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

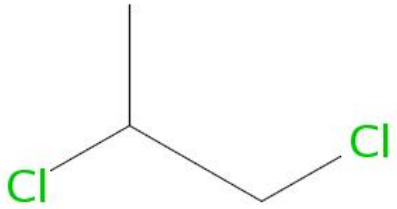
1. IDENTITY OF THE SUBSTANCE

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 χ2-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.

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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.National Toxicology Program (NTP) (1986a). Toxicology and Carcinogenesis studies of 1,2-dichloropropane (Propylene dichloride) (CAS No 78-87-5) in F344/N rats and B6C3F1 mice (gavage studies). NTP Technical Report Series No 263, NIH Publication No 86-2519.

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8. NO ANNEXES