Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,2-Dichloropropane; Propylene dichloride

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

CLH-O-0000004490-79-03/F

Adopted

4 June 2014

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4 June 2014

CLH-O-0000004490-79-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: **1,2-Dichloropropane;**
Propylene dichloride

EC number: **201-245-8**

CAS number: **80-05-7**

The proposal was submitted by **Germany** and received by the RAC on **28 October 2013.** All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **8 November 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **23 December 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Betty Hakkert**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 June 2014** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion on **1,2-Dichloropropane** that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	602-020-00-0	1,2-dichloropropane; propylene dichloride	201-152-2	78-87-5	Flam. Liq. 2 Acute Tox. 4 * Acute Tox. 4 *	H225 H332 H302	GHS02 GHS07 Dgr	H225 H332 H302		
Dossier submitters proposal	602-020-00-0	1,2-dichloropropane; propylene dichloride	201-152-2	78-87-5	**Add:** Carc. 2	**Add:** H351	**Add:** GHS08	**Add:** H351		
RAC opinion	602-020-00-0	1,2-dichloropropane; propylene dichloride	201-152-2	78-87-5	**Add:** Carc. 1B	**Add:** H350	**Add:** GHS08	**Add:** H350		
Resulting Annex VI entry if agreed by COM	602-020-00-0	1,2-dichloropropane; propylene dichloride	201-152-2	78-87-5	Flam. Liq. 2 Carc. 1B Acute Tox. 4 * Acute Tox. 4 *	H225 H350 H332 H302	GHS02 GHS08 GHS07 Dgr	H225 H350 H332 H302		

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

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.

Assessment and comparison with the classification criteria

<u>Human data</u>
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.

<u>Animal experiments</u>
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%*		*0-22%*
carcinoma overall rates	*2%*	*6%*	*8%*		
adjusted rates	*3%*	*10%*	*13%*		
terminal rates	*3*	*7%*	*8%*		*8-58%*
combined overall rates	*4%*	***16%***	***18%***		
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**	

	Dose				HC (DS)
♂ 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.

ADDITIONAL REFERENCES

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ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).