes, thyroid. - adrenals (weighed after fixation): in males, increase at all doses of absolute weight (+8%, +18%, +8% respectively in 80, 250 and 750 ppm groups), relative to body weight (+2%, +9%, +9%) and relative to brain weight (+8%, +18%, +11%) - heart: minimal focal chronic myocarditis observed in 1 male/5 in the 750 ppm group; mild vacuolar myocardial change observed in 2 females/5 in the 750 ppm group - kidneys: in females, dose-dependent decrease of the absolute weight (-5% at 750 ppm) - liver: in males, dose-dependent decrease of the absolute weight (-7% at 750 ppm), of the weight relative to brain weight (-4% at 750 ppm); in females, slight dose-dependent decrease of the liver weight. - lungs: chronic murine pneumonia observed in males and females in the control and 750 ppm groups (minimal to moderate, not dose-dependent) - ovaries: increase of the weight in the 250 and 750 ppm groups (+3-9% of absolute weight, +5-12% of weight relative to brain weight) - stomach: focal chronic gastritis observed in 2 males/5 in the 750 ppm group	Test material: DCPD (purity 98-99%) Inconsistencies were found in the report.	

Method	Results	Remarks	Reference
	- thyroid (weighed after fixation): in males, increase of the absolute weight at all doses (+20%, +33%, +13% respectivey at 80, 250 and 750 ppm) and relative to body weight (+14%, +23%, +15%). Blood chemistry: no indication that animals were fasted prio to blood collection; blood collected on 5 animals/sex/dose. - urea nitrogen: in males, decrease in the 80 and 250 ppm groups (-18% and -27%) on week 13; in females, increase in the 750 ppm group (+18%) on week 4 and decrease in the 80 ppm group (-19%) on week 13 - glucose: in males, increase on week 4 in the 80 and 750 ppm groups (+22% and +16%); in females, decrease on week 4 at all doses (-10% to -13%), and increase on week 13 at all doses (+14% to +31%) - alkaline phosphatase: decreased for males and females (in males, decrease on weeks 4 and 13 at all doses (-12% to -39%); in females, decrease on week 4 at all doses (-14% to -16%) and on week 13 in the 80 ppm group (-21%)) - GPT: decreased for males and females (males on weeks 4 and 13 at all doses (-6-44%), females on week 4 at all doses (-22-33%)) - GOT: decreased for males at all doses (-13% to -17%) on week 13 - potassium: M: dose-dependent increase (up to +13% in the 750 ppm group) on week 13 - sodium: M: dose-dependent decrease (up to -8% in the 750 ppm group) on week 13 - chlorure: no effect on week 13. Haematology (cell volume, hemoglobin, red blood cells, white blood cells): blood collected on 5 animals/sex/dose. - no effect on cell volume and hemoglobin - red blood cells: decrease in males and females on week 13 (in males of the 80 ppm group (-15%) and in females (-8%, -13% and -8% respectively in 80, 250 and 750 ppm groups)) - white blood cells: decrease in males and females (at all doses for males on weeks 4 and 13 (-19% to -29%); at all doses for females on weeks 4 (up to -15% in the 800 ppm group) and week 13 (-23% to -37%)) Urinalysis (5 animals/sex/dose): no effect Ophtalmology: all rats between normal limits (report not given).		

Method	Results	Remarks	Reference
90-day toxicity study in mice Mice (albino) male/female 32 animals/sex/dose Oral: dietary administration Exposure for 90 days Vehicle: corn oil Doses: 0, 28, 91, 273 ppm corresponding to ~ 6, 19, 56 mg/kg/day	The author concludes that there was no evidence of toxicity following dietary administration to mice for 90 days. No information on statistical significance of the findings Mortality: 1 Body weight: for males, decreased body weight on weeks 0 and 10 in the 28 ppm group (-13% to -14%), and dose-dependent increase on week 15 at all doses (up to +16%); in females, dose-dependent decrease at all doses on week 1 and 14 (up to -8%), dose-dependent increase on week 9 (up to +12%), and decrease in the 28 ppm group on week 10 (-20%). Food consumption: in males, decrease on weeks 1, 2, 3, 7, 10, 12 (up to -23%) and increase on week 11 in the 91 ppm group(+11%); in females, overall increase at most time points and doses (up to +53% in the 28 ppm group) Clinical signs: none Necropsy/histopathology and organs weight: organs examined (5 animals/sex examined in control and highest dose groups): adrenals, bone marrow, brain, eye, heart, kidneys, mesenteric lymph node, ovaries, pituitary, prostate, spleen, stomach, testes with epididymis, thyroid (control males not investigated), urinary bladder, uterus. Organs weighed: adrenals, heart, kidneys, liver, ovaries, spleen, testes, thyroid - eye: 1 male had mild corneal amylacia in the 273 ppm group - heart: increased weight in males of the 91 ppm group (+11%). No histopathological effect. - kidneys: decreased weight relative to body weight in males in the 91 ppm group (-13%). No histopathological effect. - mesenteric lymph node: 1 male of the 273 ppm group had lymphoreticullar hyperplasia; another male and 1 female had mild unidentified lesion - ovaries: decrease absolute weight and weight relative to body weight at all doses, non dose-dependent (up to -29% in the 91 ppm group). No histopathological effect. - prostate: 1 male had mild focal hyperplasia in the 273 ppm group. - spleen: in males, decreased weight at all doses (non dose-dependent, up to -23% as absolute weight and -25% relative to body weight); 1 male had a malignant lymphoma in the 273 ppm group - thyroid (weighed after fixation): in males, decreased absolute and relative weight in the 28 ppm group (-17% and -20% respectively), increased weight in the 273 ppm group(+19% as absolute weight, +16% relative to body weight); in females,	3 (not reliable) supporting study experimental result Test material: DCPD (purity 98-99%) Inconsistencies were found in the report.	Unpublished report (1976g) .

Method	Results	Remarks	Reference
	decreased weight at all doses (in the 91 ppm group, -36% as absolute weight, -35% relative to body weight, in the 273 ppm group, abs -13% as absolute weight, -14% relative to body weight). No histopathological effect. - testes: decreased weight at all doses, in a dose-dependent manner when considering absolute weight (up to -18%), and not dose-dependent relative to body weight (up to -21% in the 91 ppm group) - uterus: 1 female of the 273 ppm group had mild acute purulent cervicitis and another female had mild metritis.		

The available studies to assess the toxicity of DCPD by oral administration have the following limitations:

- In the combined repeated dose and reproduction/ developmental screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998), haematology and blood chemistry were performed only in males, no sensory reaction observations were made, some organs were not weighed (spleen, brain, heart) nor examined (spinal cord, stomach, intestine, thyroid, trachea, lungs, uterus, urinary bladder, lymph nodes, peripheral nerves, bone marrow, interstitial testicular cell structure) and the parameters defined in the last version of the OECD 422 guidance were not included. In addition, it is a screening study with a limited duration of exposure and a limited statistical power.
- No report nor robust study summary are available for the 28-day gavage study on rats, therefore it is difficult to determine its relevance. The NOAEL of 8 mg/kg/day is of the same order of magnitude than the NOAEL of the combined repeated dose and reproduction/ developmental screening test (4 mg/kg/day for males and 20 mg/kg/day for females).
- In the 3 90-day dietary studies were the authors concluded that there was no evidence of toxicity following exposure to DCPD, no information is available to determine if a part of the substance volatilized from the feed, leading to administered doses lower than the ones reported. The dose was analytically confirmed only in the 90-day studies on dogs and this was done once a week only. When asked, the Registrant(s) replied that the substance is not volatile but other references say the opposite. But, since a substance can be considered as volatile from de 10-4 – 10-5Pa et 20°C, DCPD should be considered as volatile. Additionally,
    - In the 90-day dietary study in dogs (Unpublished study report, 1980a), the doses were not properly chosen, the intermediate doses were not investigated for histopathology when lesions were observed at highest dose, some organs were not weighed (gall bladder, parathyroid, epididymis, uterus, thymus) nor examined (parathyroid, thymus, oesophagus, salivary glands, trachea, aorta, accessory sex organs), and there were errors in the report (for example in the identification of the animals).
    - In the 90-day dietary studies in rats (Unpublished study report 1976f) and mice (Unpublished study report 1976g), only a few animals per group were examined but the selection was not explained (so as to avoid bias), the intermediate doses were not investigated for histopathology when lesions were observed at highest dose, there is no indication that animals were fasted before blood collection and the statistical analysis was not documented.

Overall, no clear conclusion can be drawn for repeated toxicity by oral route. The liver and kidneys seem to be target organs and there are alerts for effects on adrenals, testes, thyroid, ovaries, and the immune system.

A 90-day study by oral route has been requested under CCH and is on-going. The opportunity for a classification for repeated toxicity shall be evaluated after all the information requested under CCH is available.

7.9.4.1.2. *Inhalation route*

The inhalation route is likely to be the main route of exposure of workers. As good-quality data are available, no further study is requested under SEv by the eMSCA.

Table 35: Data on repeated dose toxicity by inhalation route

Method	Results	Remarks	Reference
Animal data			
Dicyclopentadiene vapor 90-day inhalation study on rats Rats (Fischer 344) male/female 51 animals/sex/dose (9/dose sacrificed after 2 and 6 weeks of exposure (groups A and B), and on week 4 of recovery period (group D), 12/dose killed after 13 weeks of exposure (group C) and on week 13 of recovery period (group E) Inhalation: vapour (whole body) Exposure for 90 days, 6h/day, 5 day/week + satellite groups for a 90 days recovery Vehicle: none (air) Doses: 0, 1, 5, or 50 ppm (nominal), 0.0, 1.0, 5.1 and 51 ppm (analytical), corresponding to 0, 5, 27.6, 276 mg/m^3 (analytical) similar to OECD TG 413 (Subchronic Inhalation Toxicity: 90-Day) with deviations	The author concluded that there was no systemic toxicity at the highest dose tested, considering that the kidney effects observed on male rats (hyaline droplet nephropathy) are specific to male rats, and that increased liver weights in the absence of histopathologic changes are not adverse effects. Mortality: 1 in the control group (accidental) Body weight: no treatment-related effect. Non significant reduction of the body weight gain in the 5 ppm group during the recovery period. Food and water consumption: in males, significant increase of the water consumption on weeks 1 and 13 in the 1 ppm group; in the 5 ppm group, decrease of the water consumption on week 13; in the 50 ppm group, increase of the water consumption during the exposure period and at the beginning of the recovery period. In females, significant increase of the water consumption on weeks 3 and 4 in the 50 ppm group and on week 13 in the 5 ppm group. In females, significant decrease of the food consumption at the end of the recovery period. Clinical signs: no effect believed to be treatment-related. During exposure, urogenital area wetness and lacrimation was observed in some females of the 5 ppm group, lacrimation in some males in the 5 and 50 ppm group on week 6 and in the control group on week 13. During recovery, urogenital area wetness was observed in some males and females (non dose-dependent); lacrimation was observed in some females in the 1 and 5 ppm groups; periorbital hair loss and discharge/encrustation was observed in some females (non dose-dependently). Organs weight: organs weighed: kidneys, lungs, liver, testes. - liver: in males, significant increase of liver weight relative to body weight in the 50 ppm group during exposure (for females: slight non-significant but dose-dependent increase of the liver weight after 6 weeks of exposure). - kidneys: in males, significant increase of kidney weight (absolute weight and relative to body weight) in the 50 ppm group during exposure, significant increase in the 1 ppm group after 6 weeks of exposure. In females, significant decrease of the relative kidney weight in the 1 and 51 ppm groups at end of the recovery. - testes: at 4 weeks of recovery, the testes absolute weight in the 50 ppm group was slightly higher than in control and 1 ppm group; in the 5 ppm group, the weight was lower (with a much higher variability) than in control group. Necropsy/histopathology (9 animals per group after completing 2, 6, 13 weeks of exposure and following 4 and 13 weeks from last exposure):	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 95%; contains at least one CMR impurity)	Unpublished report (1982) Re-analysed in Bevan *et al.* (1992)

<table>
<tr><th>Method</th><th>Results</th><th>Remarks</th><th>Reference</th></tr>
<tr><td></td><td>

complete gross pathologic evaluation on all sacrified, dead and moribund animals.
histopathologic evaluation of kidneys and urinary bladders for groups A, B, C, D, E (all doses); for group C (13 weeks of exposure), the following tissues were examined microscopically for the high dose and control groups: gross lesions, adrenals, bone, bone marrow, brain, epididymis, eyes, heart, kidneys, larynx, liver, lungs, mediastinal lymph nodes, muscle, nasal turbinates, parathyroid, pituitary, sciatic nerve, spleen, testes, thymus, thyroids, trachea, urinary bladder.

kidneys: many signs of toxicity were observed, mainly in males but also some in females:

in males only:

<table>
<tr><td></td><td colspan="3">Exposure</td><td colspan="2">Recovery</td></tr>
<tr><td></td><td>group A
after 2 weeks</td><td>group B
after 6 weeks</td><td>group C
after 13 weeks</td><td>group D
4 weeks</td><td>group E
13 weeks</td></tr>
<tr><td>reticular pattern</td><td>1/9 (50 ppm)</td><td>1/9 (1 ppm)
2/9 (5 ppm)
6/9 (50 ppm)</td><td></td><td></td><td></td></tr>
<tr><td>color change</td><td>2/9 (5 ppm and 50 ppm) generalized</td><td>2/9 (50 ppm) generalized</td><td>2/9 (50 ppm) patchy</td><td></td><td></td></tr>
<tr><td>hyaline droplets</td><td>9/9 (control, 1, 5 and 50 ppm)
in the 5 and 50 ppm groups, more acidophilic (hyaline) and more variable in size, and more proximal convoluted tubules involved</td><td>7/9 (1 ppm)
5/9 (5 ppm)
7/9 (50 ppm)</td><td>8/9 (5 ppm)
9/9 (50 ppm)</td><td></td><td></td></tr>
<tr><td>glomerular basement membrane thickening</td><td></td><td>3/9 (5 ppm)
6/9 (50 ppm)</td><td>4/9 (50 ppm)</td><td>4/9 (control)
4/9 (5 ppm)
9/9 (50 ppm)</td><td>3/9 (control)
8/9 (1 ppm)
9/9 (5 ppm)
9/9 (50 ppm)</td></tr>
<tr><td>epithelial degeneration/regeneration</td><td>1/9 (5 ppm) degeneration</td><td>1/8 (control)
4/9 (1 ppm)
2/9 (5 ppm)
4/9 (50 ppm) degeneration/regeneration</td><td></td><td></td><td></td></tr>
<tr><td>glomerular protein accumulation</td><td></td><td>1/8 (control)
1/9 (1 ppm)
1/9 (5 ppm)</td><td></td><td></td><td></td></tr>
<tr><td>glomerular swelling</td><td></td><td>2/9 (1 ppm)
6/9 (5 ppm)
4/9 (50 ppm)</td><td></td><td></td><td></td></tr>
</table>
</td><td></td><td></td></tr>
</table>

Method	Results	Remarks	Reference

glomerular capillary dilatation		2/9 (50 ppm)			
cortical cyst		1/9 (5 ppm)			
cortical fibrosis		1/9 (control)			
exfoliated tubular epithelial cells		1/9 (1 ppm)			

- in females only:

	Exposure			Recovery	
	group A after 2 weeks	group B after 6 weeks	group C after 13 weeks	group D 4 weeks	group E 13 weeks
tubular concretions					1/9 (5 ppm)

- in males and females:

	Exposure			Recovery	
	group A after 2 weeks	group B after 6 weeks	group C after 13 weeks	group D 4 weeks	group E 13 weeks
interstitial nephritis	Males: 1/9 (5 ppm) 1/9 (50 ppm)		Males: 1/9 (1 ppm) 4/9 (50 ppm)	Males: 3/9 (5 ppm) 9/9 (50 ppm) Females: 1/9 (5 ppm) 2/9 (50 ppm)	Males: 2/9 (control) 2/9 (1 ppm) 1/9 (5 ppm) 7/9 (50 ppm) Females: 1/9 (control) 2/9 (1 ppm) 1/9 (50 ppm)
	occurs earlier and with more severity in exposed males in a dose-dependent manner				
tubular hyperplasia (regeneration)	Males: 3/9 (control) 3/9 (1 ppm) 7/9 (5 ppm) 9/9 (50 ppm) Females: 4/9 (control) 3/9 (1 ppm) 2/9 (5 ppm) 1/9 (50 ppm)	Males: 3/9 (control) 5/9 (1 ppm) 9/9 (5 ppm) 9/9 (50 ppm) Females: 1/9 (1 ppm) 3/9 (50 ppm)	Males: 9/9 (control, 1, 5 and 50 ppm) Females: 1/9 (1 ppm)	Males: 9/9 (control, 1, 5 and 50 ppm) Females: 2/9 (control) 3/9 (1 ppm) 3/9 (5 ppm) 1/9 (50 ppm)	Males: 9/9 (control, 1 and 50 ppm) 8/9 (5 ppm) Females: 1/9 (control) 1/9 (1 ppm) 3/9 (50 ppm)
	occurs earlier and with more severity in exposed males in a dose-dependent manner				

Method	Results	Remarks	Reference

tubular proteinosis	Males: 1/9 (control)	Males: 3/8 (control 1/9 (1 ppm) 1/9 (5 ppm) 3/9 (50 ppm)	Males: 1/9 (1 ppm) 2/9 (5 ppm) 9/9 (50 ppm)	Males: 4/9 (control) 2/9 (1 ppm) 3/9 (5 ppm) 5/9 (50 ppm) Females: 1/9 (control) 1/9 (50ppm)	Males: 7/9 (control) 9/9 (1, 5 and 50 ppm) Females: 1/9 (control) 2/9 (5 ppm) 1/9 (50 ppm)
glomerular adhesions	Males: 1/9 (1 ppm) 3/9 (5 ppm) 9/9 (50 ppm)	Males: 5/8 (control) 7/9 M 1ppm 9/9 M 5ppm 7/9 M 51ppm Females: 6/9 (control) 1/9 (1 ppm) 2/9 (5 ppm) 6/9 (50 ppm)	Males: 3/9 (control) 4/9 (1 ppm) 9/9 (5 ppm)		

- urinary bladder:
  - distended for 1 male/9 in the 1 and 50 ppm groups after 13 weeks of exposure (group C)
  - granular concretions for 1 male/9 in the 50 ppm group (group C)
  - mineralized concretions in 1 female/9 in the 1 and 5 ppm groups at 4 weeks of recovery (group D)
  - epithelial thinning in 1 female/9 in the 5 ppm group (group D).
- adrenals: for males, fatty infiltration in group C, twice as much in the 50 ppm group than in control group (intermediate doses not investigated).
- testes: at necropsy during recovery, 1 male/9 in the 5 ppm group (group D) had smaller testes than normal, and 1 male/9 in the 5 ppm group (group E) had patchy color change in testes.
- ovaries: (no microscopic examination)
  - cysts in the ovaries of females in control and exposed groups during exposure and at the end of recovery (1/9 control in group A, 1/9 in control and 1/9 for each dose group in group B, 1/9 control in group C, none in group D, and in group E: 1/9 in 1 ppm group, 2/9 in 5 ppm group and 3/9 in 50 ppm group.
  - filled with fluid in 1 female/9 in the 5 and 50 ppm groups (group C), and in group D in 1/9 in control, 5 and 50 ppm groups.

Method	Results	Remarks	Reference
	- lungs: in group B (after 6 weeks of exposure), 1 male/8 in control group and 1 male/9 in the 5 ppm group had lungs with patchy color change, and 1 male/9 in the 1 ppm group had a lobule. - liver: during recovery, in group D, 1 male/9 in control and 5 ppm group had anomalous lobulation, and in group E, 1 female/9 in the 50 ppm group had a nodule. - mediastinal lymph nodes: for group C, erythrocytes were found in sinuses of males (2/8 control, 3/9 in 50 ppm group) and females (3/9 control, 4/8 in 50 ppm group); hemosiderosis in sinuses of 3 females/9 control and 2 females/8 of the 50 ppm group (intermediate doses not investigated); mast cell infiltration in 1 male/9 in the 50 ppm group. - pancreatic lymph node: in group B, enlarged in 1 male/9 in the 50 ppm group and with a generalized color change in 1 male/9 in the 50 ppm group. - eyes: in group C, posterior synechia in 2 males/9 of control group, 1 male/9 and 1 female/9 in 50 ppm group (intermediate doses not investigated); in group E, periocular discharge in 2 females/9 in 1 ppm group and 1 female/9 in the 5 ppm group. - nasal cavity: 1 male and 1 female/9 exposed to 50 ppm (group C) had rhinitis, but also 3 control males. - jejunum: mucosal hemorrhage in 1 male/9 in the 50 ppm group from group D. - adipose tissue: nodule (steatisis and fibrosis) in 1 female/9 in the 50 ppm group (group C) (intermediate doses not investigated) and nodule in 1 male/9 in the 5 ppm group (group D). - skin: nodule in 1 female at 1 ppm in group E. Blood chemistry (no indication that animals were fasted before blood collection; recovery investigated only for males): parameters investigated: osmolarity, sodium, calcium, phosphorus, potassium, chloride, urea nitrogen, creatinine, total bilirubin, total protein, albumin, GPT, GOT, lactic deshydrogenase, alkaline phosphatase, glucose. - osmolarity: in females, significant increase in group B at 1 ppm. - potassium: in females, significant decrease in group C at 50 ppm. - sodium: in males and females, significant increase in group A (1 and 50 ppm groups). - calcium: in males, significant increase in group C (1 and 50 ppm groups). - phosphorus: in males, slight non-significant increase (+10%) in group A at 50 ppm. - urea nitrogen:		

Method	Results	Remarks	Reference
	○ in males, non-significant but dose-dependent increase in the 50 ppm group after 2, 6 and 13 weeks of exposure (groups A, B, C) (+4% to +15%), during recovery, +16% in the 5 ppm group; ○ in females, non-significant increase in group A at 1 ppm (+33%), in group B at 1, 5 and 50 ppm (respectively +19%, +14% and +13%), decrease after (-17% in 1 ppm group). - creatinine: in males, non significant increase (+26%) in group C in the 50 ppm group. - alanine aminotransferase (GPT): ○ in males, non-significant increase (+35%) in the 50 ppm group in group A; significant decrease in 5 and 50 ppm groups in group C; after recovery +18% in the 5 ppm group; ○ in females: non-significant decrease at all doses (-13% in the 50 ppm group after 6 weeks of exposure, -20% in the 5 ppm group after 13 weeks of exposure). - asparate aminotransferase (GOT): ○ in males, non-significant increase in the 5 and 50 ppm groups in group A (+11% to +32%), in the 1 ppm group in group C slight sincrease (+13%) ○ in females, non-significant increase in the 5 and 50 ppm groups in group A (+15% to +18%); decrease in group C at 5 ppm (-15%). - lactic deshydrogenase: ○ in males, non-significant decrease (-16%) in group A at 50 ppm; increase in group B (+73% with high variability at 1 ppm, +26% at 50 ppm), in group C +21% at 1 ppm and -14% at 5 ppm; after recovery, increase (+57% to +76%) at all doses; ○ in females, non-significant decrease in group A (-27% at 1 ppm, -11% at 50 ppm); increase in group B at all doses (+45% to +241%), in group C +21% at 1 ppm and -13% at 50 ppm Haematology (no indication that animals were fasted before blood collection; recovery investigated only for males): parameters investigated: red blood cells, hematocrit, mean corpuscular hemoglobin and MCH concentration, white blood cells, hemoglobin, mean corpuscular volume. - red blood cells: in males, significant increase at 1 ppm in group A, significant decrease at 50 ppm in group C - hematocrit: in males, significant increase at 1 ppm in group A - mean corpuscular hemoglobin and MCH concentration: ○ in males, significant decrease at 1 ppm in group A; ○ in females, non-significant decrease of MCHC at 50 ppm in group A (-10%)		

Method	Results	Remarks	Reference
	- white blood cells: ○ in males, non-significant decrease at 50 ppm in group B (-12%), increase at 50 ppm in group C (+12%, with significant increase of monocytes and non-significant increase of lymphocytes (+12%) and eosinophiles (+19%)), decrease post recovery at 5 ppm (-10%); ○ in females, non-significant increase at 50 ppm in group B (+11% with non-significant increase of neutrophiles (+28%), monocytes (+77%), eosinophiles (+17%)) Urinalysis: for males: - decrease of sodium excretion, significant in the 5 and 50 ppm groups, - increase of potassium excretion, significant in the 50 ppm group from week 2 to 17 - decrease in calcium excretion - for all animals in 50 ppm group and some in 5 ppm group, significant decrease in urine specific gravity and osmolarity, sometimes associated with increased volume (at all times during exposure and recovery) - evidence of toxic renal damage: dose-dependent epithelial cell casts (during exposure but not during recovery), sometimes even significant in the 1 ppm group; urine concentrating ability is decreased in the 50 ppm group even a the end of recovery; similar in the 5 ppm group during the exposure phase. Ophtalmology: 1 male of the 50 ppm and 1 male of the 5 ppm group had mild conjunctivitis with lacrimation in one eye after 6 weeks of exposure. 1 female of the 50 ppm group (on week 4 of recovery) and 1 female of the control group (on week 13) had non-reactive dilated pupil; 1 female of the 5 ppm group and 2 females in the 1 ppm group (on week 4 of recovery) had conjunctivitis with lacrimation.		
Dicyclopentadiene vapor 90-day inhalation study on mice Mice (B6C3F1) male/female 45 animals/sex/dose (9/dose killed on weeks 2, 6 and 13, and on weeks 4 and 13 of recovery period Inhalation: vapour (whole body) Exposure for 90 days, 6h/day, 5 day/week + satellite groups for a 90 days recovery Vehicle: none (air) Doses: 0, 1, 5, or 50 ppm (nominal), 0.0, 1.0, 5.1 and 51	NOAEC: 5 ppm (male/female) (27.6 mg/m^3), due to ~20% mortality in the high-dose group. Mortality: 10 males and 9 females of the 50 ppm group died, and also 2 males in the 5 ppm group. 2 dead males of the 50 ppm group had renal failure, 1 had cerebral hemorrhage. 8 had pulmonary congestion (most in the 50 ppm group). No such lesion was found in mice sacrificed after 13 weeks. 8 dead females had pulmonary congestion and 1 had severe adrenal congestion. Body weight: during the exposure, increased body weight gain in the 50 ppm group for males and females, significant for males on weeks 5-7 and for females on weeks 2 and 9-13. During recovery, for females of the 50 ppm group the body weight gain is slightly lower at all doses at the end of recovery. For males, the body weight gain is lower than control at all times in the 1 and 5 ppm groups.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity 95%; contains at least one CMR impurity)	Unpublished report (1982) Re-analysed in Kransler, K. M. (2014)

Method	Results	Remarks	Reference
ppm (analytical), corresponding to 0, 5, 27.6, 276 mg/m^3 (analytical) similar to OECD TG 413 (Subchronic Inhalation Toxicity: 90-Day) with deviations	Clinical signs: alopecia for all groups, including control. Coordination loss and/or decreased activity in a few male mice of the 50 and 5 ppm groups from week 6, and female mice of the 50 ppm group on week 13 (no information for the recovery period). Organs weight: organs weighed: kidneys, lungs, liver, testes. - liver: in females, after 2 weeks of exposure, statistically significant decrease of the absolute weight (-11%) in the 1 ppm group; after 13 weeks of exposure, in the 5 ppm group, statistically significant increase of the absolute weight -+17%) and relative weight (to body weight) (+8%) and decrease at the end of recovery (-15% as absolute weight). - lungs: in females, after 13 weeks of exposure, significant increase of absolute weight (+29%) in the 5 ppm group. - kidneys: in females, after 13 weeks of exposure, significant increase of absolute weight of the right kidney (+14%) in the 5 ppm group (+12% when considering both kidneys). - testes: significant decrease of relative weight (-7% relative to body weight) in the 50 ppm group at 4 weeks of recovery. Necropsy/histopathology (9 animals per group after completing 2, 6, 13 weeks of exposure and following 4 and 13 weeks from last exposure): ➢ complete gross pathologic evaluation on all sacrified, dead and moribund animals. ➢ histopathologic evaluation for group C (13 weeks of exposure) for the high dose and control groups: gross lesions, adrenals, bone, bone marrow, brain, epididymis, eyes, heart, kidneys, larynx, liver, lungs, mediastinal lymph nodes, muscle, nasal turbinates, parathyroid, pituitary, sciatic nerve, spleen, testes, thymus, thyroids, trachea, urinary bladder. - kidneys: the 50 ppm group in group C, 1 male/9 had enlarged kidneys with subcapsular fluid, 1 female/8 had amyloidosis, 1 male/9 had pigment droplets in tubules, 2 males/9 (and 1 female control) had tubular hyperplasia (regeneration). Despite the findings in high dose group, the intermediate doses were not investigated. - adrenals: in group C, cortical hyperplasia in 2 males/6 in the 50 ppm group, 2 females/9 control and 2 females/8 in the 50 ppm group (intermediate doses not investigated). - liver: in group C, necrosis in 1 female/9 in the 50 ppm group (intermediate doses not investigated). - testes: atrophy in 1 male/9 of the 5 ppm group in group B (6 weeks of exposure); in group C, atrophy of the seminiferous tubule in 1 male/7 in the 50 ppm group (intermediate doses not investigated).		

Method	Results	Remarks	Reference
	- ovaries: fluid filled on week 4 of recovery for 1 female/8 control, 1 female/9 in the 5 ppm group, 1 female/6 in the 50 ppm group. - uterus: dilated on week 4 of recovery for 1 female/8 control and 2 females/9 in the 5 ppm group. - lungs: on week 4 of recovery, patchy color change in 1 male/4 in the 50 ppm group. - urinary bladder: distended in 1 male/9 in the 50 ppm group in group C. - skin: in group C, hair shaft reduction/depletion for 1 male/4 and 2 females/3 in the 50 ppm group, for 5 males/6 and 4 females/4 in the 5 ppm group, for 2 males/4 and 4 females/4 in the 1 ppm group, and for 3 females/4 control; hyperkeratosis for 3 males/6 and 2 females/4 in the 5 ppm group; dermatitis for 1 male/6 in the 5 ppm group (it is not indicated if the mice displaying these findings are the same that had alopecia). Blood chemistry (no indication that animals were fasted before blood collection; recovery not investigated): parameters investigated: osmolarity, sodium, calcium, phosphorus, potassium, chloride, urea nitrogen, creatinine, total bilirubin, total protein, albumin, GPT, GOT, lactic deshydrogenase, alkaline phosphatase, glucose. - osmolarity: in males, decrease at all doses after 6 weeks of exposure (group B) (-11% to -15%), in the 1 and 5 ppm groups after 13 weeks (group C) (-13%); in females, decrease for group B in the 50 ppm group (-13%), and for group C in the 1 ppm group (-10%). - sodium: in females, statistically significant increase in group A (after 2 weeks of exposure) in the 50 ppm group; non-significant decrease in the 1 ppm group in group C (-10%). - calcium: in males and females, statistically significant increase in group A in the 5 ppm group; in group C slight increase in the 1 ppm group (for males) and 50 ppm (for males and females). - phosphorus: non-significant increase in group B in the 50 ppm group (+11% to +12% for males/females) and in the 1 ppm group (+10% for females); in the group C for females of the 50 ppm group (+13%). - urea nitrogen: o in males, non-significant increase in group A in the 5 ppm group (+12%), in group B in the 5 and 50 ppm groups (+22% to +26%), in group C in the 50 ppm group (+10%); o in females, non-significant decrease in group A in the 1 and 5 ppm groups (-13% to -22%), in group C increase in the 5 ppm group (+26%) and decrease in the 1 ppm group (-20%).		

Method	Results	Remarks	Reference
	- creatinine: in males, decrease at all doses (-10%) in group A, increase in group C in the 50 ppm group (+10%); in females, decrease in group A in the 1 ppm group (-38%) (high variability of control). - total bilirubin: in males, decrease at all doses (-13% to -29%) in group A, increase at all doses (+33% to -38%) in group B, decrease in groupC in the 1 ppm group (-15%); in females of group C, decrease in the 5 ppm group (-19%) and increase in the 1 ppm group (+12%) (high variability of control and no analysis possible for groups A and B due to low sample volume). - albumin: in females, statistically significant decrease in group C in the 5 and 50 ppm groups (no analysis possible for group A due to low sample volume). - alanine aminotransferase (GPT): o in males, decrease in group A at all doses (-34% to -58%), in group B decrease in the 50 ppm group (-17%), in group C increase at all doses (+12% to +42%) o in females, in group A, statistically significant increase in the 1 ppm group (and non-significant increase in the 5 and 50 ppm groups (+32 to +46%)), in group B, increase in the 1 and 50 ppm groups (+19% to +61%), in group C, increase in the 1 and 50 ppm groups (+23% to +168%) and decrease in the 5 ppm group (-29%), high variability of 50 ppm group. - asparate aminotransferase (GOT): o in males, in group A, decrease at all doses (-18% to -26%), in group B, increase in the 50 ppm group(+30%), in group C, decrease in the 1 ppm group (-17%) o in females, in group A, statistically significant increase in the 1 ppm group (and non-significant increase in the 5 and 50 ppm groups (+15% to +55%), in group B, increase in the 5 and 50 ppm groups (+10% to +66%), in group C, increase in the 1 and 50 ppm groups (+16% to +109%, high variability at 50 ppm) and decrease at 5 ppm (-12%). - lactic deshydrogenase: in males, in group A, decrease in the 1 and 50 ppm groups (-11% to -17%); no analysis possible in groups B and C for males and for females due to low sample volume. - alkaline phosphatase: o in males, in group B, increase in the 5 ppm group (+20%); in group C, statistically significant increase in the 5 ppm group o in females, in group B, increase in the 1 and 5 ppm groups (+14-13%), no analysis possible in groups A and C due to low sample volume. - glucose:		

Method	Results	Remarks	Reference
	○ in males, in group A, increase in the 50 ppm group (+12%), in group C, statistically significant increase in the 50 ppm groups (non-significant in the 1 and 5 ppm groups (+13-11%)) ○ in females, in group B, decrease in the 1 ppm group (-10%), no analysis possible in groups A and C due to low sample volume. Haematology: no indication that animals were fasted before blood collection; recovery not investigated): parameters investigated: red blood cells, hematocrit, mean corpuscular hemoglobin and MCH concentration, white blood cells, hemoglobin, mean corpuscular volume. - hematocrit: in females, statistically significant decrease after 13 weeks of exposure (group C) in the 5 ppm group. - mean corpuscular hemoglobin concentration: in males, after 6 weeks of exposure (group B), increase in the 1 ppm group (+11%). - white blood cells: ○ in males, after 2 weeks of exposure (group A), decrease in the 5 and 50 ppm groups (-13%) and increase in the 1 ppm group (+16%), in group B, decrease in the 1 ppm group (-27%), in group C, increase in the 50 ppm group (+32%) (neutrophiles); ○ in females, in group A, increase in the 1 and 5 ppm groups (+31-28%), in group B, increase in the 50 ppm group (+16%) and decrease in the 1 ppm group (-20%), in group C, decrease in the 5 ppm group (-16%) (neutrophiles). Ophalmology: 1 male in the 50 ppm group had mild conjunctivitis after 6 weeks of exposure.		
90-day inhalation toxicity study in rats Rats (Harlan-Wistar) male/female 12 animals/sex/dose Inhalation: vapour (whole body) Exposure for 90 days, 7h/day, 5 day/week Vehicle: none (air) Doses: 0, 19.7, 35.2 or 73.8 ppm corresponding to 0, 107, 190 and 399 mg/m^3 (analytical)	NOAEC < 19.7 ppm (male/female) (107 mg/m^3) due to the observation that one female exposed to 19.7 ppm had a 5 minutes convulsion after 45 days exposure. Mortality: none Body weight: for males and females exposed to 73.8 ppm, the body weight was significantly lower after 4 days, but there was no significant difference from day 13 to the end. For males, the body weight was higher (up to +15%) at all doses at day 89 (non statistically significant). Clinical signs: in the 73.8 ppm group, 1 female had convulsions for about 5 minutes immediately after the exposure on day 19. In the 19.7 ppm group, 1 female had convulsions for 5 minutes upon removal from the chamber on day 45. In the intermediate group (35.2 ppm), no convulsion was observed.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 96.7%)	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
	Organs weight: organs weighed: liver, kidneys. For both liver and kidneys, the absolute weight and the weight relative to body weight was significantly increased at all doses for males, in a non dose-dependent manner Necropsy/histopathology: organs examined: adrenals, colon, heart, kidneys, liver, lungs, mesentery, prostate, testis, trachea, spleen, urinary bladder - kidneys: in the 73.8 ppm group and to a lesser degree in the 35.2 ppm group: kidney effects such as round cell accumulation, dilated tubules, casts, tubular degeneration, that were more frequent and more severe in males than in females. In the 73.8 ppm group, 5 females/12 had calcium spicules (2/12 in control group). - lungs: 3 males of the 73.8 ppm group had chronic pneumonia and bronchiectasis. - urinary bladder: protein concretions were observed in males at all doses and in the control group, but none in females.		
90-day inhalation study in dogs Dogs (Beagles) males 3 animals/dose Inhalation Exposure for 90 days, 7h/day, 5 day/week Vehicle: none (air) Doses: 0, 8.9, 23.5, 32.4 ppm corresponding to 48, 127, 175 mg/m^3 (analytical)	NOAEC: between 8.9 and 23.5 ppm (48 and 127 mg/m^3) according to the author Mortality: none Body weight: increase in the body weight gain in the 23.5 and 32.4 ppm groups (+ 21% and +67% respectively) Clinical signs: none Organs weight: (organs weighed: liver, kidneys) - liver: increase of the absolute weight in a dose-dependent manner (up tp +24%) and of the liver weight relative to body weight (+18%, +7% and +27% in the 8.9, 23.5 and 32.4 ppm groups respectively) - kidneys: increase of the absolute weight in a dose-dependent manner (up to +25%) and of the kidney weight relative to body weight (+24%, +18% and +29% in the 8.9, 23.5 and 32.4 ppm groups respectively) Necropsy: no dose-related pathologic changes in lungs, liver, kidney, heart, spleen, adrenal, thyroid, parathyroid, esophagus, diaphragm, lymph node, gall bladder, maxillary gland, tongue, stomach, duodenum, pancreas, ileum, jejunum, colon, urinary bladder, prostate, testis, epididymis, brain, pituitary, skin, eye. Splenic infarcts were observed but not considered relevant (common in dogs, and no dose-dependence) Blood chemistry: - blood urea nitrogen: slight increase in the 32.5 ppm group after 20 days - serum acid phosphatase: slight increase in the 32.5 ppm group and increase in the 23.5 ppm group after 20 days - serum alkaline phosphatase: increased after 85 days in the 32.5 ppm group serum GOT: increase in the 23.5 ppm group after 20 days	3 (not reliable) supporting study experimental result Test material: DCPD (purity 96.7%) Due to the low number of animals per group, the significance of any statistical analysis is questionable.	Kinkead *et al.* (1971)

Method	Results	Remarks	Reference
	- serum GPT: no effect Haematology: - total and differencial white blood cells: in the 23.5ppm group, minimal decrease in neutrophils after 85 exposures - hematocrit: no effect Electrocardiograms were performed at the end of the study and were normal.		
Human data			
Human sensory response test and odour threshold test Inhalation In studies in human volunteers to ascertain the odour threshold of dicyclopentadiene vapour for man and to determine the human sensory response, some inadvertent exposure to dicyclopentadiene vapour occurred during the 5 month investigation period.	Three workers experienced transitory headaches during the first 2 months, but not during the last 3 months.	3 (not reliable) supporting study experimental result Test material: DCPD (purity 96.7%)	Kinkead *et al.* (1971)

Despite some flaws, the 90-day study in rats and mice (Unpublished report, 1982) is of relatively good quality and provides some information on the potential toxicity of the Substance. The data were re-analysed for rats in 1992 (Bevan *et al.*, 1992) and mice in 2014 (Kransler, 2014). For rats, the authors conclude that DCPD produces adverse effects to kidneys which are relevant to males only, considering that no "overt signs, body weight changes, hematologic or clinical chemistry values were related to DCPD exposure" and that the significantly increased relative liver weight should not be considered adverse in the absence of histopathologic change. Regarding effects on kidneys, more specifically, as described in Bevan *et al.* (1992):

- adverse effects were observed in male rats at all dose levels
- kidney structure was altered (increase of the incidence of hyaline droplets with angular or crystalline shapes, regenerative epithelium, accumulation of tubular proteinaceous material)
- epithelial cells were observed in urine
- excretion rate of sodium was decreased and excretion rate of potassium was increased
- ability of kidneys to concentrate urine was affected.

The authors conclude that exposure to DCPD leads to hyaline droplets nephropathy in male rats, due to accumulation of hyaline droplets containing α_{2u}-globulin in proximal tubular cells. α_{2u}-globulin is excreted by male rats in higher amounts than by females rats and is believed to bind to a number of chemicals (Swenberg *et al.* , 1989, Lehman-McKeeman *et al.* , 1989) which prevents its degradation in lysosomes in proximal tubular cells (Lehman-McKeeman *et al.* , 1990). Hamamura *et al.* (2006) further demonstrated that the hyaline droplets induced by treatment with DCPD was directly associated with α_{2u}-globulin accumulation.

Effects on liver weight were observed in rats, mice and dogs without relevant findings in the histopathological examinations.

The opportunity for a classification for repeated toxicity shall be evaluated after all the information requested under CCH are available.

7.9.4.1.3. *Dermal route*

The Registrant(s)s provided a data waiving stating that "*In accordance with column 2 of REACH Annex IX, testing shall be performed using the most appropriate route of administration. Testing by the inhalation route is appropriate if exposure of humans is likely to occur via inhalation; this is the main route of exposure to 3a,4,7,7a-tetrahydro-4,7-methanoindene. In accordance with column 2 of REACH Annex IX, testing shall be performed using the most appropriate route of administration. Testing by the inhalation route is appropriate if exposure of humans is likely to occur via inhalation; this is the main route of exposure to 3a,4,7,7a-tetrahydro-4,7-methanoindene*."

The eMSCA does not fully support the Registrant(s)'s assumption. Indeed, based on the uses described in the dossier, dermal route is also a relevant route of exposure for human. Moreover, the molecular weight is below 500 g/mol. No test is available to determine dermal absorption, but considering the phys/chem properties, some extent of dermal absorption is expected. However, the acute toxicity studies suggest a very low toxicity via dermal route and the substance is already classified as Skin Irrit 2 H315. Therefore the eMSCA does not consider proportionate to request an additional study by dermal route.

7.9.5. Mutagenicity

Five *in vitro* and one *in vivo* studies are available in the dossier to investigate the genetic toxicity of DCPD.

Table 36: Data on genetic toxicity

Method	Results	Remarks	Reference
***In vitro* data**			
L5178Y TK +/- Mouse Lymphoma Assay Mammalian cell gene mutation assay (OECD TG 476) Mouse lymphoma L5178Y cells (with and without metabolic activation) S9-mix from rat livers induced with phenobarbital/β-naphthoflavone Concentrations: - Initial toxicity test: 0, 5.16, 10.31, 20.63, 41.25, 82.5, 165, 330, 660, 1320 µg/mL - Experiment 1: 10, 15, 20, 25, 30, 35 µg/mL (4h -S9) - Experiment 1: 10, 20, 30, 40, 50, 60 µg/mL (4h +S9) - Experiment 2: 5, 10, 20, 30, 40, 50 µg/mL (24h -S9) - Experiment 2: 10, 20, 30, 40, 45, 50 µg/mL (4h +S9) Positive control substances: thylmethanesulphonate; cyclophosphamide Vehicle: DMSO	Negative with and without metabolic activation.	1 (reliable without restriction) key study experimental result Test material: DCPD (purity 95%)	Unpublished report (2014)
Reverse mutation assay OECD TG 471 (Bacterial Reverse Mutation Assay) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (with and without metabolic activation) *E. coli* WP2 uvr A (with and without metabolic activation) S9-mix from rat livers induced with Aroclor 1254 Concentrations: - Dose-range finding test: 3, 10, 33, 100, 333, 1000, 3330 and 5000 µg/plate (+/- 5% S9) - Experiment 1: TA1535, TA1537 and TA98 ○ -S9: 1, 3, 10, 33 and 100 µg/plate ○ +5% S9: 3, 10, 33, 100 and 167 µg/plate - Experiment 2: TA1535, TA1537, TA98 and TA100: ○ -S9: 1, 3, 10, 33 and 100 µg/plate ○ +10% S9: 3, 10, 33, 100 and 167 µg/plate WP_2uvrA: ○ -S9: 3, 10, 33, 66 and 100 µg/plate ○ +10% S9: 10, 33, 100, 333 and 666 µg/plate Positive control substances: sodium azide (TA1535 –S9), 9-aminoacridine (TA1537 –S9), daunomycine (TA98 –S9), methylmethanesulfonate (TA100 –S9), 4-nitroquinoline N-oxide (WP_2uvrA –S9), 2 aminoanthracene (all +S9) Vehicles: ethanol (test substance and negative control, no justification provided), DMSO or saline (positive controls)	Negative with and without metabolic activation.	1 (reliable without restriction) key study experimental result Test material: DCPD (**purity 75%**)	Unpublished report (2000)

Method	Results	Remarks	Reference
***In Vitro* Chromosomal Aberration Test of DCPD on Cultured Chinese Hamster Cells** *In vitro* mammalian chromosome aberration test (JAPAN Guidelines for Screening Mutagenicity Testing Of Chemicals) *combined with in vitro micronucleus test (assumed)* Chinese hamster lung (CHL/IU) cells (with and without metabolic activation) S9-mix from rat livers induced with Phenobarbital and 5,6-benzoflavone Concentrations: a range of doses up to approximately 0.1 mg/ml (approximately 10 mM) was used - Continuous treatment: First experiment: 24 and 48 hour continuous treatment (-S9): 0.0, 0.014, 0.029, 0.057 mg/mL Second experiment: 24 hour continuous treatment (-S9): 0.0, 0.029, 0.043, 0.057 mg/mL *(assumed by eMSCA as being a micronucleus test)* - Short-term treatment (6 hours exposure): (-S9): 0.0, 0.014, 0.029, 0.057 mg/mL (+S9): 0.0, 0.03, 0.05, 0.10 mg/mL Positive control substances: (-S9): 0.00005 mg/mL Mitomycin C, (+S9): 0.005 mg/mL cyclophosphamide Vehicle: acetone	24h –S9 (DCPD purity=95%): slightly positive at the highest dose (gaps, chromatid breaks and chromatid exchanges) 24h –S9 (micronucleus test with DCPD purity > 95%): negative 48h –S9: negative 6h –S9: negative *(but positive control not appropriate, see below)* 6h +S9: negative	4 (not assignable) supporting study experimental result Test material: DCPD (purity 95% for chromosome aberration test and > 95% for micronucleus test)	JETOC (1998), Hatano Research Institute (1993) *Report in Japanese*
Microbial mutagenesis Reverse mutation assay (equivalent or similar to OECD TG 480 - [guideline deleted 2 April 2014]) *Saccharomyces cerevisiae* (with and without metabolic activation) S9-mix from rat livers induced with Aroclor 1254 Concentrations: - -S9: 0.001, 0.01, 0.1, 1.0 or 5.0 µL/plate - +S9: 0.001, 0.01, 0.1, 1.0, 5.0 or 10 µL/plate Positive control substances: methylnitrosoguanidine (base-pair substitution -S9), 2-nitrofluorene (frameshift –S9), quinacrine mustard (frameshift –S9), 2-anthramine (base-pair substitution +S9), 2-acetylaminofluorene (frameshift +S9) and 8-aminoquinoline (frameshift +S9)	Negative with and without metabolic activation.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity not specified)	Unpublished report (1980b)
Microbial mutagenesis Reverse mutation assay (equivalent or similar to OECD TG 471) S. typhimurium, TA98, TA100, TA1535, TA1537, TA1538 (with and without metabolic activation) S9-mix from rat livers induced with Aroclor 1254 Concentrations: - -S9: 0.001, 0.01, 0.1, 1.0 or 5.0 µL/plate - +S9: 0.001, 0.01, 0.1, 1.0, 5.0 or 10 µL/plate Positive control substances: methylnitrosoguanidine (base-pair substitution -S9), 2-nitrofluorene (frameshift –S9), quinacrine mustard (frameshift –S9), 2-anthramine (base-pair substitution +S9), 2-acetylaminofluorene (frameshift +S9) and 8-aminoquinoline (frameshift +S9) Vehicle: DMSO or saline	Negative with and without metabolic activation.	2 (reliable with restrictions) supporting study experimental result Test material: DCPD (purity not specified)	Unpublished report (1980c)

Method	Results	Remarks	Reference
In vivo data			
Mouse Bone Marrow Micronucleus Test OECD TG 474 (Mammalian Erythrocyte Micronucleus Test) Mouse (Crl:CD-1®(ICR)BR) male/female 5 animals/dose/sex Oral: gavage Two doses of dicyclopentadiene / co-dimer concentrate, 24h apart Doses: 0, 437.5, 875, or 1750 mg/kg bw (nominal in corn oil) Positive control substances (5 animals/sex) cyclophosphamide, 30 mg/kg once by oral intubation. Vehicle: corn oil	Negative. Decreased PCE/NCE ratio in females in the highest dose. Signs of systemic toxicity were observed at the highest dose (decreased body weight, ataxia, lethargy, and hyperactivity in both sexes; in males, spasms; in females, exhibited ruffled fur, prostration, and hyperreactivity).	1 (reliable without restriction) supporting study experimental result **Test material:** **Naphtha (petroleum), light steam-cracked, debenzenized, C8-16-cycloalkadiene conc. (CAS: 68478-10-4) containing ~30% DCPD**	Unpublished report (2004)

Notes:

- For all studies, no information is available on the impurities (identification and content) in the tested DCPD (which purity varies between 75 and 95% or is unknown for the in vitro tests). Based on the information available on registered DCPD, the presence of impurities which have mutagenic properties cannot be excluded.
- For all studies, no information is available to determine if volatilisation of the Substance could be avoided.
- For the reverse mutation assays performed on Saccharomyces cerevisiae (with and without metabolic activation) (Unpublished report, 1980b) and S. typhimurium, TA98, TA100, TA1535, TA1537, TA1538 (with and without metabolic activation) (Unpublished report, 1980c), some deviations from the guidelines were noted (OECD TG 471 and 480 [deleted 2 April 2014])
    - 2 independent experiments were performed, but each one with a single replicate (no duplicates nor triplicates).
    - The cytotoxicity results are not reported.
    - The positive control substances are not the ones recommended in the guideline (except 2-nitrofluorene)

  In addition, it should be noted that the two reverse mutation assays performed I unpublished reports (1980b and 1980c) are second attempts to study the genotoxicity of DCPD. Indeed, in a first study performed in 1976, the authors concluded that the ambiguous results should be attributed to impurities present in the tested substance, and decided to conduct a new experiment with a purified sample. The results of the first assay are not given, as indicated in the Foreword, page 4: "*[…] this report does not include the results of mutagenesis […] tests. Several considerations, most important being impurities in the samples of […] dicyclopentadiene provided to* [redacted]*. for mutagenesis testing, make interpretation of the results ambiguous. Mutagenesis tests have been repeated using highly purified samples of both compounds and will be reported under Contract DAMD17-77-C-7003*" (Contract DAMD17-77-C-7003 corresponds to the reference [redacted] 1980). The identity of the tested samples in the first and second experiment (and especially the identity and content of the impurities) are not given.
- In the *in vitro* mammalian chromosome aberration test (Unpublished report, 1993), no details are available regarding the protocol considering that the study report is

available in Japanese. However tables and graphs are available in English. There is no indication that the authors intended to follow the OECD TG 473, however if it were the case the following deviations would be noted (based on the legible parts of the report):

- 200 cells were analysed instead of 300 per dose and conditions
- In the short-term experiment without metabolic activation, the positive control used was cyclophosphamide and was negative. However, without metabolic activation, Mitomycin C should have been used instead. Therefore it is not possible to conclude on the test performance for this testing conditions.

  The eMSCA assumes that the *in vitro* mammalian chromosome aberration test, performed with DCPD with a purity of 95%, which gave slightly positive results for one test condition, was followed by an *in vitro* micronucleus test performed with a purified DCPD sample (purity >95%) which was negative and enable the authors to conclude that the study was negative. However, as a translation of this study report was not available at the time of completion of this report (despite being requested-expected March 2017), the eMSCA draw the hypothesis that DCPD is likely to contain mutagenic impurities but cannot at this stage conclude on the mutagenic potential of pure DCPD.

- The *in vivo* micronucleus test is of good quality and its result is negative. The test was performed using a UVCB (Naphtha (petroleum), light steam-cracked, debenzenized, C8-16-cycloalkadiene conc., CAS RN: 68478-10-4, EC No: 270-790-1) containing ~30% DCPD and ~70% other consituents (including CPD/MCPD codimers). It is self-classified (as reported in ECHA website) as CMR (Muta 1B H340, Carc 1A H350, Carc 1B H350, Repr. 2 H361). Therefore, its relevance in demonstrating the non-genotoxicity of DCPD is questionable and it is not possible, based on this study, to draw a conclusion regarding the genotoxicity of DCPD.

The eMSCA highlights that several of the registered compositions of DCPD may contain mutagenic impurities. The classification of these registered substances shall be revised.

7.9.6. Carcinogenicity

No data available.

Based on the negative genotoxicity studies, the substance is not likely to be a genotoxic carcinogen but no data is available to conclude.

The eMSCA highlights that several of the registered compositions of DCPD may contain carcinogenic impurities. The classification of these registered substances shall be revised.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

7.9.7.1. Observations on reproductive performances

Table 37: Effects on reproductive performances

	Registrant conclusions	eMSCA conclusions
Combined repeated dose and reproduction/ developmental screening test by oral administration in rats (OECD 422) Unpublished report (1993) / JETOC (1998) **RI=2** Rats 10/sex/ dose Gavage in olive oil Doses: 0, 4, 20, 100 mg/kg/day Males: 44d, 1/day Females: from 14d before mating through gestation (14 days) and parturition until PND4, 1/day purity: 94,65% (no information on impurities)	No effect on reproductive parameters.	<u>Reproductive system</u>: - no information regarding onset of puberty - **atrophy of seminiferous tubules of testes** (1/10 control, 2/10 at 20 mg/kg/d, 1/10 at 100 mg/kg/d), no effect on weight. In the 20 mg/kg/d group, it is not known whether the males with atrophied testes were in the pairs that failed to reproduce. - mammary adenoma seen at 20 mg/kg/d in 1 female - no effect on epididymis and ovaries in controls and 100 mg/kg groups, no effect on epididymis weight - thyroid, uterus, interstitial testicular cell structure, other endocrine organs not examined - thyroid hormone not measured <u>Reproductive performance</u>: - reduced fertility index at 20 mg/kg/d - slightly reduced mating index at 20 mg/kg/d - reduced gestation index at 4 mg/kg/d - no effect on gestation length, number of corpora lutea, delivery index, parturition - **non-significant reduction of number of offspring at all doses** (-16% at 4 mg/kg/d, -21% at 20 mg/kg/d, -10% at 100 mg/kg/d); **reduced number of implantation sites** (-24%, -19%, -11% at 4, 20 and 100 mg/kg/d respectively) **and implantation index** (-19%, -22%, -11% at 4, 20 and 100 mg/kg/d respectively). (Effects on the offspring reported below)
Continuous breeding (NTP) *Jamieson et al.* (1995) **RI=4 (no report)** Rats 20/sex/dose Gavage in corn oil Doses: 0 (assumed), 10, 30,	/	<u>Effects on reproductive system</u>: - no information <u>Effects on reproductive performance</u>: - increased gestation length at 100 mg/kg (Effects on the offspring reported below)

<table>
<tr><td>100 mg/kg
Treatment of cohabitated rats for 17 weeks, newborn sacrificed PND1, after 17 weeks litters reared 3 weeks, some offspring treated for 7-10 weeks then during mating and gestation until delivery)
Purity: not specified (no information on impurities)</td><td></td><td></td></tr>
<tr><td>3 generations
Unpublished report (1980)
RI=3
Rats
10 males/dose and 20 females/dose
Dietary (weekly mixing & analysis)
Doses: calculated 0, 5.8, 58 mg/kg/d (male) and 0, 8.7, 87 mg/kg/d (female)
Purity: 98-99%; no information on impurities</td><td>/</td><td>Reproductive system: no conclusion possible (no sufficient information)
Reproductive performance:
- only parameters investigated: fertility and gestation index
- slight non-significant reduction in fertility index
<table>
<tr><th>Parents</th><th colspan="2">F0</th><th colspan="2">F1</th><th colspan="2">F2</th></tr>
<tr><th>Mating</th><th>1st</th><th>2nd</th><th>1st</th><th>2nd</th><th>1st</th><th>2nd</th></tr>
<tr><td>Fertility ♂</td><td>↘ 750ppm (-10%)</td><td>-</td><td>↘ 750ppm (-10%)</td><td rowspan="2">↘ 750ppm (-10%, uncertain if ♂ or ♀; same pair with no litter tested twice)</td><td colspan="2" rowspan="2">low in all groups incl. controls</td></tr>
<tr><td>Fertility ♀</td><td>↘ dose-dep (-5%, -16%, resp.)</td><td>↗ 750ppm (+6%)</td><td>↘ dose-dep (-5%, -26%, resp.)</td></tr>
</table></td></tr>
</table>

7.9.7.2. Observations in subacute and repeated toxicity studies

The following observations were made (refer also to Table 26, Table 34, Table 35):

Table 38: Effects observed in subacute and repeated toxicity studies on reproductive and endocrine organs

Except when specified, results are not statistically significant. Non-indicated organs were not weighed/examined.

	Thyroid	Testes	Ovaries	Other organs
90-day study on dogs Unpublished report (1980a) RI=2 Dietary administration Doses: 0, 100, 300 and 1000 ppm (nominal in diet) corresponding to 0, 2.5, 7.5, 25 mg/kg/day 4 animals/sex/dose	Weight: non significant increase for females and decrease for males at all doses, in a non-dose dependent manner (for females: up to + 41%, +21% and +34% as absolute weight, as percentage of body weight and as percentage of brain weight respectively, and for males up to -29%, -23% and -34% respectively). Lesions (intermediate doses were not investigated): - Minimal cystic remnant of ultimobranchial duct of thyroid in 1/4 female at 1000ppm. - Minimal cystic remnant of ultimobranchial duct of parathyroid in another 1/4 female at 1000ppm. - No lesion seen at necropsy for males.	Weight:non significant decrease at all doses (% brain weight: -9%, -13% and -9% at 100, 300 and 1000 ppm respectively; absolute testes weight and testes weight relative to body weight (less clear): respectively +3%, -6%, -8% and 3-%, +5% et -4% at 100, 300 and 1000 ppm) Lesions: no effect seen at necropsy.	Weight: non significant increase at all doses non-dose dependent, as absolute weight (up to +222%), percentage of body weight (up to +183%) and percentage of brain weight (up to +220%). Lesions: no effect seen at necropsy.	Weight: - **Adrenals**: non-significant decrease at all doses for males and females (non-dose dependent) (up to -6% for males and -13% for females as absolute weight, -12% for males and -25% for females as percentage of body weight, -17% for males and females as percentage of brain weight). - Brain: (non-significant) reduction of relative brain weight was noted in females at all doses Lesions: - Cysts in **pituitary gland** in 2/4 males at 1000ppm, in 3/4 females control and in 1/4 female at 1000ppm. - No effect seen at necropsy uterus, epididymis, prostate and adrenals.
90-day study on rats Unpublished report (1976f) RI=3 Dietary administration Doses: 0, 80, 250, 750 ppm corresponding to ~ 6, 20, 62 mg/kg/day	Weight: **increase for males at all doses** in a non-dose dependent manner, up to +33% as absolute weight and +23% as percentage of body weight. (statistical significance not known) Lesions: no effect seen at necropsy.	Weight: no effect. Lesions: no effect seen at necropsy.	Weight: **increase at 250 and 750ppm** as absolute weight (+2.5% and 9.2%) and percentage of brain weight (+4.9% and 11.5%). (statistical significance not known)Lesions: no effect seen at necropsy.	Weight: **Adrenals**: **increase for males at all doses** in a non-dose dependent manner (up to +18% as absolute weight, +9% as percentage of body weight and 18% as percentage of brain weight) (statistical significance not known) Lesions: no effect seen at necropsy in epididymis, uterus, prostate, seminal vesicles, pituitary gland.

	Thyroid	Testes	Ovaries	Other organs
90-day study on mice Unpublished report (1976g) RI=3 Dietary administration Doses: 0, 28, 91, 273 ppm corresponding to ~ 6, 19, 56 mg/kg/day	Weight: **decrease for males at 28ppm** (-17% as absolute weight, -20% as percentage of body weight) **and for females at all doses** (non dose-dependent, up to -36% as absolute weight, -35% as percentage of body weight), **increase for males at 273ppm** (+19% as absolute weight, +16% as percentage of body weight). (statistical significance not known) Lesions: no effect seen at necropsy.	Weight: **decrease at all doses** in a dose-dependent manner when expressed as absolute weight (up to -18% at 273 ppm, roughly 56 mg/kg/d), and in a non-dose dependent manner when expressed as percentage of body weight (up to -21% at 91 ppm, roughly 19 mg/kg/d). (statistical significance not known) Lesions: no effect seen at necropsy.	Weight: **decrease at all doses**, in a non-dose dependent manner (up to -29% as absolute weight and percentage of body weight). (statistical significance not known) Lesions: no effect seen at necropsy.	Weight: no effect on adrenals. Lesions: - **Uterus**: mild acute purulent cervicitis in 1/32 female, mild metritis in another female at 273ppm. - **Prostate**: mild focal hyperplasia in 1/32 male at 273ppm. - No effect seen at necropsy in epididymis, pituitary gland.
14-day study on dogs Unpublished report (1976h) RI=3 Dietary administration Doses: 0, 40, 125, 375 ppm corresponding to ~ 8, 25, 59 mg/kg/day 1 animal/sex/dose	Weight: **decrease for males at all doses, dose-dependent** (as % body weight and as absolute at highest doses); **increase for females at highest doses** (as absolute and relative weight). Lesions: no effect seen at necropsy.	Weight: **decrease at 40ppm** (-17% abs. wt of right testis), **increase at 375ppm** (+60% abs. wt of right testis) (as absolute and relative weight). Lesions: not examined.	Weight: **slight decrease.** Lesions: not examined.	Weight: **adrenals: increase for males at 125ppm, decrease for females at 125ppm** (as absolute and relative weight). Lesions: no effect seen at necropsy in adrenals.

	Thyroid	Testes	Ovaries	Other organs
90-day inhalation study on rats with additional 90 day of recovery Unpublished report (1982), Bevan *et al.* (1992) RI=2 Exposure by inhalation Doses: 0, 1, 5, or 50 ppm (nominal conc.), 0.0, 1.0, 5.1 and 51 ppm (analytical conc.), 0, 5, 27.6, 276 mg/m^3 (analytical conc.)	Weight: not examined. Lesions: no effect seen at necropsy on thyroid and parathyroid.	Weight: - slight increase at 51ppm at 4 weeks of recovery (as absolute weight); - decrease (with high variability) at 5ppm. Lesions: - small testes in 1 male at 5ppm; - patchy color change in another male at 5ppm (sacrificed during recovery period).	Weight: not examined. Lesions: - cystic ovaries in control and treated groups during exposure and at end of recovery; - ovary filled with fluid in 1/9 female at 5 and 51ppm at 13 weeks, in 1/9 female at 5, 51ppm and control at 4 weeks of recovery.	Weight: not examined. Lesions: - **Adrenals**: fatty infiltration in males at 13 weeks (twice as much in 51ppm group than control group, but intermediate doses not investigated) - No effect seen at necropsy on pituitary gland, epididymis, oviduct, uterus, cervix (for control and 51ppm groups).
90-day inhalation study on mice with additional 90 day of recovery Unpublished report (1982), Kransler, K. M. (2014) RI=2 Exposure by inhalation Doses: 0, 1, 5, or 50 ppm (nominal conc.), 0.0, 1.0, 5.1 and 51 ppm (analytical conc.), 0, 5, 27.6, 276 mg/m^3 (analytical conc.)	Weight: not examined. Lesions: no effect seen at necropsy.	Weight: **statistically significant decrease at 51ppm** (as relative weight) at 4 weeks of recovery. Lesions: - atrophy in 1/9 male at 5ppm at 6 weeks; - atrophy of the seminiferous tubule in 1/7 male at 51ppm at 13 weeks, but intermediate doses not investigated.	Weight: not examined. Lesions: fluid filled at 4 weeks of recovery (1/8 control, 1/9 at 5ppm, 1/6 at 51ppm).	Weight: not examined. Lesions: - **Uterus**: dilated at 4 weeks of recovery (1/8 control, 2/9 at 5ppm). - **Adrenals**: cortical hyperplasia at 13 weeks in 2/6 males at 51ppm, 2/9 females control and 2/8 females at 51ppm, but intermediate doses were not investigated. - No effect seen at necropsy in epididymis, oviduct, cervix, pituitary gland (for control and 51ppm groups).
90-day study on rats Kinkead *et al.* (1971) RI=3 Exposure by inhalation Doses: 0, 19.7, 35.2 or 73.8 ppm (analytical conc.), 0, 107, 190 and 399 mg/m^3 (analytical conc.)	Weight: not examined. Lesions: not examined.	Weight: not examined. Lesions: no effect seen at necropsy.	Weight: not examined. Lesions: not examined.	Weight: not examined. Lesions: no effect seen at necropsy in prostate.

	Thyroid	Testes	Ovaries	Other organs
9-day inhalation study on rats Unpublished report (1981) RI=3 Exposure by inhalation Doses: 0, 5, 33, 100 ppm (target), 0, 5.1, 33, 99.9 ppm (analytical), ~ 0, 28, 179, 541 mg/m^3 (analytical)	Weight: not examined. Lesions: not examined.	Weight: no significant effect. Lesions: not examined.	Weight: not examined. Lesions: not examined.	Weight: not examined. Lesions: not examined.
9-day inhalation study on mice Unpublished report (1981) RI=3 Exposure by inhalation Doses: 0, 5, 33, 100 ppm (target), 0, 5.1, 33, 99.9 ppm (analytical), ~ 0, 28, 179, 541 mg/m^3 (analytical)	Weight: not examined. Lesions: not examined.	Weight: no significant effect. Lesions: not examined.	Weight: not examined. Lesions: not examined.	Weight: not examined. Lesions: not examined.
90-day study on dogs Kinkead *et al.* (1971) RI=3 Exposure by inhalation Doses: 0, 8.9, 23.5, 32.4 ppm, ~ 48, 127, 175 mg/m3 (measured) 3 male animals/dose	Weight: not examined. Lesions: no effect seen at necropsy on thyroid, parathyroid	Weight: not examined. Lesions: no effect seen at necropsy.	Weight: not examined. Lesions: not examined.	Weight: not examined. Lesions: no effect seen at necropsy on prostate, epididymis, pituitary gland.

	Thyroid	Testes	Ovaries	Other organs
28-day study on rats Satoh *et al.* (1990) RI=4 Oral exposure (gavage) Doses: 0, 8, 40, 80 mg/kg/day 6 animals/sex/dose *Only abstract available.*	No information	No information	No information	Adrenals: increase of weight in the 200 mg/kg/day groups in both sexes hypertrophy of the adrenal cortex observed in the 200 mg/kg/day groups of both sexes.

7.9.7.3. Toxicity to offsprings

Table 38: Toxicity to offsprings

	Registrant conclusions	eMSCA conclusions
Combined repeated dose and reproduction/ developmental screening test by oral administration in rats (OECD 422) Unpublished report (1993) / JETOC (1998) **RI=4 (no report)** Rats 10/sex/ dose Gavage in olive oil Doses: 0, 4, 20, 100 mg/kg/day Males: 44d, 1/day Females: from 14d before mating through gestation (14 days) and parturition until PND4, 1/day purity: 94,65% (no	NOAEL 20 mg/kg/d for parental female/offsprings and 100 mg/kg/d for parental males, based on litter loss, lower viability index, lower birth weight, reduced body weight gain at 100 mg/kg/d. At 100 mg/kg/d mortality in females, reduced food consumption, reduced body weight gain.	<u>Effects on offsprings</u>: - **significant reduction of litter viability at 100 mg/kg/d** (66,1%) at PND4 (males 35%, females 42%) – 2 dams lost all their litter - **non-significant reduction of body weight and body weight gain** (-20%) at 100 mg/kg/d - external features, clinical signs, necropsy: no effect - no investigation of the behaviour and sensory activity of the offspring, no measure of anogenital distance, no count of nipples for males, sacrifice at PND4 and not PND13, no evaluation of cause of death for dead pups - maternal effects at 100 mg/kg/d: ○ 2 dams died before start of gestation at 100 mg/kg/d ○ 2 dams at 100 mg/kg/d did not nurse their litters and lost them completely within 2 days of lactation ○ reduced body weight gain at 100 mg/kg/d ○ slight reduction of food consumption during gestation and significant reduction during lactation at 100 mg/kg/d, however may not be relevant since reduced food consumption during lactation was also seen at 20 mg/kg/d without any consequence on survival and body weight of offspring ○ no adverse findings on all dams at necropsy and histopathology at 100 mg/kg/d and 20 mg/kg/d, except 1/10 mammary adenoma at 20 mg/kg/d (but no information whether this

<table>
<tr><td>information on impurities)</td><td></td><td>female was pregnant ; 5/10 were pregnant in this group)</td></tr>
<tr><td>Continuous breeding (NTP)
Jamieson et al. (1995)
RI=4 (no report)
Rats
20/sex/dose
Gavage in corn oil
Doses: 0 (assumed), 10, 30, 100 mg/kg
Treatment of cohabitated rats for 17 weeks, newborn sacrificed PND1, after 17 weeks litters reared 3 weeks, some offspring treated for 7-10 weeks then during mating and gestation until delivery)
Purity: not specified (no information on impurities)</td><td>reduced pup body weights, increased pup mortality and decreased pup survival in F1 litter at 100 mg/kg; effect in F2 not greater than in F1; systemic effects on males only; uncertain if pups weight reduction in F1 (9%) and F2 (12%) are secondary to maternal toxicity</td><td><u>Effects on offspring</u>:
- F1: reduced gestation index, higher pup mortality and decreased survival at 100 mg/kg, reduced pup weight at 30 and 100 mg/kg
- F2: reduced pups weight associated with parental male toxicity (increased F1 liver and kidney weights), difficult to interpret since during the cross-over mating, the reduced pups weight was seen for pups of treated females and not treated males
- No information on potential maternal toxicity

<u>Maternal effects</u>:
- increase in the incidence of clear cell foci at 30 and 100 mg/kg</td></tr>
<tr><td>3 generations
Unpublished report (1980)
RI=3
Rats
10 males/dose and 20 females/dose
Dietary (weekly mixing & analysis)
Doses: calculated 0, 5.8, 58 mg/kg/d (male) and 0, 8.7, 87 mg/kg/d (female)
Purity: 98-99%; no information on impurities</td><td>treatment-related pup weight reduction at PND21 in F3 pups of 2nd mating</td><td><u>Effects on offspring</u>:
- no effect on pup survival and number of offspring
- <u>significant</u> reduction of <u>offspring</u> body weight gain of F3 on 2nd mating
<table>
<tr><td>Parents</td><td colspan="2">F1</td><td colspan="2">F2</td><td colspan="2">F3</td></tr>
<tr><td>Mating</td><td>1st</td><td>2nd</td><td>1st</td><td>2nd</td><td>1st</td><td>2nd</td></tr>
<tr><td>Birth weight</td><td>♂ -
♀ ↘ 80 and 750ppm</td><td>↘ 80ppm</td><td>-</td><td>-</td><td>♂ ↗ 750ppm
♀ ↘ 80 and 750ppm</td><td>♂ ↗ 80 and 750ppm
♀ -</td></tr>
<tr><td>Body weight gain</td><td>♂ ↘ dose-dep
♀ ↘ 80 and 750ppm</td><td>↗ 80ppm (↗ variability), ↘ 750ppm</td><td>-</td><td>↗ dose-dep</td><td>♂ ↗ 750ppm
♀ ↘ 80ppm, ↗ 750ppm</td><td>♂ ↘ 80 and 750ppm
♀ ↘ 80 and 750ppm (statistically significant)</td></tr>
</table>
- <u>external features and necropsy</u>: no effect (except dark red lungs of F1 pups of 1st mating)</td></tr>
</table>

		- histopathology no examined
Pre-natal development Unpublished report (1980) **RI=2** Rats 20/dose Dietary (no analytical verification) Doses: calculated 0, 6.4, 20, 60 mg/kg/day d6-d15 of gestation, 1/d; sacrifice at d19 Purity 98-99% (no information on impurities)	no effect (some delayed ossifications among all dose groups including control)	<u>Maternal toxicity</u>: - tendency to lower food consumption of treated rats from d6 and d19 - tendency to lower body weight gain for treated rats at d15 and d19 <u>Effects on offspring</u>: - slight reduction of number of implantation sites? (non-statistically significant) - reduced number of live offsprings for treated rats (non-statistically significant) - reduced sex ratio (more females) at 80 and 750ppm (-17%, -18%) and higher (more males) at 250ppm (+15%) (potential selection bias) - some skeletal changes (potential selection bias and some damage on pups during the examination): o increased incidence of reduced ossification for treated rats: **pubes**, **supraoccipital bone**; uncommon but with low incidence: **maxilla**, **nasal bones**; low incidence: sternebrae, thoracic vertebral centra, ischium, , lumbar vertebral centra, interparietal bone o increased incidence of non-ossified bones for treated rats: **supraoccipital bone**, **lumbar vertebral centra** (or non-fused ossification centers); uncommon but with low incidence: **metatarsals**; low incidence: sternebrae, hyoid bone o **surnumerary rib 14: low but dose-dependent increase of incidence** of bilateral rib 14 in treated rats; unilateral rib 14 observed at all doses (non-dose dependent) and in control o malaligned sternbrae for 1/199 control and 1/192 at 750ppm 80ppm = ~ 6.4 mg/kg/d 250ppm = ~ 20 mg/kg/d 750ppm = ~ 60 mg/kg/d
Dose-range finding for pre-natal development Unpublished report (1993) **RI=3** Rats 10/dose Gavage in corn oil Doses: 0, 50, 200, 300, 400 mg/kg/d d6-d15 of gestation; 1/d; sacrifice at d20	No developmental toxicity	Maternal toxicity at chosen doses, except maybe at the lowest (50 mg/kg/d) where the only sign of toxicity is a **significant reduction of body weight at d8 and d10, and of body weight gain from d6 to d15.** At this dose, **reduced number of implantations** (-11%).

Purity 98% (no information on impurities)		
Dose-range finding for pre-natal development Unpublished report (1993) **RI=3** **Rabbits** 10/dose Gavage in corn oil Doses: 0, 25, 100, 200, 300 or 400 mg/kg/day (nominal conc.) d6-d19 of gestation, 1/d; sacrifice at d30 Purity 98% (no information on impurities)	abortion of 1 litter in the 100 mg/kg/d group in the absence of statistically-significant reduction in maternal body weight, and no data in food consumption is provided maternal toxicity observed in 3 highest doses groups	Maternal toxicity: - Mortality (10% at 300 mg/kg/d and 30% at 400 mg/kg/d) and decreased food consumption (>90% eating little from d9 at 300 mg/kg/d, 100% not eating on d9, reversible for 60% at 400 mg/kg/d) - Body weight: **dose-dependent (100+ mg/kg/d) decrease of absolute weight from d8, significant from d10 to d18 (300 mg/kg/d) and from d8 to d30 (400 mg/kg/d); significant decrease of body weight gain from d6 to d19 (200+ mg/kg/d), dose-dependent decrease of corrected body weight (body weight - uterus weight) at all doses** - 20% (2/10) with vaginal bleeding, for 1 followed by abortion at 100 mg/kg/d, associated with body weight reduction of the group) - 20% and 30% with vaginal bleeding at 300 and 400 mg/kg/d, 1 abortion at 300 mg/kg/d, 1 death at 400 mg/kg/d - At 25 mg/kg/d, 1/10 with pale liver and 71% dead pups/late resorptions Effects on offsprings: - few parameters investigated, difficult to conclude - lower body weight of pups (non-statistically significantly)

7.9.7.4. Other available assessments

The **OECD SIDS (1998)** conclusions of no further concern regarding reprotoxicity was based on the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993) / JETOC, 1998) and the pre-natal development study (Unpublished study report 1980) analysed above.

The **US Hazardous Substances Data Bank (HSDB) dataset** consulted on October 2016 refers to the continuous breeding NTP study (Jamieson, 1995), the pre-natal development study (Unpublished study report 1980), the dose-range finding study for pre-natal development study on rabbits (Environmental Health Research and Testing, Inc, 1993), the 3-generation reproduction study (Unpublished study report 1980), and the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993) / JETOC, 1998) analysed above.

Note: in both OECD SIDS and HSDB reports, the doses investigated in the pre-natal development study (Unpublished study report 1980) were inadequately reported as in mg/kg/d instead of ppm.

A OECD pilot CLH dossier established by the Registrant and the Russian authorities was made available in May 2016. Among other endpoints, the reproductive effects of dicyclopentadiene were evaluated for classification purpose based on the same dataset as the Reach registration dossier.

- For fertility, the findings in the continuous breeding NTP study (Jamieson, 1995), the 3-generation reproduction study (Unpublished study report 1980) and the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993) / JETOC, 1998), were not considered adverse except for an increase in days to litter stated in the continuous breeding NTP study. Therefore, no classification was proposed for fertility.
- For developmental effects, the conclusions were based on the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993) / JETOC, 1998), the pre-natal development study (Unpublished study report 1980) and the two dose-range finding studies for pre-natal development studies on rabbits and rats (Environmental Health Research and Testing, Inc, 1993). Based on the observed adverse effects in the rabbits dose-range finding study in the absence of maternal toxicity at 100 mg/kg/d and below (abortion and bloody vaginal discharge), and based on adverse effects noted in the continuous breeding NTP study (increased days to litter, increased pup mortality, fewer pups born alive and lower pup weights), **it was proposed to classify DCPD as reproductive toxicant Category 2 for developmental toxicity**. The malformations observed in the rabbits study were not considered as relevant for classification purpose since they occurred in the presence of high maternal toxicity.

7.9.7.5. Conclusions for toxicity to reproduction

In relation to reproductive toxicity, the main findings of the available dataset are:

- **Decreased fertility**: in a combined repeated dose and reproductive/developmental toxicity screening test, performed in rats exposed by gavage to the Substance (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998), decreased fertility was reported at mid dose (-38% at 20 mg/kg/d). In a 3-generation toxicity dietary study performed in rats (Unpublished study report, 1980d), which included two matings per generation, a non statistically significant decreased fertility was observed: decreased for F0 males on the first mating (-10% at 750 ppm, roughly equal to 58 mg/kg/d), decreased for F0 females on the first mating (-5%, -16% at 80 ppm and 750 ppm respectively, roughly equal to 8.7 and 87 mg/kg/d) but increased on the second mating (+6% at 750 ppm); decreased for F1 males on both matings at 750 ppm (-10%), decreased for F1 females on the first mating (-5% and -26% at 80 and 750 ppm respectively) and likely decreased at 750 ppm on the second mating. However it is difficult to conclude on the attribution of infertility to the male or the female or both,

because a same pair was tested twice and gave no litter at either mating; decreased for F2 males and females on both matings for the control rats and at 80 and 750 ppm (1 male of the control group was shown infertile which makes the interpretation difficult).

- **Reduced number of implantations**:
  - In the screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998), non-significant and non-dose dependent reductions of the number of implantations (-24%, -19%, -11% at 4, 20 and 100 mg/kg/d respectively) and implantation index (-19%, -22%, -11% at 4, 20 and 100 mg/kg/d respectively) were observed.
  - In a prenatal developmental toxicity study performed in rats by dietary administration (Unpublished study report 1980e), the number of implantations was reduced in the left uterine horn of treated females (-19%, -14% and -13% at 80, 250 and 750 ppm respectively, roughly equal to 6, 20 and 60 mg/kg/d). No difference was found in the right horn and there were more implantations on the right than the left horn at all doses and control. This last finding was previously described in the literature (Wiebold and Becker, 1987; Barr *et al.* , 1970).
  - In a dose-range finding (DRF) study performed in rats by gavage (Environmental Health Research and Testing, Inc, 1993a), the number of implantations was found reduced at the lowest dose of 50 mg/kg/d (-11%); no conclusion can be drawn for the higher doses due to maternal toxicity.
- **Increased gestation length**: an increased gestation length (duration not reported) was observed in a continuous breeding study performed in rats (NTP, Jamieson, 1995).
- **Reduced litter survival**: reduced litter survival during lactation was observed in the screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998) at 100 mg/kg/d, since 2 dams out of 8 did not nurse their litters and lost them totally within 2 days (as reported in the OECD SIDS, 1998). Higher F1 pup mortality and decreased F1 pup survival in the final litter were seen in the continuous breeding study (NTP, Jamieson, 1995) (no figures reported).
- **Decreased pup weight during lactation**:
  - In the screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998), decreased pup weight (-13% at 100 mg/kg/d) and decreased body weight gain (-19% for males and -22% for females at 100 mg/kg/d) were observed at PND4. At this dose, some maternal toxicity was observed: reduced body weight gain during lactation (-30%) and reduced food consumption (-21%); blood chemistry and haematology was not investigated in females.
  - In the 3-generation study (Unpublished study report 1980d), body weight gain was significantly reduced at the highest dose of 750 ppm (-17%) for female pups on the 2nd mating of F3 generation at PND21.
- **Reduced number of pups**: in the screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998), a non-significant and non-dose dependent reduction was observed (-26% or -16% at 4 mg/kg/d (2 versions of the report give 2 different figures), -21% at 20 mg/kg/d, -10% at 100 mg/kg/d).
- **Effect on sex ratio**: possibly an effect on the sex ratio was observed in the 3-generation study (Unpublished study report 1980d), as the relative number of male pups compared to females is higher in the second mating of F2 and in both 1st and 2nd mating of F3. In addition, Okubo *et al.* (2000) reported a statistically significant excess of female births among the 15 male workers exposed to epoxy resin, dicyclopentadiene and cyclopentadiene from 1980 to 1997 in a company in Japan.

Additionally, some findings observed in repeated toxicity studies suggest that endocrine organs may be affected following exposure to DCPD. In particular:

- **Effects on testes:**
  - In a 90-day dietary study performed in 4 dogs per sex and dose (Unpublished study report 1980a, RI=2), non-statistically significant decrease in testes weight (relative to brain weight) was found at all doses (-9%, -13% and -9% at 100, 300 and 1000

ppm respectively, corresponding roughly to 2.5, 7.5 and 25 mg/kg/d); effects on absolute testes weight and testes weight relative to body weight are less clear (respectively +3%, -6%, -8% and 3-%, +5% et -4% at 100, 300 and 1000 ppm); no effect was seen at necropsy.

- Decreased testes weight (statistical significance not known) was also observed in a low quality 90-day dietary study performed in mice (Unpublished study report 1976g) in a dose-dependent manner when expressed as absolute weight (up to -18% at the highest dose of 273 ppm, roughly 56 mg/kg/d), and in a non-dose dependent manner when expressed as percentage of body weight (up to -21% at 91 ppm, roughly 19 mg/kg/d); no effect seen at necropsy.
- In a 90-day inhalation study performed in mice (Unpublished study report, 1982, Kransler, 2014, RI=2), a **statistically significant decrease of testes weight** (-7% relative to body weight) was observed at 51 ppm (276 mg/m^3) after 4 weeks of recovery and atrophy of the seminiferous tubule was seen in 1 out of 7 male at this dose after 13 weeks of exposure (examination was done only at this time point and the intermediate doses were not investigated).
- In the 90-day inhalation study performed in rats (Unpublished study report, 1982, Bevan, 1992, RI=2), no clear conclusion can be drawn regarding testes weights, but 1 male at 5ppm had small testes and another at 5ppm had patchy color changes on testes.
- Atrophy of the seminiferous tubules was also observed in some animals in the combined repeated/reproductive screening test in rats (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998, RI=2) but no clear tendency can be found as the lesion was observed in one or two animals only per dose and in control.
- No effect on testes weight were observed in a 90-day dietary study on rats (Unpublished study report 1976)
- A decrease of testes weight as absolute and relative weight at 40ppm (~ 8 mg/kg/day) (-17% abs. wt of right testis) and increase at 375ppm (+60% abs. wt of right testis) were noted in a 14-day dietary study on dogs (Unpublished study report 1976, RI=3, 1 animal/sex/dose).

- **Effects on ovaries**:
  - In the 90-day dietary study in dogs (Unpublished study report 1980a), non-statistically significant increase in ovaries weight was seen at all doses in a non-dose dependent manner, when expressed as absolute weight (up to +222%), as percentage of body weight (up to +183%) and as percentage of brain weight (up to +220%). According to Bailey *et al.* (2004), organ-to-brain weight ratios is predictive for evaluating ovary weights. No lesion was seen at necropsy.
  - In the low quality 90-day dietary study on rats (Unpublished study report 1976f), increased ovaries weight was observed at 250 and 750 ppm (roughly 20 and 62 mg/kg/d), as absolute weight (+2.5% and 9.2%) and as percentage of brain weight (+4.9% and 11.5%). Statistical significance is not known. No lesion was seen at necropsy.
  - In the low quality 90-day dietary study on mice (Unpublished study report 1976g), decreased ovaries weight was observed at all doses in a non-dose dependent manner (up to -29% as absolute weight and percentage of body weight). Statistical significance is not known. No lesion was seen at necropsy.
  - In the two 90-day inhalation studies on rats and mice (Unpublished study report, 1982, RI=2), ovaries weights were not measured but ovaries filled with fluid were seen in 1/9 rats at 5 and 51ppm after 13 weeks of exposure, in 1/9 rats in control, 5 and 51ppm groups after 4 weeks of recovery, and in 1/8 mouse in control group, 1/9 mouse at 5ppm, 1/6 mouse at 51ppm after 4 weeks of recovery. Cystic ovaries were seen in rats in control and treated groups during exposure and at the end of recovery.

- **Effects on adrenals:**

- In the 90-day dietary study in dogs (Unpublished study report 1980a), a non-significant decrease of the adrenals weight was observed at all doses, in a non-dose dependent manner (up to -6% for males and -13% for females as absolute weight, -12% for males and -25% for females as percentage of body weight, -17% for males and females as percentage of brain weight). According to Bailey *et al.* (2004), organ-to-brain weight ratios is predictive for evaluating adrenal gland weights. No lesion was seen at necropsy.
- In the low quality 90-day dietary study on rats (Unpublished study report 1976f), increase adrenals weight was observed for males at all doses, in a non-dose dependent manner (up to +18% as absolute weight, +9% as percentage of body weight and 18% as percentage of brain weight). No lesion was seen at necropsy.
- In a 90-day inhalation study performed in rats (Unpublished study report, 1982, Bevan *et al.* , 1992), adrenals were not weighed but histopathological examination revealed fatty infiltrations in the adrenals of males (twice as much in the 51 ppm group (276 mg/m^3) as in control group, but the intermediate doses were not investigated). Enlargement and fatty infiltrations were also observed in the combined repeated/reproductive screening test in rats (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998;)
- In the 90-day inhalation study performed in mice (Unpublished study report, 1982, Kransler, 2014), cortical hyperplasia of the adrenals was seen in 2 out of 6 males at 51 ppm and 2 out of 8 females at 51 ppm (but also in 2 out of 9 control females), but the intermediate doses were not investigated.

- **Effects on thyroid:**
  - In the 90-day dietary study in dogs (Unpublished study report 1980a, RI=2), non-statistically significant increase of the thyroid weight was observed for females and decrease for males, at all doses, in a non-dose dependent manner (for females : up to + 41%, +21% and +34% as absolute weight, percentage of body weight and percentage of brain weight respectively, and for males up to -29%, -23% and -34% respectively). According to Bailey *et al.* (2004), organ-to-body weight ratios is predictive for evaluating thyroid gland weights. For females, lesions were observed at necropsy at 1000 ppm (roughly 25 mg/kg/d): minimal cystic remnant of ultimobranchial duct in 1 female out of 4, minimal cystic remnant of ultimobranchial duct of parathyroid in another 1 female out of 4. Intermediate doses were not investigated. No lesion was seen at necropsy for males.
  - In the other RI=2 studies, 90-day inhalation studies on rats and mice (Unpublished study report, 1982), weight was not measured and no effects were seen at necropsy.
  - In the low quality 90-day dietary study on rats (Unpublished study report 1976f, RI=3), increased thyroid weight was seen for males at all doses, in a non-dose dependent manner, up to +33% as absolute weight and +23% as percentage of body weight. Statistical significance is not known. No lesion was seen at necropsy.
  - In the low quality 90-day dietary study on mice (Unpublished study report 1976g, RI=3), decreased thyroid weight was observed for males at 28 ppm (roughly 6 mg/kg/d) (-17% as absolute weight, -20% as percentage of body weight) and at all doses (non dose-dependent) for females (up to -36% as absolute weight, -35% as percentage of body weight), and increased weight was observed for males at 273 ppm (roughly 56 mg/kg/d) (+19% as absolute weight, +16% as percentage of body weight). Statistical significance is not known. No lesion was seen at necropsy.
  - A dose-dependent decrease for males at all doses (as % body weight and as absolute at highest doses) and an increase for females at the highest doses (as absolute and relative weight) were noted in the 14-day dietary study on dogs (Unpublished study report 1976, RI=3, 1 animal/sex/dose).

- **Other organs:**

- cysts in **pituitary gland** were seen in 2/4 male dogs at 1000ppm, in 3/4 female dogs in control group and in 1/4 female dog at 1000ppm (90-day dietary study on dogs, Unpublished study report 1980, RI=2).
- dilated **uterus** was seen after 4 weeks of recovery (1/8 control, 2/9 at 5ppm) in the 90-day inhalation studies on mice (Unpublished study report, 1982, RI=2) and mild acute purulent cervicitis in 1/32 female at 273ppm and mild metritis were seen in another 1/32 female at 273ppm in the 90-day dietary study on mice (Unpublished study report 1976, RI=3).
- mild focal hyperplasia of the **prostate** was seen in 1/32 male at 273ppm in the 90-day dietary study on mice (Unpublished study report 1976, RI=3).

It is difficult to draw any conclusion regarding these results since the observations are usually not statistically significant and are not consistent across studies except for testes weight.

In addition, numerous limitations were noted in the protocols and reporting, as presented above. In particular, the following parameters were not appropriately examined:

- haematology and clinical biochemistry on males and females parents: examined *for males only* in the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998).
- gravid uterine weight: measured in the 2 DRF studies (Environmental Health Research and Testing, Inc, 1993).
- number of corpora lutea: counted in the combined repeat dose and reproductive/developmental toxicity screening test (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998).
- oestrous cycle of parents: not examined.
- sperm parameters of parents: not examined.
- skeletal changes in pups: examined in the pre-natal development study (Unpublished study report 1980).
- functional observations in parents: not examined in reprotoxicity studies, but some investigations done in a 9-day toxicity study by inhalation on rats and mice (Unpublished study report, 1981).
- functional observations in pups: not examined.
- thyroid hormone levels in pups: not examined.
- anogenital distance in pups: not examined.
- nipple retention in male pups: not examined.
- age of vaginal opening and preputial separation in pups: not examined.

The available information does not allow to conclude firmly on the effects of the DCPD on fertility and furthermore does not allow to conclude on the relevant classification of the substance for fertility, and for risk assessment. However, they raise alerts.

Further studies are necessary to investigate the affected organs and the possible mode of action involved in the effects seen.

Information requirements under Section 8.7.3. of Annex IX/X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) have not yet been addressed under CCH because the information from the on-going 90-day study is relevant for the design of the EOGRTS. A EOGRTS is expected to provide useful information to address the concern identified on the possible reproductive effects of the substance. Hence no further data is requested by the eMSCA under SEv at this stage.

Regarding neurotoxicity potential, some occurrence of lethargy, ptosis, ataxia, tremors, convulsion, spasms, incoordination were observed in acute toxicity studies via oral route in rats and mice (Safepharm Laboratories Ltd, 1989a; Unpublished study report 1976b,c). In one acute toxicity study on calves (Cysewski *et al.* , 1981), small haemorrhages and meningeal congestion were observed in brains at high doses. In acute toxicity studies by

inhalation performed in rats, mice, rabbits, guinea pigs and dogs (Unpublished study report, 1981; Kinkead *et al.* , 1971; Gage, 1970), the main findings are stereotypic behavior, convulsions, tremors, loss of coordination; additionally one study in rats reports hypersensitivity to noise and handling. Coordination loss and/or decreased activity was also noted in a few treated mice in a 90-day inhalation study on mice (Unpublished study report, 1982, Kransler, 2014); decreased responses to stimuli, stereotypic behaviour, abnormal reflex were noted in a 9-day inhalation study on mice and rats (Unpublished study report, 1981). The Registrant established a NOAEC of 46 ppm (248.74 mg/m^3) for irregular breathing and **stereotypic behaviour** for male and female mice and rats based on Unpublished study report, 1981. Very few data are available on organs of the nervous system but in a 90-day dietary study on dogs (Litton Bionetics 1980a), a non-significant reduction of relative brain weight was noted in females at all doses. Finally, observations from accidental repeated exposure of workers for 5 months reported headaches for 2 months but not the last 3 months (Kinkead *et al.* , 1971). **These findings raise alerts on potential developmental neurotoxicity. They justify the inclusion of the DNT cohort in the EOGRTS to be performed.**

Regarding potential adverse effects on the immune system, some findings in repeated toxicity studies raise alerts on effects to organs involved in immune responses and in haematology. More specifically, some changes in *thymus* weight were reported in rats in two different studies (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998; Satoh *et al.* , 1999) and hemorrhage in thymus of dead females were observed (Kinkead *et al.* , 1971) with lymphocytes infiltration. Some changes in *spleen* size or weight were observed in rats, dogs and mice (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998; Unpublished study report 1980a; Unpublished study report 1976g, h), one mouse had malignant lymphoma in the spleen (Unpublished study report 1976g). Leukocyte infiltrates in mesenteric *lymph nodes* were observed in dogs (Unpublished study report 1980a), some lesions were seen in mesenteric lymph nodes in mice (lymphoreticullar hyperplasia, unidentified lesion) (Unpublished study report 1976g) and hemorrhage, erythrophagocytosis, reddening of medullary area in dogs (Unpublished study report 1976h). In rats, erythrocytes in sinuses, hemosiderosis and mast cell infiltration in the mediastinal lymph nodes were observed; enlarged pancreatic lymph node with generalised color change was seen (Unpublished study report, 1982, Bevan at al., 1992). Regarding haematology, a slight increase of neutrophils count was observed in rats (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998; only the males were investigated; as noted above, increased thymus weight and enlarged spleen were also observed in this study). An increase of leukocytes count was observed in the 90-day study on dogs (Unpublished study report 1980a; as noted above, leukocyte infiltrates were observed in mesenteric lymph nodes and increased spleen weight were also observed in this study). Decrease of white blood cells count was noted in the rats 90-day oral study (Unpublished study report 1976f). In a 90-day inhalation study on rats (Unpublished study report, 1982, Bevan *et al.* , 1992), increase of neutrophils, monocytes and eosinophils counts were observed at the highest dose for females after 6 weeks of exposure; for males, the trend is less clear but a statistically significant increase of monocytes count and non-significant increase of lymphocytes and eosinophil counts were observed after 13 weeks of exposure. **These findings raise alerts on potential developmental immunotoxicity. They justify the inclusion of the DNT cohort in the EOGRTS to be performed.**

In relation to developmental toxicity, the main findings of the available dataset are:

- **Decreased fetus viability**: fewer pups born live were reported at 100 mg/kg in a continuous breeding study performed in rats (NTP, Jamieson, 1995) and at the lowest dose of 80 ppm in feed (roughly 6 mg/kg/d) and up to the highest dose in the prenatal developmental toxicity study performed in rats by dietary administration (Unpublished study report 1980e);
- **Decreased fetus weight**:
    - A statistically significant decreased fetus weight (-11%) was reported at 200 mg/kg/d, in the dose-range finding (DRF) gavage study performed in rats (Environmental Health Research and Testing, Inc, 1993a); at this dose maternal toxicity was also reported (42% mortality, statistically significant reduction of

absolute body weight and body weight gain in an overall dose-dependent manner). Food consumption was not investigated. No maternal effect was reported at the only one lower dose. However, this dose was much lower (50 mg/kg/d).

- A slight and non-statistically significant decreased fetus weight was observed at 100 mg/kg/d (-4%) and 200 mg/kg/d (-7%) in the absence of maternal toxicity (also noted at 300 (-5%) and 400 mg/kg/d (-7%) in the presence of maternal toxicity), in a DRF gavage study performed in rabbits (Environmental Health Research and Testing, Inc, 1993b).
- A decreased pup weight at birth was observed at the highest dose of 100 mg/kg/d (-20%), in the combined repeated dose and reproductive/developmental toxicity screening test, performed in rats by gavage (Mitsubishi Chemical Safety Institute, 1993, JETOC, 1998); at this dose some maternal toxicity was also reported: 20% mortality before gestation, slight reduction of food consumption at 4 mg/kg/d (-4% at day 7 of gestation) and 100 mg/kg/d (-5%, -8% and -4% at days 7, 14 and 20 of gestation), reduction of body weight at all doses and body weight gain at all doses (roughly -10%, -9% and -14% at 4, 20 and 100 mg/kg/d respectively, during gestation); blood chemistry and haematology were not investigated in females.
- A decreased pup weight was observed in the continuous breeding study (NTP, Jamieson, 1995) in F1 pups at 30 (-4% for female pups) and 100 mg/kg (-8%) and in F2 pups (-12%) at 100 mg/kg. As only an abstract is available, no details are available to determine if the pup weights reported correspond to their weights at birth or later, nor if maternal toxicity was present. Maternal toxicity seems unlikey since systemic effects were reported in male parents only (increased liver and kidney weight) and at crossover mating, reduced pup weight was noted for pups of the treated females (-9%) but not the treated males.
- A tendency to decreased pup weight at birth was observed for female pups in the 3-generation dietary study performed in rats (Unpublished study report 1980d), in F1 and F3 pups.

- **Skeletal abnormalities:** some reduced and/or absence of ossification and increased incidence of ribs 14 were observed at all doses but also in control, in the prenatal developmental toxicity study on rats (Unpublished study report 1980e), and were considered not relevant by the author; however no historical control are given there may be a selection bias for the examined pups and some pups were damaged during the examination. In the DRF study on rabbits (Environmental Health Research and Testing, Inc, 1993b), some pups had open eyes at high dose.
- **Vaginal bleeding and abortions:** in the DRF study on rabbits (Environmental Health Research and Testing, Inc, 1993b), vaginal bleedings were reported at 100, 300 and 400 mg/kg/d (20%, 22% and 33% of females respectively) and were followed by spontaneous abortions for one female (10%) at 100 mg/kg/d and one (11%) at 300 mg/kg/d.

Furthermore, as mentioned above, in an update of the registration dossier following the publication of the CoRAP, the Registrant(s) decided to classify DCPD as toxic for reproduction category 2 H361, based on an overall weight of evidence of foetotoxic effects (reduced pup body weight, increased pup mortality, and decreased pup survival).

However, the available information does not allow to conclude firmly on the effects of the DCPD on development and furthermore does not allow to conclude on the relevant classification of the Substance as Reprotoxic category 1 or 2, and for risk assessment.

The eMSCA considers that the observed effects justify the need to investigate this endpoint more deeply by conducting additional studies.

A CCH is on-going requesting a PNDT study in a first species. Additionally a TP is also on-going requesting a PNDT study in a second species.

These two studies are expected to provide useful information to address the concern identified on the possible developmental effects of the Substance and clarify if the Substance needs to be classified.

7.9.8. Hazard assessment of physico-chemical properties

- DCPD is considered a flammable substance;

The DCPD liquid is self-classified Flam. Liq. Cat. 3 H226.

The DCPD solid is self-classified Flam. solid. Cat. 2 H228.

- The DCPD liquid is self-classified Asp. Tox. 1 H304 due to its viscosity.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The Registrant(s) derived DNELs for the following endpoints:

- For the inhalation route:
  - Systemic effects, long-term
  - Local effects, acute
  - Local effects, long-term
- For the dermal route:
  - Systemic effects, long-term
- For the oral route (general population only):
  - Systemic effects, long-term
  - Systemic effects, acute

For local effects to the eyes, no DNEL was derived but a qualitative approach was applied.

Acute systemic effects via inhalation

The Registrant(s) considered that no DNEL was necessary to account for the acute systemic effects by inhalation, as "*no hazard [was] identified*" for systemic effects following acute exposure. However, DCPD has a harmonised classification (index No 601-044-00-9) for acute toxicity by inhalation as Acute Tox 4* H332 (harmful if inhaled)[6], and based on the available data, the Registrant(s) classifies DCPD as Acute Tox 2 H330 (fatal if inhaled). Therefore, the eMSCA disagrees with the Registrant(s) and considers that **the Registrant(s) shall derive an acute inhalation DNEL for systemic effects** based on the data obtained on the most sensitive species and recommendations of the Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1, November 2012).

Local dermal effects

No threshold nor hazard category for qualitative assessment of the risk related to skin irritation were derived. The Registrant(s) considered that "no hazard [was] identified" for local dermal effects. However, DCPD has a harmonised classification (index No 601-044-00-9) as Skin Irrit. 2 H315 (causes skin irritation). Therefore, the eMSCA disagrees with the Registrant(s). **The Registrant(s) shall provide a risk characterisation for local dermal effects.**

Assessment factors

The eMSCA considers that the assessment factors (AF) used by the Registrant(s) do not meet the requirements of the Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1, November 2012).

However, the eMSCA did not recalculate the DNELs at that time since new toxicology studies are ongoing and may impact the choice of the dose descriptors.

[6] The asterisk (*) indicate that this classification is a minimal classification due to the conversion from the criteria of Directive 67/548/EEC to the CLP Regulation EU 1272/2008.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

A CLH dossier should be considered in order to establish the classification for acute toxicity (revision of the classification), reprotoxicity and repeated dose toxicity. Classification for reprotoxicity and repeated dose toxicity will be considered following the completion of the ongoing data generation required in compliance check (CCH 90-day study and two Pre-natal developmental toxicity study (PNDT) studies, followed by an extended one-generation reproductive toxicity study (EOGRTS)).

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not assessed. No data available in the dossier.

7.10.2. Endocrine disruption - Human health

ED was in the scope of the evaluation for human health.

The available studies were not designed to address endocrine disruption. However some alerts were noted (see section 7.9.7 on toxicity to reproduction above).Therefore, this concern remains unresolved due to on-going CCH data generation.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

No conclusion reached and remains unresolved due to on-going CCH data generation.

7.11. PBT and VPVB assessment

Persistence

According to an unpublished study report, (2004), on ready biodegradability which follows OECD TG 301F on DCPD/Codimer Concentrate and which has been read across to DCPD, 0% biodegradation in 28 days is showed. Therefore DCPD is considered to be not readily biodegradable. Based on the screening criteria dicylopentadiene is potentially P/vP. Nevertheless, QSAR predictions are in contradiction with this result.

Bioaccumulation

A log Kow of 2.78 is reported in the WHO ICSC (2005).

Criteria based on Annex XIII of REACH

An unpublished study report (1976) indicated a BCF value of 53. Nevertheless this study cannot be considered as sufficient to conclude definitively that the substance is not bioaccumulative. A weight of evidence approach is needed:

- A low Bioconcentration Factor (BCF) values (56.91 – 300.2 L/kg $_{wet\ wt}$) was estimated by QSAR;
- In a MITI study (report not available), an estimated BCF between 58.9 and 384 is reported.

Existing information indicates that dicyclopentadiene does not meet Annex XIII criteria. Dicyclopentadiene is not B/vB according to REACH regulations.

Toxicity

The most acute sensitive aquatic species are invertebrates, with EC50 = 0.823 mg. L^{-1}.

The most chronic sensitive aquatic species are fish, with NOEC = 0.98 mg. L^{-1}.

However, none of the studies evaluated exceed the acute LC50 toxicity screening criteria of <0.1 mg/L or the NOEC criteria of <0.01 mg/L in Annex XIII. Therefore, DCPD is not considered to be T.

Therefore DCPD is not considered to fulfil the T criteria for the environment.

Nevertheless reliable study for long-term aquatic toxicity on invertebrates should be provided.

The substance does not meet the criteria for B/vB, so no further assessment on the P criterion and T criterion for human health is needed.

Conclusion

Based on the assessment described in the subsections above the Substance is not a PBT / vPvB substance.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

7.12.1.1.1. *Uses of DCPD by workers*

The Registrant(s) included 6 exposure scenarios in the registration dossier:

- ES 1 (M 1): Manufacture
- ES 2 (IW 1): Use at industrial site - Distribution of a substance
- ES 3 (IW 2): Use at industrial site - Use as an intermediate
- ES 4 (IW 3): Use at industrial site - Polymer Production
- ES 5 (IW 4): Use at industrial site - Polymer Processing
- ES 6 (PW 1): Use by professional worker - Polymer Processing

In particular PROC 5 and 6 and to a lesser extent PROC 4, 8a, 9, 13, 14 and 15 suggest a potential for workers exposure.

- PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises
    - General exposures (open systems) [CS16] Batch process [CS55] With sample collection [CS56] (ES 1, 2, 3)
    - Intermediate polymer storage [CS66] (ES 4)
    - Additive premixing [CS92] (open systems) [CS108] With sample collection [CS56] (ES 5)
- PROC 5: Mixing or blending in batch processes for formulation of mixtures and articles (multistage and/or significant contact)
    - Mixing in containers [CS23]. Batch process [CS55] (ES 4)
    - Additive premixing [CS92] General exposures (open systems) [CS16] (ES 5)
- PROC 6 Calendering operations
    - Pelletizing [CS53]. Extrusion and masterbatching [CS88] (ES 4)
    - Calendering (including Banburys) [CS64] (ES 5)
    - Injection moulding of articles [CS89] (ES 6)
- PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities
    - Equipment cleaning and maintenance [CS39] (ES 1, 2, 3)

  - Equipment maintenance [CS5] (ES 4, 5, 6)
- PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
  - Drum and small package filling [CS6] (ES 2)
  - Small scale weighing [CS90] (ES 5)
  - Bulk transfers [CS14] Small package filling [CS7] (ES 5)
- PROC 13: Treatment of articles by dipping and pouring
  - Production of articles by dipping and pouring [CS113] (ES 5)
- PROC 14: Production of mixtures or articles by tabletting, compression, extrusion, pelletisation
  - Pelletizing [CS53] (ES 4)
  - Extrusion and masterbatching [CS88] (ES 5)
  - Injection moulding of articles [CS89] (ES 5, 6)
- PROC 15: Use as laboratory reagent
  - Laboratory activities [CS36] (ES 1, 2, 3)

The Registrant(s) assessed the workers exposure by modelisation with ECETOC TRA version 3. The following estimates were calculated by the Registrant(s):

- Long-term inhalation exposure ($mg.m^{-3}$) compared to the DNEL for long-term systemic effects by inhalation and to the DNEL for long-term local effects by inhalation.
- Acute inhalation exposure ($mg.m^{-3}$) compared to the DNEL for acute local effects by inhalation.
- Long-term dermal exposure ($mg.kg_{bw}^{-1}.d^{-1}$) compared to the DNEL for long-term systemic effects by dermal route.
- For eye irritation, a qualitative approach was developed.
-

Since the DNELs are not set yet, because of on-going requests under CCH, the eMSCA has not performed its own exposure assessment and risk characterisation.

Based on the current registration dossier, there is a concern that the risk by inhalation due to exposure of workers over a day may be underestimated. Taking into account the available information, it is difficult to assess whether worker exposure to DCPD is adequately controlled. In the registration dossier, estimates were provided for the inhalation route for each contributing exposure scenario (corresponding to a PROC) individually. A RCR for inhalation and dermal routes was calculated for each PROC. However, no combined inhalation exposure estimate was provided to take into account all the possible sources of exposure by inhalation for a worker over a day (time weighted average of 8 hours). Up to 18 different contributing exposure scenarios are included within each exposure scenarios for workers. A reduction factor for exposure duration was used for many contributing scenarios, some of which lead to high RCR nevertheless, for example ES2-WCS8 or ES4-WCS7. So, it is likely that workers may be exposed to DCPD via several processes during a day and that exposure by inhalation may be underestimated. **The Registrant(s) are required to provide combined exposure estimations and risk characterisation by inhalation for workers (time weighted average over 8 hours for a similar exposed group).**

DCPD is classified for acute toxicity by inhalation and peak exposure by inhalation is likely to occur. The long-term risk assessment for systemic effects and the acute risk assessment for local effects are not sufficient to address the acute risk for systemic effects. Therefore there may be a risk for workers resulting from acute exposure to DCPD. The acute risk due to systemic effects following exposure of workers by inhalation is not currently addressed

in the exposure scenarios. The acute exposure is modelled with ECETOC TRA but this approach is possible only if the activities assessed are considered to lead to stable exposure levels (without any task leading to exposure peaks). However, this assumption was not justified by the Registrant(s) and ECHA considers that acute exposure may be expected based on the exposure scenarios (PROC 4, 5, 8a, 9, 14, 15, 21), but since no details on the tasks performed by workers are given, ECHA is not able to assess whether the use of ECETOC TRA for the purpose of acute exposure assessment is suitable. If not suitable, the exposure must be either modelled with adequate tools such as the Advanced REACH Tool (ART) or Stoffenmanager, or be estimated from adequate measurements. **The Registrant(s) are required to provide an acute risk characterisation for systemic effects via the inhalation route for workers, for all exposure scenarios, to demonstrate that the risk related to acute systemic effects by inhalation is adequately controlled.**

DCPD is classified for skin irritation. Dermal exposure is likely to occur, and gloves are not recommended for all scenarios where exposure may occur. Therefore there may be a risk for workers resulting from dermal exposure to DCPD. The risk due to local effects following dermal exposure of workers is not currently addressed in the exposure scenarios. **The Registrant(s) are required to provide a qualitative risk characterisation for workers to demonstrate that the risk related to skin irritation is adequately controlled for all exposure scenarios.**

In many exposure scenarios in the registration dossier, personal protective equipments (PPE) for eyes and skin are required as risk reduction measures, but no sufficient information is provided in the dossier to ensure that adequate protection are worn. The Registrant(s) used generic statements to describe the PPE but they do not integrate the physico-chemical properties of the substance, nor the conclusions of the risk characterisation. In particular, **the type of eye protection, the type of gloves (material, thickness, typical or minimum breakthrough times of the glove material), and the type of any additional protective equipment deemed necessary following the update of the risk characterisation, shall be documented in the CSR and communicated downstream.**

7.12.1.1.2. *Downstream and end-uses of polymers by workers*

The use of polymers made from DCPD shall be assessed as part of the registration dossier of the monomer, since polymers are not registered themselves according to Article 2(9) of the REACH regulation. In other words, downstream and end-uses of polymers formed from DCPD must be addressed in the registration dossier of DCPD.

Polymers made from DCPD are integrated in mixtures and are used to produce a wide range of articles, which can be used by workers (elastomers, paints, varnishes, flame retardants, plasticizers, resins, adhesives, inks, etc). As DCPD is registered for intermediate uses, release of DCPD from mixtures and articles is not intentional nor expected in significant amounts, as it is consumed during the process of polymer synthesis. However, unreacted monomer may remain as residues in the polymers and thus in the mixtures and articles, and exposure to this residual monomer may be possible during the use of the mixtures and the service life of the articles. Furthermore, hazardous impurities were identified in the registered compositions of the substance and are expected in this type of substance due to its manufacturing process. These impurities may remain in the polymers and may be released during the use of the mixtures and the service life of the articles, which would lead to workers exposure.

The chemical safety assessment do not currently include any information on the possible concentration of unreacted monomer and potential hazardous impurities in polymers and thus in mixtures and articles incorporating or made of these polymers. According to Annex I, 0.3, of the REACH Regulation, "*the chemical safety assessment shall consider the use of the substance on its own (including any major impurities and additives), in a mixture and in an article, as defined by the identified uses. The assessment shall consider all stages of the life-cycle of the substance resulting from manufacture and identified uses.*" Some

Registrants consider that articles service life is relevant for DCPD, but the corresponding exposure scenarios have not been included in the registration dossier.

The information currently provided in the dossier is not sufficient to enable to conclude whether there is a risk for human[7] and the environment due to exposure during the use of mixtures and the service life of articles. It is acknowledged that, for the exposure scenarios "polymer processing" by industrial (ES 5) and professional (ES 6) workers currently included in the registration dossier, all risk characterisation ratios (RCR) are below 1 when taking into account 1 to 5% of DCPD in the mixture depending on the contributing scenario. However, these exposure scenarios and subsequent risk characterisations cannot be considered as sufficient to cover (overestimate) the exposure during end-uses of polymers, since the situations leading to exposure of workers during polymer processing and of workers and the general public during end-uses of mixtures and articles incorporating or made of these polymers are different.

The Registrant(s) further justified that the low odour threshold of DCPD implies that products must have very low levels of residual monomer to be odour free. This information is noted but odour is subjective and is not sufficiently robust as a guarantee of the users safety, especially for mixtures and/or articles with strong odour, such as for instance paint or gasoline.

Therefore, information on residual (unreacted) monomer and hazardous impurities in polymers synthesized from DCPD is necessary to conclude whether monomer and/or other hazardous impurities may be released from polymers, thus from mixtures and articles.

If release of residual monomer and/or hazardous impurities from the polymers are found relevant, exposure scenarios for workers corresponding to the use of mixtures where polymers are incorporated and to the service life of articles made from the polymers are necessary to determine the adequate operational conditions and risk reduction measures to ensure safe use of mixtures and articles by workers.

Therefore, the Registrant(s) shall provide in their registration dossiers information on the range of concentrations of unreacted monomer and potential hazardous impurities in polymers for each grade of the substance; AND a list of the mixtures incorporating polymers and of articles formed with polymers, by indicating for each grade of the substance the product categories (PC codes), articles categories (AC codes) and sectors of use (SU codes) for each PC and AC.

In addition, if unreacted monomer and/or hazardous impurities are present in the polymers, the Registrant(s) shall provide exposure scenarios for human and the environment corresponding to the use of mixtures and to the service life of articles, and exposure assessment based on residual monomer and/or hazardous impurities in the polymers.

7.12.1.2. Consumer

7.12.1.2.1. *Uses of DCPD by consumers*

DCPD is not intended to be used by consumers. Therefore, no direct (primary) exposure of consumers nor the general population is expected.

7.12.1.2.2. *End-uses of polymers by consumers and the general population*

The argumentation detailed above for workers also applies to consumers and the general population, who may also be exposed to residual monomer and hazardous impurities during the use of the mixtures and the service life of the articles.

Therefore, the Registrant(s) shall provide the information detailed in 0.

[7] 'Human' should be understood here in the broad sense as the available information is not sufficient to determine which users and non-users may be exposed.

7.12.2. Environment

Environmental exposure assessment was carried out for the following emission scenarios:

- Industrial manufacture of DCPD (ES 1):
- Use at industrial sites - Distribution (ES 2);
- Use at industrial sites - Intermediate use of the substance (ES 3);
- Use at industrial sites - Polymer Production (ES 4);
- Use at industrial sites - Polymer Processing (ES 5);
- Widespread use by professional workers - Polymer Processing (ES 6).

See confidential annex (not published).

7.13. Risk characterisation

7.13.1. Human health

Not assessed.

7.13.2. Environment

Environmental risk assessment was carried out for the following emission scenarios:

- Industrial manufacture of DCPD (ES 1):
- Use at industrial sites - Distribution (ES 2);
- Use at industrial sites - Intermediate use of the substance (ES 3);
- Use at industrial sites - Polymer Production (ES 4);
- Use at industrial sites - Polymer Processing (ES 5);
- Widespread use by professional workers - Polymer Processing (ES 6).

Unacceptable risks are identified for all scenarios. The discrepancy with Registrant(s) assessment originates mainly from an alternative approach to derive the hazards endpoints (PNEC value for aquatic compartment) justified by the limitations of the available data provided in the dossiers by the Registrant(s).

See confidential annex (not published).

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