Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

1,2-Dichloropropane;
Propylene dichloride

EC number: 201-152-2
CAS number: 78-87-5

CLH-O-0000004490-79-03/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

4 June 2014

CLH Report

Proposal for

Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Substance Name:

PROPYLENE DICHLORIDE (PDC)

EC Number: **201-152-2**

CAS Number: **78-87-5**

Index Number: **602-020-00-0**

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Part A – PROPOSAL, BACKGROUND, AND JUSTIFICATION

1. PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1. Substance

Table 1. Substance identity

Substance name:	**Propylene Dichloride**
EC number:	201-152-2
CAS number:	78-87-5
Annex VI Index number:	602-020-00-0
Degree of purity:	>= 99%
Impurities:	Impurities are not present at concentrations that affect the Classification and Labelling of this substance.

1.2. Harmonised classification and labelling proposal

Table 2. Current Annex VI entry and proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Flam. Liq. 2 (H225) Acute Tox. (oral) 4*, H302 Acute Tox (inhal.) 4*, H332
Current proposal for consideration by RAC	Add classification for carcinogenicity Cat 2, H351
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Flam. Liq. 2 (H225) Acute Tox. (oral) 4*, H302 Acute Tox (inhal.) 4*, H332 Carcinogenicity Carc. 2, H351

1.3. Proposed harmonised classification and labelling based on CLP Regulation

Table 3. Proposed classification according to CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	No change		Not classified	Conclusive but not sufficient for classification
2.2.	Flammable gases	No change		Not classified	Conclusive but not sufficient for classification
2.3.	Flammable aerosols	No change		Not classified	Conclusive but not sufficient for classification
2.4.	Oxidising gases	No change		Not classified	Conclusive but not sufficient for classification
2.5.	Gases under pressure	No change		Not classified	Conclusive but not sufficient for classification
2.6.	Flammable liquids	No change (Flam. Liq. 2 H225)		Flam. Liq. 2 H225	
2.7.	Flammable solids	No change		Not classified	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	No change		Not classified	Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	No change		Not classified	Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	No change		Not classified	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	No change		Not classified	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	No change		Not classified	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	No change		Not classified	Conclusive but not sufficient for classification
2.14.	Oxidising solids	No change		Not classified	Conclusive but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.15.	Organic peroxides	No change		Not classified	Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	No change		Not classified	Conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	No change (Acute Tox. 4* H302)		Acute Tox. 4* H302	
	Acute toxicity - dermal	No change		Not classified	Conclusive but not sufficient for classification
	Acute toxicity - inhalation	No change (Acute Tox. 4* H332)		Acute Tox. 4* H332	
3.2.	Skin corrosion / irritation	No change		Not classified	Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	No change		Not classified	Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	No change		Not classified	Conclusive but not sufficient for classification
3.4.	Skin sensitisation	No change		Not classified	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	No change		Not classified	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	**Carc. 2 H351**		Not classified	
3.7.	Reproductive toxicity	No change		Not classified	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	No change		Not classified	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	No change		Not classified	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	No change		Not classified	Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	No change		Not classified	Conclusive but not sufficient for classification

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
5.1.	Hazardous to the ozone layer	No change		Not classified	Conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Labelling based on the classification now proposed is shown below.

Signal word: Danger
Hazard pictograms: GHS02, GHS07, GHS08
Hazard statements: H225, H302, H332, H351

Proposed notes assigned to an entry:

None

2. BACKGROUND TO THE CLH PROPOSAL

2.1. History of the previous classification and labelling

PDC was not previously classified for carcinogenicity, as the only supporting data were considered equivocal evidence of cancer from a bioassay conducted by National Toxicology Program (1986), which concluded 'equivocal evidence for carcinogenicity' for female rats based on marginally increased adenocarcinomas in mammary tissue, and 'some evidence of carcinogenicity' in male and female mice based on an increased incidence of hepatocellular neoplasms, primarily adenomas. These results, alone, did not support a classification for cancer. Recent data have reported an increased incidence in nasal tumors in rats following a 2-year inhalation exposure to PDC (Umeda *et al*., 2010). Given the additional evidence, the lowest cancer classification is now supported for PDC (Cat 3 under DSP; Cat 2 under CLP/GHS) as a self-classification.

2.2. Short summary of the scientific justification for the CLH proposal

Oral gavage studies were conducted in F344 rats and B6C3F1 mice by NTP (1986), which reported 'equivocal evidence for carcinogenicity' for female rats based on marginally increased adenocarcinomas in mammary tissue, and 'some evidence of carcinogenicity' in male and female mice based on an increased incidence of hepatocellular neoplasms, primarily adenomas. These results, alone, did not support a classification for cancer. When reviewing the rat and mouse tumor findings reported by NTP, IARC (1999) concluded that 1,2-dichloropropane is not classifiable as to its carcinogenicity to humans (Group 3).

Recently, the toxicity and carcinogenicity of 1,2-dichloropropane (DCP) were examined by inhalation exposure of male and female F344 rats to DCP for 2 years (Umeda *et al.,* 2010). In the 2-year study the DCP concentrations were 80, 200, or 500 ppm (v/v). Two-year exposure to DCP significantly increased incidences of papilloma in the nasal cavity of male and female rats exposed to 500 ppm DCP. In addition, three cases of esthesioneuroepithelioma were observed in the DCP-exposed male rats, without a dose-response relationship and with no such tumors identified in female rats, so it is not clear whether these tumors were treatment-related. Total nasal tumors increased in a concentration-dependent manner. Hyperplasia of the transitional epithelium and squamous cell hyperplasia, both of which were morphologically different from the hyperplasia of the respiratory epithelium observed in the 13-wk exposure study, occurred in a concentration-dependent manner; these lesions are considered to be preneoplastic lesions. Atrophy of the olfactory epithelium, inflammation of the respiratory epithelium, and squamous cell metaplasia were also reported in the 2-year study at all doses. These results demonstrate that DCP is a nasal carcinogen in rats. The additional evidence is considered sufficient to support a self-classification as a DSD Cat 3 carcinogen and as a CLP Cat 2 carcinogen under GHS.

2.3. Current harmonised classification and labelling

2.3.1. Current classification and labelling in Annex VI, Table 3.1. in the CLP Regulation

Classification:

Flam. Liq. 2	H225: Highly flammable liquid and vapour.
Acute Tox. 4 *	H302: Harmful if swallowed.
Acute Tox. 4 *	H332: Harmful if inhaled.

Labelling:

Signal word:	Danger
Hazard pictograms:	GHS02, GHS07, GHS08
Hazard statements:	H225, H302, H332

2.4. Current self-classification and labelling

Currently the applicant, registrant for Propylene Dichloride as a transported intermediate under strictly controlled conditions, applies the proposed self classification and labelling.

2.4.1. Current self-classification and labelling based on the CLP Regulation criteria

Flam. Liq. 2	H225: Highly flammable liquid and vapour
Carc. 2	H351: Suspected of causing cancer.
Acute Tox 4*	H332: Harmful if inhaled.
Acute Tox. 4 *	H302: Harmful if swallowed

Labelling:

Signal word:	Danger
Hazard pictograms:	GHS02, GHS07, GHS08
Hazard statements:	H225, H302, H332, H351

3. JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The addition of classification for carcinogenicity is now proposed:

In the inhalation study (Umeda *et al.*, 2010), papillomas were observed in the nasal cavity of male rats exposed to 200 ppm and male and female rats exposed to 500 ppm DCP. No papillomas were noted in the nasal tissues of male or female rats exposed to 80 ppm or female rats exposed to 200 ppm DCP for 2 years. Although two esthesioneuroepitheliomas were observed in male rats exposed to 80 ppm and one male rat exposed to 200 ppm DCP which the authors considered to be due to DCP exposure, there were no tumors of this type noted in male rats exposed to the highest concentration, 500 ppm, nor were any of these tumors noted in female rats at any exposure level. As the authors stated that there was no effect on survival at any concentration of DCP, and given the lack of an exposure-response relationship for these tumors in male rats and no esthesioneuroepitheliomas in the females, it is unclear whether the esthesioneuroepitheliomas are related to DCP exposure. Inflammation of the respiratory epithelium was seen in all exposed groups. There was no increase in the tumor incidence noted in other tissues. Therefore, the nasal tumors were seen at the site of contact in rat respiratory epithelium that is significantly susceptible to irritation and irritation-based carcinogenicity.

Based on the inhalation cancer bioassay results demonstrating an increased incidence of nasal tumors in rats, PDC is self-classified as a Category 3 carcinogen according to DSD/DPD criteria; this equates with a GHS Category 2 cancer classification under CLP.

Part B – SCIENTIFIC EVALUATION OF THE DATA

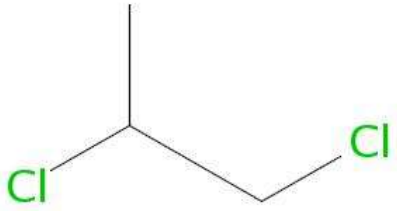
1. IDENTITY OF THE SUBSTANCE

1.1. Name and other identifiers of the substance

Table 4. Substance identity

EC number:	**201-152-2**
EC name:	**1,2-dichloropropane**
CAS number (EC inventory):	**78-87-5**
CAS number:	**78-87-5**
CAS name:	**1,2-dichoropropane**
IUPAC name:	**1,2-dichloropropane**
CLP Annex VI Index number:	**602-020-00-0**
Molecular formula:	**C3H6Cl2**
Molecular weight range:	**112.9857**

Structural formula:



1.2. Composition of the substance

1.2.1. Composition of test material

Table 5. Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
1,2-dichloropropane	ca. 99.9 % (w/w)	> 99.0 — <= 100.0 % (w/w)	

Current Annex VI entry:

Table 6. Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Unspecified impurities, each < 0.1%	ca. 0.1 % (w/w)	> 0.0 — < 1.0 % (w/w)	Impurities are not present at concentra-tions that affect the Classification and Labelling of this substance

Current Annex VI entry:

Table 7. Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

1.3. Physico-chemical properties

Table 8. Summary of physico-chemical properties

Property	Value	Reference	Comment (e.g., measured or estimated)
State of the substance at 20°C and 101,3 kPa	liquid at 20°C and 101.3 kPa Colour: Colourless. Odour: chloroform-like	The Dow Chemcial Company: CoA	
Melting/freezing point	Melting point is -100.4 °C.	Literature	
Boiling point	96.5°C	Literature	
Relative density	1.156 g/cm-3 at 20 °C.	Literature	
Vapour pressure	5.1 kPa at 20 °C	Literature	
Surface tension	0.03 N/m at 20 °C	Literature	The substance, 1,2-dichloropropane, is a low molecular weight organic compound which does not meet the definition of a surface active substance as it has no surface-active properties and does not consist of one or more hydrophilic and one or more hydrophobic groups of such a nature and size that it is capable of reducing the surface tension of water, and of forming spreading or adsorption monolayers at the water-air interface, and of forming emulsions and/or microemulsions and/or micelles, and of adsorption at water-solid interfaces.
Water solubility	2700 mg/L at 20 °C	Literature	The solubility of 1,2-dichloro-propane in water at 20°C is 2500 - 2800 mg/L and the solubility of water in 1,2-dichloropropane at 20°C is 1600 mg/L. 1,2-dichloropropane is soluble (1000 - 10000 mg/L)
Partition coefficient n-octanol/water	is logP = 2.25 by estimation.	Literature	
Solubility in organic solvents / fat solubility	1,2-dichloropropane is soluble in ethanol, diethylether and benzene.	Literature	

Property	Value	Reference	Comment (e.g., measured or estimated)
Flammability	Flammability limits (explosion limits in air) for 1,2-dichloropropane are 3.4 vol% for the lower limit and 14.5 vol% for the upper limit. 1,2-dichloropropane has a low flash point of 13 °C. Therefore 1,2-dichloropropane is classified as highly flammable according to EU criteria.	Literature	
Explosive properties	The substance is non explosive		
Self-ignition temperature	557 °C	Literature	According to DIN 51 794 method.
Oxidising properties	The substance is non oxidizing.		
Granulometry	1,2-dichloroproane is a liquid under normal conditions and is used in a non solid or non granular form.		
Stability in organic solvents and identity of relevant degradation products	1,2-dichloropropane is known to be miscible with and stable in many organic solvents. 1,2-dichloropropane is a known solvent.	Literature	Examination of the structure of 1,2-dichloropropane shows that there are no reactive groups that may give rise to instability of 1,2-dichloropropane in common organic solvents. 1,2-dichloropropane is miscible with most common solvents.
Dissociation constant	Examination of the chemical structure of 1,2-dichloropropane shows that there is no functional group that could dissociate. The substance does not contain both, acidic or basic functional groups. 1,2-dichloropropane is not an ionisable organic substance and as non-ionisable substance will not tend to dissociate in water.		
Viscosity	The dynamic viscosity is 0.85 mPa$_*$s at 20 °C	Literature	

2. MANUFACTURE AND USES

Not relevant for this report.

3. CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this report: no change to the existing harmonized classification in respect of physico-chemical properties is proposed.

4. HUMAN HEALTH HAZARD ASSESSMENT

4.1. Toxicokinetics (absorption, metabolism, distribution, and elimination)

Toxicokinetics are not relevant for this report and are not considered in this dossier.

4.2. Acute toxicity

Acute toxicity is not relevant for this report: no change to the existing harmonized classification is proposed.

4.3. Specific target organ toxicity – single exposure (STOT SE)

No classification in respect of specific target organ toxicity is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.4. Irritation

4.4.1. Skin irritation

No classification in respect of skin irritation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.4.2. Eye irritation

No classification in respect of eye irritation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.4.3. Respiratory tract irritation

No classification in respect of respiratory tract irritation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.5. Corrosivity

No classification in respect of corrosivity is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.6. Sensitisation

4.6.1. Skin sensitisation

No classification in respect of skin sensitization is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.6.2. Respiratory sensitisation

No classification in respect of respiratory sensitisation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.7. Repeated dose toxicity

No classification in respect of repeated dose toxicity is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.8. Germ cell mutagenicity (Mutagenicity)

No classification in respect of mutagenicity is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.9. Carcinogenicity

4.9.1. Non-human information

4.9.1.1. Carcinogenicity: oral

The results of studies on carcinogenicity after oral administration are summarized in the following table:

Table 9. Studies on carcinogenicity after oral administration

Method	Results	Remarks	Reference
rat (Fischer 344) male/female oral: gavage 0 mg/kg/day (nominal conc.) 62 mg/kg/day (only male) (nominal conc. (target concentration: 21 mg/l, analytical concentration: 20 mg/l (mean)) 125 mg/kg bwt/day (male and female) (nominal conc. (target concentration: 42 mg/l, analytical concentration: 41.6 mg/l (mean)) 250 mg/kg bwt/day (only female) (nominal conc. (target concentration: 83 mg/l, analytical concentration: 83.1 mg/l (mean)) Exposure: 103 wk (5 d/wk) equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies)	NOEL (carcinogenicity): 125 mg/kg bw/day (male) (based on overall effects) dose level: (carcinogenicity): 250 mg/kg bw/day (female) (Based on female rats, there was equivocal evidence of carcinogenicity in that 250 mg/ kg/day 1 ,2-dichloropropane caused a marginally increased incidence of adenocarcinomas in the mammary gland; these borderline malignant lesions occurred concurrent with decreased survival and reduced body weight gain.) Neoplastic effects: yes	1 (reliable without restriction) key study experimental result Test material (EC name): 1,2-dichloropropane	National Toxicology Program (NTP) (1986a)
mouse (B6C3F1) male/female oral: gavage 0 mg/kg/day (nominal conc.) 125 mg/kg/day (nominal conc. (target concentration: 42 mg/l, analytical concentration: 41.6 mg/l (mean)) 250 mg/kg/day (nominal conc. (target concentration: 83 mg/l, analytical concentration: 83.1 mg/l (mean)) Exposure: 103 wk (5 d/wk) equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies)	dose level: (carcinogenicity): 250 mg/kg bw/day (male/female) (Based on some evidence of carcinogenicity for male and female B6C3F1 mice exposed to 1,2-dichloropropane, as indicated by increased incidences of hepatocellular neoplasms, primarily adenomas) Neoplastic effects: yes	1 (reliable without restriction) key study experimental result Test material (EC name): 1,2-dichloropropane	National Toxicology Program (NTP) (1986a)

4.9.1.2. Carcinogenicity: inhalation

The results of studies on carcinogenicity after inhalation exposure are summarized in the following table:

Table 10. Studies on carcinogenicity after inhalation exposure

Method	Results	Remarks	Reference
rat (Fischer 344/DuCrj) male/female inhalation: vapor (whole body) 0 (clean air control), 80, 200, or 500 ppm (nominal conc.) 80.2 ± 0.5, 200.5 ± 1.3, and 500.2 ± 2.4 ppm for the three exposed groups. (analytical conc.) Exposure: 6 hours/day (5 days/week for 104 weeks) Publication does not state whether any guidelines were followed. Animals were exposed to test material for 2 years. Animals were weighed weekly for the first 14 weeks and then every 4 weeks thereafter. Blood was obtained for hematology and clinical chemistry determinations (specific tests not stated in publication) at necropsy. A complete gross necropsy was performed and histopathological examination of tissues conducted (only nasal tissues specified in methods section of publication although results from other tissues were reported in the results section).	NOEC (carcinogenicity): 80 ppm (nominal) (male) based on: test mat. (No papillomas were noted in the nasal tissues of male rats exposed to 80 ppm DCP for 2 years. Although two esthesioneuroepitheliomas were observed in male rats exposed to 80 ppm and in one male rat exposed to 200 ppm DCP, there were no tumors of this type noted in male rats exposed to the highest concentration, 500 ppm, nor any such tumors in females at any concentration. As the authors stated that there was no effect on survival at any concentration of PDC, and given the lack of an exposure-response relationship for these tumors in male rats and no esthesioneuroepitheliomas in the females, it is unclear whether the esthesioneuroepitheliomas are related to PDC exposure.) NOEC (carcinogenicity): 200 ppm (nominal) (female) based on: test mat. (No papillomas were noted in the nasal tissues of female rats exposed to 200 ppm DCP for 2 years.) LOEC (toxicity): 80 ppm (nominal) (male/female) based on: test mat. (Histopathological changes and inflammation were noted in the nasal tissue of rats exposed to 80 ppm, the lowest concentration examined.)	2 (reliable with restrictions) key study experimental result **Test material (EC name): 1,2-dichloro-propane** Form: liquid	Umeda, Y., Matsumoto, M., Aiso, S., Nishizawa, T., Nagano, K., Arito, H., Fukushima, S. (2010)

Method	Results	Remarks	Reference
	Neoplastic effects: yes (Microscopic examination revealed that 2-year inhalation exposure to DCP induced tumors in the nasal cavity.)		

4.9.1.3. Carcinogenicity: dermal

4.9.2. Human information

4.9.3. Other relevant information

4.9.4. Summary and discussion of carcinogenicity

Discussion

The carcinogenic potential of DCP has been investigated in a standard NTP design, long term oral gavage study using male and female animals from two species: F344 rats and B6C3F1 mice (NTP, 1986). Due to poor survival, statistical analysis of tumor incidence was adjusted for survival in both species. No significant or treatment-related increase in tumor incidence was observed in male rats given 0, 62 or 125 mg/kg bw/day for 103 wk. Female rats given 125 or 250 mg/kg bw/day showed a positive trend for mammary adenocarcinoma incidence (adjusted rates: 3%, 5%, 27%), which was increased significantly in the high dose group. These were neither metastatic, anaplastic, nor highly invasive, and were diagnosed by NTP pathologists as highly cellular fibroadenomas (NTP, 1986). Affected high dose females showed a marked decrease in survival (32% alive at study end versus 74%-86% in the control and low dose groups) and a significant reduction (>20%) in body weight, suggesting that 250 mg/kg bw/day was in excess of the Maximum Tolerated Dose for DCP; compromised metabolic, immune, or hormonal status were possible under such conditions (NTP, 1986). It is pertinent that there was no increase in liver tumors despite the occurrence of chronic histopathological changes, including foci of clear change and necrosis. Based on these findings, NTP concluded that there was no evidence for the carcinogenicity of DCP in male rats, while in females given 250 mg/kg bw for 103 wk, there was equivocal evidence of an increased incidence of mammary adenocarcinoma; these were considered borderline malignant lesions by NTP, which occurred concurrently with significantly decreased survival and reduced body weight gain.

In mice, there was a positive trend for liver adenoma (adjusted for survival) in both sexes given 0, 125, or 250 mg/kg bw/day for 103 weeks. Tumor incidences in high dose males (45%) and both groups of treated females (17-19%) were increased significantly relative to the controls (20% in males, 3% in females). The findings in male mice occurred in the presence of hepatocytomegaly and hepatic focal necrosis in both treatment groups. The incidence of liver tumors in female mice was essentially identical in the two treated groups, despite a 2-fold difference in dose. High dose females also showed an increased incidence of thyroid tumors but this was not clearly dose-related (combined follicular cell carcinomas and adenomas, adjusted rates 3%, 0%, or 21% in control, low, and high dose groups), and occurred in the presence of liver changes (hepatocytomegaly, focal necrosis, tumors), which may have affected the metabolic and/or hormonal status of the animals. Body weights (both sexes) were unaffected by treatment, while survival at week 103 was reduced in treated females due to reproductive tract infection (70%, 58% and 52% for control, low and high dose animals; males unremarkable). NTP concluded that there was some evidence of carcinogenicity for DCP in male and female mice, based upon an increased incidence of hepatocellular neoplasms, primarily adenomas (thyroid tumors disregarded). While the mechanism underlying these changes is unknown, the occurrence of histopathological liver lesions in male mice (LOAEL 125 mg/kg bw/day) suggests that chronic target organ toxicity may have played a contributing role in the expression of these benign tumors.

Hepatocellular adenoma is a common finding in control B6C3F1 mice. Historical control data for this lesion from contemporaneous NTP studies conducted to 1995 (corn oil, gavage, 16 studies) returned an incidence of 267/813 (33%) in males (range 14-58%) and 111/809 (14%) in females (range 2-28%) (Analytical Services Inc., 1995). Comparison of this historical control information with findings from the NTP study shows that the control incidence for males and females from this study (20%, 3%, respectively) was lower than the mean historical control data, while the incidence for high dose males (45%) and both treated females groups (17%, 19%) was below the upper bound of the historic control data. Spontaneous biological variation in the control data may therefore have influenced the results of this study. These bioassay data, alone, were not considered sufficient to support classification of DCP as a carcinogen in previous reviews. When reviewing the rat and mouse tumor findings reported by NTP, IARC (1999) concluded that 1,2-dichloropropane is not classifiable as to its carcinogenicity to humans (Group 3).

More recently, the toxicity and carcinogenicity of 1,2-dichloropropane (DCP) were examined by inhalation exposure of male and female F344 rats to DCP for 2 years (Umeda *et al*., 2010). In the 2-year study the DCP concentrations were 80, 200, or 500 ppm (v/v). Two-year exposure to DCP significantly increased incidences of papilloma in the nasal cavity of male and female rats exposed to 500 ppm DCP. In addition, three cases of esthesioneuroepithelioma were observed in the DCP-exposed male rats with no dose-response relationship and none of these tumors found in female rats. Total nasal tumors increased in a concentration-dependent manner. Hyperplasia of the transitional epithelium and squamous cell hyperplasia, both of which were morphologically different from the hyperplasia of the respiratory epithelium observed in the 13-wk exposure study, occurred in a concentration-dependent manner; these lesions can be considered preneoplastic lesions. Atrophy of the olfactory epithelium, inflammation of the respiratory epithelium, and squamous cell metaplasia were also seen in the 2-year study at all doses. Specific lesion frequency, as presented in the publication, is presented in the table below. These results demonstrate that DCP is a nasal carcinogen in rats.

Table 11. Number of rats bearing the selected histopathological lesions of the nasal cavity in the rats exposed by inhalation to DCP or clean air for 2 years

	Male				Female			
Group (ppm)	0	80	200	500	0	80	200	500
Number of animals examined	50	50	50	50	50	50	50	50
Neoplastic lesions								
Papilloma	0	0	3	15##	0	0	0	9##
Esthesioneuoepithelioma	0	2	1	0	0	0	0	0
Total nasal tumors	0	2	4	15##	0	0	0	9##
Pre-neoplastic lesions								
Hyperplasia: transitional epithelium	0	31** [1.1]	39** [1.1]	48** [1.8]	2 [1.0]	21** [1.2]	39** [1.1]	48** [1.5]
Squamous cell hyperplasia	0	2 [1.0]	6* [1.0]	27** [1.1]	0	0	3 [1.0]	20** [1.3]
Total pre-neoplastic lesions	0	31**	39**	50**	2	21**	39**	48**
Non-neoplastic lesions								
Squamous cell metaplasia: respiratory epithelium	5 [1.0]	31** [1.0]	41** [1.0]	49** [1.2]	3 [1.0]	15** [1.0]	37** [1.2]	46** [1.5]
Inflammation: respiratory epithelium	20 [1.0]	35** [1.0]	47** [1.0]	47** [1.2]	10 [1.0]	30** [1.0]	39** [1.0]	40** [1.1]
Atrophy: olfactory epithelium	0	48** [1.1]	50** [1.9]	49** [2.0]	0	50** [1.0]	50** [1.9]	50** [2.0]

***Note*:** The values in brackets indicate the averaged severity grade index of the lesion in affected animals, according to the following equation. [E(grade × number of animals with grade)]/number of affected animals. Grade: "slight" scored as 1, "moderate" as 2, "marked" as 3, and "severe" as 4.
***Significant difference*:** *$p < 0.05$; **$p < 0.01$ by $\chi 2$-test, #$p < 0.05$; ##$p < 0.01$ by Fisher's Exact test T: $p < 0.05$, Tt: $p < 0.01$ by Peto's test.

The NTP studies indicate and IARC concluded in 1987 that PDC is not a direct-acting carcinogen *via* the oral route, that there is equivocal evidence of an increase in mammary tumors in female rats, and that other factors (such as spontaneous biological variation) may have contributed to the increased incidence of mouse liver tumors. However, the more recent chronic inhalation exposure results (Umeda *et al*., 2010) indicate that 1,2-dichloropropane is capable of inducing nasal tumors in rodents.

4.9.5. Comparison with criteria

Classification for carcinogenicity is based on data demonstrating that a substance or a mixture induces cancer or increases its incidence in an exposed population. Induction or increased incidences of benign or malignant tumors in well-conducted experimental studies on animals are also considered evidence that could support a classification as a suspected human carcinogen, unless there is strong evidence that the mechanism of tumor formation is not relevant to humans. Classification is based on strength of evidence and additional considerations (*e.g*., weight of evidence). In certain instances, route-specific classification may be warranted.

Previously available data on the carcinogenicity potential of PDC *via* oral route was assessed by NTP to be 'equivocal' (female rat), 'no evidence' (male rat), or 'some evidence' (mouse liver tumors) of carcinogenicity, and the data were judged inadequate to support a cancer classification. However, chronic PDC exposure by the inhalation route resulted in a significant increase in papillomas in the nasal cavity of rats (200 ppm, males; 500 ppm males and females), with no effect on survival. These data, in conjunction with the previous oral dataset, provide adequate support to classify PDC as a carcinogen. The data on esthesioneuroepitheliomas, together with no effect on survival at any concentration of PDC, and no exposure-response relationship for the few tumors identified in male rats and no esthesioneuroepitheliomas in the females, are unclear as to their possible relationship to PDC exposure.

Based on the inhalation cancer bioassay results demonstrating an increased incidence of nasal tumors in rats, combined with the previous oral data, PDC is self-classified as a Category 3 carcinogen according to DSD/DPD criteria; this equates with a GHS Category 2 cancer classification under CLP.

4.9.6. Conclusions on classification and labelling

Equivocal evidence of an increase in morphologically atypical mammary tumors (adenocarcinoma or highly cellular fibroadenoma) was reported in female rats in the presence of a marked reduction in survival and body weight, while some evidence of an increased incidence of hepatic adenocarcinomas was found in male and female mice relative to concurrent (but not historic) controls in the presence of liver damage and decreased body weight (females only). Overall it is considered that DCP is not a direct-acting carcinogen, that there is equivocal evidence of an increase in mammary tumors in female rats, and that other factors (such as spontaneous biological variation) may have contributed to the increased incidence of mouse liver tumors.

Based on the NTP study, IARC concluded in 1987 that 1,2-dichloropropane is not classifiable as to its carcinogenicity to humans (Group 3).

In the Umeda *et al.* (2010) chronic inhalation exposure study, papillomas were observed in the nasal cavity of male rats exposed to 200 ppm and male and female rats exposed to 500 ppm DCP. No papillomas were noted in the nasal tissues of male or female rats exposed to 80 ppm or female rats exposed to 200 ppm DCP for 2 years. Although two esthesioneuroepitheliomas were observed in male rats exposed to 80 ppm and one male rat exposed to 200 ppm DCP which the authors considered to be due to DCP exposure, there were no tumors of this type noted in male rats exposed to the highest concentration, 500 ppm, nor were any of these tumors noted in female rats at any exposure level. As the authors stated that there was no effect on survival at any concentration of DCP, and given the lack of an exposure-response relationship for these tumors in male rats and no esthesioneuroepitheliomas in the

females, it is unclear whether the esthesioneuroepitheliomas are related to DCP exposure. Inflammation was seen in the respiratory epithelium of all exposed groups. There was no increase in the tumor incidence noted in other tissues. Therefore, the nasal tumors were seen at the site of contact in rat respiratory epithelium that is significantly susceptible to irritation and irritation-based carcinogenicity.

Based on the inhalation cancer bioassay results demonstrating an increased incidence of nasal tumors in rats, PDC is self-classified as a Category 3 carcinogen according to DSD/DPD criteria; this equates with a GHS Category 2 cancer classification.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

The dossier submitter (DS) included three carcinogenicity studies in the CLH report. Two 2-year oral gavage studies, conducted in rats and mice according to OECD Test Guidelines (TG) 451 were reported (NTP, 1986a). In addition, one 2-year inhalation (whole body) rat study (Umeda *et al*. 2010) was included. No test guidelines are reported for the inhalation study. All studies were conducted using 1,2-dichloropropane (DCP).

In the 2-year oral rat study, no significant or treatment-related increase in tumour incidence was observed in male rats given 62 or 125 mg/kg bw/day, while female rats given 125 or 250 mg/kg bw/day showed a positive trend for mammary adenocarcinoma (incidence rates adjusted for survival were 3%, 5% and 27% at 0, 125 and 250 mg/kg, respectively). These tumours consisted of highly cellular fibroadenomas which were not metastatic, anaplastic, or highly invasive, but were significantly increased in the high dose group. High dose females showed a marked decrease in survival and a significant reduction in bodyweight, indicating that the maximum tolerated dose (MTD) was exceeded.

In the 2-year oral mouse study (doses were 0, 125 and 250 mg/kg bw/day for both sexes) incidences of liver adenoma were increased in high dose males (45%) and at both doses in females (17 and 19%, respectively). Control incidences were 20% in males and 3% in females. An increased incidence of thyroid tumours was also observed in females at the high dose (21% compared with 3% in control, 0% in low dose). Liver changes (hepatocytomegaly, focal necrosis) occurred in all treatment groups, which may have affected the metabolic and hormonal state of the animal. In addition, the concurrent control incidence of hepatocellular adenomas was lower than the mean historical control incidence while the highest incidences in the treated mice were below the upper bounds of the historical control incidence (mean 33%, range 14-58% in males; mean 14%, range 2-28% in females).
In the 2-year inhalation rat study (Umeda et al., 2010; concentrations of 0, 80, 200 and 500 ppm (v/v), 50 rats/sex/concentration) there was a clear increased incidence of nasal papillomas in the highest dose groups of both sexes. Three cases of olfactory esthesioneuroepitheliomas were also seen in males exposed to 80 and 200 ppm. Concentration-dependent increased incidences in hyperplasia of the transitional epithelium and in squamous cell hyperplasia were also seen in both sexes, as well as atrophy of the olfactory epithelium, inflammation of the respiratory epithelium and squamous cell metaplasia. A summary of neoplastic and non-neoplastic lesions reported in Umeda *et al*. (2010) is provided in the table below.

Non-neoplastic, pre-neoplastic and neoplastic lesions in the rat inhalation study by Umeda et al (2010).

	male				**female**			
Dose (ppm)	**0**	**80**	**200**	**500**	**0**	**80**	**200**	**500**
Squamous cell metaplasia: respiratory epithelium	5	31**	41**	49**	3	15**	37**	46**
Inflammation: respiratory epithelium	20	35**	47**	47**	10	30**	39**	40**

Atrophy: olfactory epithelium	0	48**	50**	49**	0	50**	50**	50**
Hyperplasia: transitional epithelium	0	31**	39**	48**	2	21**	39**	48**
Squamous cell hyperplasia	0	2	6*	27**	0	0	3	20**
Papilloma	0	0	3	15*	0	0	0	9*
Esthesioneuroepitheliomas	0	2	1	0	0	0	0	0

*p < 0.05; **p < 0.01

The dossier submitter (DS) concluded, in agreement with an IARC evaluation (1987), that the oral studies show either equivocal (female rats), none (male rats) or some (mice) evidence of carcinogenicity, and as a consequence are inadequate for classification. However, the 2-year inhalation study in rats clearly demonstrated that DCP is a nasal carcinogen in rodents. The DS however considered it unclear whether the three cases of olfactory esthesioneuroepitheliomas in males only without a clear dose relationship were related to DCP exposure. However, based on the increased incidence of nasal papillomas in male and female rats, the DS proposed that DCP should be classified as Carc. 2 – H351 under CLP.

Comments received during public consultation

Comments were received from one company and three member state competent authorities (MSCA). The company submitted an independent review of the 2-year inhalation rat study, agreeing with the conclusions reached by the DS. Both the commenter and the DS were in agreement that the exact mechanism of nasal tumour formation remains unclear and that the limited details in the published report do not enable the mechanism of action (MoA) to be determined.

The three commenting MSCAs requested more detailed reporting on the studies used for classification as well as more firm argumentation for the classification proposal. In addition, they requested information on repeated dose toxicity and mutagenicity as supporting information.

In response, the DS included a more thorough review of the carcinogenicity studies in the RCOM as well as evaluation of a newly published mouse 2-year inhalation carcinogenicity study on DCP (Matsumoto *et al*., 2013), indicating statistically significantly increased incidences of combined bronchiolo-alveolar adenomas/carcinomas in females exposed to the highest concentration only (200 ppm) and in males exposed to 32 and 200 ppm but with no apparent dose-response relationship. Despite some positive *in vitro* mutagenicity tests, the DS concluded that DCP is non-genotoxic, mostly based on negative *in vivo* data. A review of repeated dose toxicity studies is also included in the RCOM by the DS.
One MSCA commented that human data, indicating bile duct cancer as a result of exposure to DCP, are available from the Japanese Ministry of Health, Labour and Welfare (2013). The DS responded that while biliary duct cancers were observed in workers, co-exposure to other carcinogens and confounding factors such as smoking did not allow for firm conclusions to be made.

One commenting MSCA disagreed with the proposed classification and stated that the data support classification as at least Carc. 1B – H350, while the other two commenting MSCAs stated that the data reported in the CLH report do not allow for a conclusion. The DS noted in the RCOM that they maintained their proposal of Carc. 2 – H351.

Additional key elements

<u>Repeated dose toxicity</u>
In a 13 week inhalation study, 10 F344/DuCrj rats/sex/concentration were exposed to 0, 125, 250, 500, 1000, and 2000 ppm DCP for 6 hours/day, 5 days/week (Umeda *et al*., 2010). One female of the 2000 ppm dose group died during the study. Growth rates were suppressed at ≥ 1000 ppm. Anaemia was seen in rats of both sexes exposed to ≥ 500 ppm.

Relative spleen weights were significantly increased in males and females at 2000 ppm. Absolute and relative liver weights were significantly increased in females exposed to ≥ 500 ppm. In the nasal cavity, hyperplasia of the respiratory epithelium and atrophy of the olfactory epithelium occurred in both sexes at ≥ 125 ppm. Inflammation of the respiratory epithelium was significantly increased in male rats exposed to ≥ 1000 ppm. In addition, at 2000 ppm swelling of the liver was observed in both sexes. Increased hemosiderin deposition resulting from hemolysis of erythrocytes was observed in the spleen of male rats exposed to ≥ 1000 ppm and female rats exposed to ≥ 500 ppm.

In a subchronic inhalation study (Matsumoto *et al*., 2013, conducted according to the authors in accordance with OECD TG 413), BDF1/Crlj (SPF) mice (10/sex/dose) were exposed to DCP at 0 (clean air control), 50, 100, 200, 300 or 400 ppm (v/v) for 6 h/day, 5 days/week for 13 weeks. Six males and one female from 400 ppm group and two males from 300 ppm groups died during the study. Growth rates were suppressed dose-dependently reaching statistical significance in males exposed to ≥ 200 ppm (9-18% lower than control); no growth retardation was reported for females. The absolute and relative liver weights were significantly increased in both sexes exposed to ≥ 300 ppm DCP. The relative spleen weights were significantly increased in both sexes at 400 ppm. Platelet counts increased in males exposed to ≥ 300 ppm and in high dose females. Anaemia was seen in all DCP-treated male mice, and in ≥ 300 ppm treated females. Respiratory metaplasia, atrophy and necrosis of the olfactory epithelium occurred in both sexes exposed to ≥ 300 ppm DCP. Desquamation of the olfactory epithelium occurred in all dead males at 400 ppm. Hyperplasia in the forestomach was significantly increased in 400 ppm dose males and ≥ 300 ppm dose females. Histopathological changes in liver of male and female mice exposed to ≥ 300 ppm DCP were reported, including swelling and necrosis of centrilobular hepatocytes. In addition, as a consequence of anaemia, increased extramedullary hematopoiesis was observed in males exposed to 400 ppm and females exposed to ≥ 300 ppm. Hemosiderin deposition and increases in megakaryocyte numbers were significant at 400 ppm.

In a subchronic inhalation study (Dow, 1988, conducted according to OECD TG 413), B6C3F1 mice (0, 150, 500 and 1000 ppm), F344 rats and NZW rabbits (both 0, 100, 300 or 1000 ppm) were exposed to DCP. Body weight gains of rats exposed to DCP (all levels) were lower compared to controls. The olfactory mucosa of the nasal turbinates in rats was affected at all exposure levels. Male and female mice exposed to 300 ppm DCP had increased liver weights and decreased thymus weights. Some mice exposed to 100 and 300 ppm DCP showed degenerative changes in the olfactory mucosa. Male rabbits exposed to 1000 ppm DCP presented equivocal degenerative changes in the olfactory mucosa.

Mutagenesis

Microbial tests in bacteria and fungi have shown mixed outcomes. In mammalian cells *in vitro*, a thymidine kinase assay was negative in absence of liver activation (S9), but positive in the presence of S9 at concentrations around the toxicity threshold. In Chinese hamster ovary (CHO) cells in culture, DCP induced sister chromatid exchanges (SCE) and chromosomal aberrations. DCP did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. *In vivo*, a micronucleus study in mice was negative, as well as a dominant lethal study in rats.

Carcinogenesis

In a 2-year inhalation study (Matsumoto *et al*., 2013; conducted according to the authors in accordance with OECD TG 451), BDF1/Crlj (SPF) mice (50/sex/dose) were exposed to DCP at 0 (clean air control), 32, 80, or 200 ppm (v/v) for 6 h/day, 5 days/wk for 104 weeks. There was no significant effect on survival or body weight. A statistically significant increase in combined bronchiolo-alveolar adenomas/carcinomas was observed in high dose females and low and high dose males. In females the increase in lung neoplasms was dose-dependent whereas in males, no dose-response was seen. Incidences of combined

bronchiolo-alveolar adenomas/ carcinomas exceeded JBRC historical control ranges (not given). No increase was observed in pre-neoplastic bronchiolo-alveolar hyperplasia. In the nasal cavity, atrophy in the olfactory epithelium was increased in males and females exposed at ≥ 80 ppm. Respiratory metaplasia in the olfactory epithelium was significantly increased in both sexes at the highest concentration tested whereas the metaplasia located in the submucosal gland was increased at the top dose in females only. In males, the incidence of benign Harderian gland adenomas of the eye was increased in a dose-dependent manner. Although the increase was not statistically significant, the incidence at the high concentration exceeded the maximum incidences of the JBRC historical control data (ranges not given). The incidence of spleen hemangiosarcomas was significantly increased in high dose males, but the incidences were within JBRC historical control data. A summary of neoplastic, pre-neoplastic and non-neoplastic lesions from Matsumoto et al. (2013) is provided in the table below.

Tumour incidence in the inhalatory mouse bioassay.

	male (%)				Female (%)			
Dose (ppm)	0	32	80	200	0	32	80	200
Atrophy: olfactory epithelium	1	1	19**	20**	8	8	19*	16
Respiratory metaplasia: olfactory epithelium	19	27	23	21	32	14**	34	44**
Respiratory metaplasia: submucosal gland	9	13	12	18*	16	11	13	43**
Bronchiolo-alveolar hyperplasia	2	5	5	1	3	2	4	2
Bronchiolo-alveolar adenoma	5	14*#	9	12#	1	4	4	4
Bronchiolo-alveolar carcinoma	4	6	6	8	1	1	1	4
Bronchiolo-alveolar adenoma/carcinoma combined	9	18*#	14	18*#	2	4	5	8*#
Harderian gland adenoma	1	2	3	6#	2	2	2	2
Spleen hemangiosarcoma	0	3	3	5*	2	0	0	0

*p < 0.05; **p < 0.01; # > JBRC historical control range

Human data carcinogenesis

Several cases of cholangiocarcinoma were reported among employees of a printing firm in Japan that has around 70 employees, of which 30 regularly work in the printing room. The standardised incidence ratio (the ratio of the observed number of cancer cases to the expected number of cases multiplied by 100) of the workers in the printing plant in Osaka was 1226 (95% CI: 714-1963). The background incidence of cholangiocarcinomas worldwide is 0.1-85/100.000, the background incidence in Osaka is 3.4/100.000 (Bragazzi *et al*., 2012). Out of 16 cases, all were exposed to DCP from March 1991 to October 2006. Eleven were also exposed to dichloromethane used from April 1991 to August 1996. The cases could not be linked to chronic biliary inflammation, chronic hepatitis or malfunction of the pancreaticobiliary ducts, which are important risk factors for the induction of cholangiocarcinomas. All 13 cases of which pathology specimens were available were adenocarcinomas.

Experiments performed by the National Institute for Occupational Safety and Health, Japan (JNIOSH) showed that the airborne concentration of DCP at the printing plant reached values three to eight times higher than the TLV-TWA (threshold limit value – time weighted average). The Biliary Cancer Investigation Team from the Japanese Ministry of Health, Labour and Welfare (2013) concluded that, considering the fact that all 16 cases used to be exposed to 1,2-dichloropane, it was highly probable that the biliary tract cancer was caused

by the long-term exposure to high concentrations of DCP (Biliary cancer investigation team, 2013). In 2013, three additional cases were added from the same plant. In Japan, there are currently 83 claims filed on biliary tract cancer at printing plants. Of these claims, 29 were concluded to be work-related, 22 were denied (Ministry of Health, Labour and Welfare, 2014).

Assessment and comparison with the classification criteria

Human data

Several cases of cholangiocarcinoma are reported among employees of printing firms in Japan. According to the dossier submitter, co-exposure to other carcinogens and confounding factors such as smoking did not allow for firm conclusions. However, 5 out of 11 cases were not exposed to dichloromethane, which is the most likely other carcinogen to which workers were exposed. Dichloromethane is metabolised via reactive and probably genotoxic glutathione conjugates (Anders, 2004). DCP is also metabolised via glutathione conjugation, with three cysteine-conjugates identified in rat urine (ATSDR, 1989). It has been shown that there is more glutathione S-tranferase (GSTT1) in the human biliary tract than in the human liver (Sherratt *et al*., 2002) and it could be speculated that a higher formation of reactive intermediates in the biliary tract of humans is the cause of the biliary tract tumours of humans.

In addition, although there are no data on confounding factors as smoking, the incidence at the printing plant in Osaka is very high: 15-20 cases that were exposed in a 15-20 year time-frame at a firm with only 70 employees, of which only 30 were frequently exposed. RAC therefore agrees with the Japanese Ministry of Health, Labour and Welfare that it is likely that the cases of bile duct cancer are related to exposure to DCP.

Animal experiments

Two oral 2-year (gavage in corn oil) carcinogenicity studies are available, one in rats and one in mice (NTP, 1986). In addition, two 2-year) carcinogenicity studies with inhalation exposure are available, one in rats (Umeda *et al.* 2010) and one in mice (Matsumoto *et al*. 2013). The table below summarises the neoplastic lesions seen in animal experiments.

Tumour incidence rates in rat and mouse bioassays*

	Dose				**HC (DS)**
RAT 2-year oral study	**0 mg/kg bw**	**125 mg/kg bw**	**250 mg/kg bw**		
♀ Mammary					Historical control data only limitedly available (see text)
Adenocarcinomas					
overall rates	2%	4%	10%		
adjusted rates	3%	5%	**27%**		
terminal rates	3%	5%	***25%***		
MOUSE 2-year oral study	**0 mg/kg bw**	**125 mg/kg bw**	**250 mg/kg bw**		
♂ Hepatocellular					
Adenoma overall rates	*14%*	*20%*	***34%***		14-58%
adjusted rates	20%	29%	**45%**		*(21-58%)*
terminal rates	*20%*	*27*	***43%***		
carcinoma overall rates	*22%*	*34%*	*32%*		*7-38%*
adjusted rates	*28%*	*42%*	*37%*		
terminal rates	*23%*	*30%*	*26%*		
combined overall rates	*36%*	*52%*	***66%***		*25-72%*

adjusted rates	*47%*	*63%*	***75%***		
terminal rates	*43%*	*55%*	***69%***		
♀ Hepatocellular					
Adenoma overall rates	*2%*	*10%*	*10%*		2-28% (*6-40%*)
adjusted rates	3%	17%	19%		
terminal rates	*3%*	*17%*	*19%*		
carcinoma overall rates	*2%*	*6%*	*8%*		*0-22%*
adjusted rates	*3%*	*10%*	*13%*		
terminal rates	*3*	*7%*	*8%*		
combined overall rates	*4%*	***16%***	***18%***		*8-58%*
adjusted rates	*6%*	***26%***	***31%***		
terminal rates	*6%*	***24%***	***27%***		
RAT 2-year inhalation study	**0 ppm**	**80 ppm**	**200 ppm**	**500 ppm**	
♂ Nasal					
Papilloma	0%	0%	6%	**30%**	
esthesioneuroepithelioma	0%	4%	2%	0%	
♀ Nasal					
Papilloma	0%	0%	0%	**18%**	
MOUSE 2-year inhalation study	**0 ppm**	**32 ppm**	**80 ppm**	**200 ppm**	
♂ Lung					
bronchiolo-alveolar adenoma	*10%*	***28%***	*18%*	*24%*	*exceeded*
bronchiolo-alveolar carcinoma	*8%*	*12%*	*12%*	*16%*	*within*
combined	*18%*	***32%***	*28%*	***36%***	*exceeded*
♀ Lung					
bronchiolo-alveolar adenoma	*2%*	*8%*	*8%*	*8%*	
bronchiolo-alveolar carcinoma	*2%*	*2%*	*2%*	*8%*	*within*
combined	*4%*	*8%*	*10%*	***16%***	*exceeded*
♂ Harderian gland					
adenoma	*2%*	*4%*	*6%*	*12%*	*exceeded*
♂ Liver					
Histiocytic sarcoma	*1%*	*4%*	***7%***	*0%*	
♂ Spleen					
hemangiosarcoma	*0%*	*6%*	*6%*	***10%***	*within*

* Not all incidences are included in the background dossier. Incidences in italic are included by RAC and derived from original publications: NTP 1986a and Matsumoto 2013.
Historical control values indicated by the DS are from contemporaneous NTP studies conducted until 1995. Historical control values for the oral rat studies included by RAC are from NTP studies conducted until 1999 (NTP 2012)
Numbers in bold indicate statistical significance ($p<0.05$)

Oral exposure in rats

In male rats, no evidence of carcinogenicity was seen upon oral exposure to DCP. In female

rats, a positive trend for mammary adenocarcinoma incidence was observed, which was increased significantly in the high dose group. The tumours were not metastatic, anaplastic or highly invasive. According to the NTP report, some pathologists diagnosed these tumours as highly cellular fibroadenomas. The incidence of fibroadenomas, which is generally high in F344 rats, was reduced at the highest dose level in this study. Comparison with historical control data is not possible as only three additional studies are available from the same laboratory (3 cases of adenocarcinomas in 150 females) and mammary adenocarcinoma are not present in the NTP historical background database. Since the high dose clearly exceeded the maximum tolerated dose (survival only 32% and a significant reduction of 14% in bodyweight), the relationship between mammary adenocarcinomas and DCP exposure is at best equivocal. Therefore, the RAC agree with the DS that the results of this study are not sufficient for classification.

Oral exposure in mice
In mice, statistically significant increased incidences of liver adenomas were observed in the high dose group in males. In females (low and high dose), increased incidences of liver adenomas were also observed, but these were not statistically significant. Incidences of adenomas and carcinomas combined were significantly increased in females and in high dose males. Liver changes (hepatocytomegaly, focal necrosis) occurred in all treatment groups. Nevertheless, background incidences of hepatocellular adenomas and carcinomas in B6C3F1 mice are high and almost all incidences of liver tumours observed with DCP were within NTP historical control ranges (from several laboratories).
Hence, RAC supports the conclusion of the dossier submitter that the hepatocellular tumours do not warrant classification.

Inhalation exposure in rats
In males and females, nasal papillomas were significantly increased in the high dose group. This dose did not exceed the MTD based on comparable mortality and limited decrease in body weights. In the carcinogenicity study, as well as in a 13 week inhalation study in rats and a 13 week inhalation study in mice, pre-neoplastic and non-neoplastic changes were observed in the nasal cavity (increased hyperplasia of the transitional epithelium and in squamous cell hyperplasia, atrophy of the olfactory epithelium, inflammation of the respiratory epithelium and squamous cell metaplasia). In rats, but not in mice, these changes showed a dose response relationship. Also, in subchronic inhalation studies in rats, mice and rabbits, the olfactory epithelium was affected.
The three cases of esthesioneuroepitheliomas observed in low and high dosed male rats may be related to DCP exposure, although the incidences were not dose-related and only observed in males. Nevertheless, since it is a rare tumour type (no cases in 48 studies involving 2399 male F344 rats) the small increase is considered to be of concern. In view of the effects observed in the repeated dose studies in rat and mice and the carcinogenicity study in rats, RAC concludes, in line with the DS, that DCP is carcinogenic in rats.

Inhalation exposure in mice
In mice an increase in spleen hemangiosarcomas was observed in high dose males. The incidence was within historical control ranges and no effect was observed in females. The hemangiosarcomas may be secondary to the heamolytic anaemia resulting in hemosiderosis in the spleen. Signs of anaemia were clearer in males than in females. RAC concludes that there is no clear direct relationship with DCP. In addition, a dose-dependent increase in adenomas of the Harderian gland was observed in males. Since the increase was not significant and humans do not have a Harderian gland, these tumours are also not considered relevant for classification.
Statistically significant increases in bronchiolo-alveolar adenomas in low dose males and in combined bronchiolo-alveolar adenomas/carcinomas in low and high dose males and high dose females were observed. The response was concentration-dependent in females only. However, significantly increased incidences did exceed historical control ranges. In repeated inhalation studies pre-neoplastic lesions were not reported in the lungs. RAC

concludes that there is some evidence that inhalation exposure to DCP induces bronchiolo-alveolar tumours in mice.

Mechanism

The fact that DCP induces irritation in rats, mice and rabbits following inhalation suggests that the nasal papillomas observed in rats may be secondary to irritation and that the mechanism of action is non-genotoxic. Indeed, findings indicate that propylene dichloride does not induce chromosomal aberrations or germ cell mutations *in vivo*. Nevertheless, it is noted that *in vivo* mutagenicity has not been assessed following inhalation exposure. Furthermore, no signs of irritation were observed in the lungs in any study. It is therefore unlikely that the lung tumours observed in mice are secondary to irritation.
In addition, several positive results were found in bacterial and *in vitro* mutagenicity tests and weak binding to liver DNA has been demonstrated. A genotoxic mode of action can therefore not be excluded based on the available data.

RAC conclusion

According to the CLP criteria a substance should be classified in Category 1A if there is sufficient evidence for carcinogenicity from studies in humans: a positive relationship has to be observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.
A substance should be classified in Category 1B if there is sufficient evidence for carcinogenicity from animal studies. There is sufficient evidence when a causal relationship has been established in animal studies between the agent and an increased incidence of malignant neoplasms or of a combination of benign and malignant neoplasms in at least two species or in two independent studies in one species. Substances may also be classified in Category 1B according to CLP if they produce an increased incidence of tumours in both sexes of a single species in a well-conducted study or if the substance leads to an unusual degree of malignant neoplasms in one species and sex. In addition, classification as 1B may be warranted based on data derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

A substance should be classified in Category 2 if there is only limited evidence for carcinogenicity from animal studies. There is limited evidence when the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

In animal experiments, tumours were observed in all 4 available studies. As explained above, the tumours observed in the oral rat and mouse studies do not warrant classification. In the inhalation studies however, tumours are observed that RAC considers relevant for classification. In rats, benign nasal papillomas were observed in males and females. Although it is possible that these tumours are non-genotoxic and secondary to irritation, a genotoxic mechanism cannot be excluded based on the limited available data. In addition, a small increase (3/50 males) in the incidence of very rare olfactory esthesioneuroepitheliomas was observed which, although not showing a dose response relationship, is of concern. There is no evidence that these tumours and suggested mechanism of action are not relevant for humans. In mice, bronchiolo-alveolar adenomas/carcinomas were observed in males (although not with a dose-response relationship) as well as in females. Although it seems plausible that these tumours are confined to the point of contact with DCP, secondary to irritation, in inhalation exposure studies (subchronic and chronic) pre-neoplastic lesions were not reported in the lung. Also for these tumours, a genotoxic mechanism cannot be excluded.

Thus, since there is an increased incidence of a combination of benign and malignant neoplasms in both sexes of one species in a well-conducted study, together with an increased incidence in benign tumours in two sexes of another species and a small increase in a rare tumour type (olfactory esthesioneuroepitheliomas) in male rats, RAC concludes that there is sufficient evidence for carcinogenicity in animals, resulting in classification as Carc. 1B; H350.

As to human data, several cases of cholangiosarcomas are reported in employees of a Japanese printer firm. Although it is likely that these tumours are related to DCP exposure, human data are only limited and a well performed epidemiological study also analysing confounding factors is not available. Therefore, Carc. 1A is excluded. Yet, the indications in humans are so strong that they support classification as Carc. 1B. The tumour types are different to those observed in animals. This might be due to differences in toxicokinetics, exposure length or tumour latency in humans and animals; however, there are no data that can further explain these differences.

Both due to the strong indications in humans and the evidence in animals (nasal and lung tumours), RAC concludes that DCP is presumed to have carcinogenic potential for humans and should therefore be classified as Carc. 1B; H350 under CLP.

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4.10. Toxicity for reproduction

No classification in respect of toxicity to reproduction is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.11. Other effects

No classification in respect of other effects is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

5. ENVIRONMENTAL HAZARD ASSESSMENT

No classification in respect of environmental hazard is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

6. OTHER INFORMATION

Not relevant for this dossier.

7. REFERENCES

(All data sources relevant to the proposed classification change are detailed in the associated IUCLID file, submitted with this report.)

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8. NO ANNEXES