Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

1,2-Dichloropropane

ECHA/RAC/OEL-O-0000007250-84-01/F

16 March 2023

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR 1,2-Dichloropropane

Commission request

The Commission asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some carcinogenic chemical substances, in support of the preparation of proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens mutagens or reprotoxic substances at work (CMRD)[1].

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for 1,2-dichloropropane with a deadline of 22 February 2024.

Chemical name(s): 1,2-Dichloropropane (EC number 201-152-2)

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values at the workplace. This scientific report was made available at: Occupational exposure limits-Consultations on OEL recommendation on **19 October 2022** and interested parties were invited to submit comments by **19 December 2022**.

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to ensure alignment.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Andrea Hartwig.**

The opinion was adopted by **consensus** on **16 March 2023**.

RAC Opinion of the assessment of the scientific relevance of OELs for 1,2-dichloropropane (1,2-DCP)

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for 1,2-dichloropropane (hereafter 1,2-DCP; EC number 201-152-2) is set out in the tables below and in the following summary of the evaluation, supported by Annex 1.

1,2-DCP is considered to be a non-threshold carcinogen.

Consequently, no health-based occupational exposure limit (OEL) nor a short term exposure limit (STEL) can be identified. Instead, RAC derived an exposure-risk-relationship (ERR) expressing the excess cancer risk in function of the air concentration of 1,2-DCP.

SUMMARY TABLE

The tables present the outcome of the RAC evaluation to derive limit values, notations and exposure-risk-relationsships for 1,2-DCP.

Derived Limit Values

OEL as 8-hour TWA:	None
STEL:	None
BLV:	None
BGV:	None

Notations

Notations:	Skin

Cancer exposure-risk relationships (ERR)*

1,2-DCP concentration in air (mg/m³)	1,2-DCP concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.028	0.0059	4
0.28	0.059	40
2.8	0.59	400
28	5.9	4000

* Assuming an 8-hour exposure per day and 5 days per week, over a 40-year working life

RAC notes that the European Commission and its Advisory Committee on Safety and Health at the workplace (ACSH) aim to set limit values for non-threshold carcinogens between predetermined upper and lower risk levels. ACSH (2022) agreed in its opinion that the upper risk level is 4:1 000 (corresponding to 4 predicted cancer cases in 1 000 employees), that the lower risk level is 4:100 000, assuming exposure over 8 hours per day, 5 days a week over a 40-year working lifetime and concluded that "*The OEL cannot be set above the risk level of 4:1 000*".

Since 1,2-DCP is considered to be a non-threshold carcinogen, it is not possible to derive a safe level for a biological limit value (BLV). Also, no correlations between biomonitoring and air levels can be derived.

No biological guidance value (BGV) can be stated. Even though in animal studies, S-(2-hydroxypropyl)mercapturic acid (2-HPMA) has been described as a main metabolite of 1,2-DCP, and background values of 2-HPMA acid in human urine are sufficiently well known, this marker is not specific, since it is also a metabolite of several other substances.

Accidental dermal exposure to a paint containing 1,2-DCP caused significant renal and hepatic function effects in the exposed person. Therefore, marked systemic uptake via the skin needs to be considered, and a 'skin' notation is proposed.

RAC OPINION

Background

This opinion on 1,2-DCP is based on Annex 1, which includes international assessments such as ATSDR (2021), EPA (2016), Hartwig and MAK Commission (2022), IARC (2017), OECD (2006). A literature search of published papers from the last ten years completed the source of information (date of last literature search: October/2022).[1] Databases used were last accessed: October/2022

Key conclusions of the evaluation

- 1,2-DCP has a harmonised classification as Carcinogen category 1B.
- Workplace exposure to 1,2-DCP occurs mainly by inhalation via the respiratory tract, but also via skin upon dermal contact. In addition, systemic toxicity effects in humans after ingestion show that absorption of 1,2-DCP also occurs through the gastrointestinal tract.
- Animal studies show that 1,2-DCP is rapidly and nearly completely absorbed after oral and inhalation exposure and distributed to the whole body. Mainly in the liver, 1,2-DCP is rapidly metabolized via CYP2E1 oxidation. 1,2-DCP and its metabolites are excreted via urine (37-65% of the dose) and exhaled air (18-40% of the dose) extensively within one day after a single exposure. After oral exposure, a small amount was also detected in the faeces.
- In exposed workers in the plastics and paint industries as well as in printing workers, air concentrations were correlated with the urine content of 1,2-DCP.
- According to clinical case reports with largely unknown exposure levels, acute poisonings in humans have been observed after oral, dermal and inhalation exposure to 1,2-DCP in occupational, accidental and domestic settings, involving exposures to 1,2-DCP-containing solvents and also after sniffing such solvents. In some cases also concomitant exposure to other solvents occurred. The observed toxic effects have included liver and kidney damage, intravascular coagulation, haemolytic anaemia and various central nervous system symptoms. Fatal cases have been described following oral and inhalation exposure. In one occupational non-fatal case retrospective industrial hygiene measurements indicated 8-hour TWA levels of 8–42 ppm and 15-minute levels of 50–77 ppm based on three and two measurements, respectively. Available acute toxicity animal studies on 1,2-DCP indicate a comparatively low acute toxicity via all routes of exposure.
- The most relevant health effect after chronic exposure to 1,2-DCP is carcinogenicity. Workers in printing plants in Japan who carried out cleaning operations with 1,2-DCP developed cholangiocarcinomas (CCA; bile duct /biliary tract cancer) with a

[1] All references are listed at the end of the report.

standardized incidence ratio (SIR) increased by more than a factor of 1000 compared to the general population. Tumour tissue from affected printers exhibited specific mutation patterns compared to bile duct tumour tissue from unaffected patients. In rats, after thirteen weeks of inhalation exposure, nasal irritation effects occurred starting from 71 ppm and nasal tumours after two years of exposure to 500 ppm. In mice, after two years of exposure, adenomas in the lungs occurred at 32 ppm.

- Due to the specific mutations detected in CCA in exposed workers, 1,2-DCP is considered as a non-threshold carcinogen.
- There are no human data on longer-term 1,2-DCP exposure and non-cancer chronic disease. Therefore, due to the lack of such quantitative data, the exposure-risk-relationship (ERR) is derived from animal experiments. **Since the human tumour type and location is not mirrored in the experimental animals, the ERR contains significant uncertainties, which may lead to an underestimation of human cancer risk.**
- Repeated dose toxicity of 1,2-DCP in animals has been examined in oral and inhalation studies with durations from a few days to 2 years. Adverse health effects were observed mainly in the liver and in the respiratory tract. The most sensitive endpoint was nasal hyperplasia, starting at 15 ppm (70.5 mg/m^3) in a 13-week rat inhalation study. Liver toxicity was observed in mice after 13 weeks of exposure starting from 300 ppm.
- Based on the available data reproductive toxicity does not appear to be relevant at realistic exposure conditions. Even though delays in skeletal development were observed in rats and rabbits, effects were restricted to dose levels with concurrent maternal toxicity. Teratogenic effects were not detected in either species. No effects on sexual function and fertility were observed in a 2-generation study in rats.
- There are no reliable data available relating to possible sensitizing effects induced by 1,2-dichloropropane.
- No correlations between biological and air levels can be derived from the available data. Even though there are some methods available to measure urinary levels of 1,2-DCP, showing best results without creatinine correction, respective correlations have been reported only for higher air concentrations of 1,2-DCP (> 1 ppm), which would correspond to an excess life-time cancer risk of > 1% (for details see Annex 1, section 6.2.2). No BLV is proposed.
- Also, no BGV can be stated. Even though the background value of 2-HPMA acid in human urine is sufficiently well known, due to the non-specificity of this parameter, a BGV for 1,2-DCP is not proposed.
- A skin notation is proposed. Even though no quantitative data are available, accidental dermal exposure to a paint containing 1,2-DCP caused significant renal and hepatic function effects in the exposed person, indicating significant systemic toxicity due to uptake via the skin. This is also supported by the physico-chemical properties of the substance.

Carcinogenicity and Mode of action considerations (see sections 7.6, 7.7 and 8.1 of Annex 1 for full discussion)

Epidemiological evidence

A number of publications and a report prepared by the Japanese government investigated a cluster of CCA found in printing workers in Japan (IARC, 2017; Hartwig and MAK Commission, 2022). In Japan, CCA is a rare form of tumour with a mean age of onset of 66.5 years for intrahepatic tumours and 68.9 years for extrahepatic tumours. However, workers in printing plants in Japan, who carried out cleaning operations with 1,2-DCP, developed CCA with a standardized incidence ratio (SIR) increased by a factor of more than 1000 compared to the general population. Additionally, the mean age of onset was much earlier in the printing workers, ie. 35 years (31 to 39 years).

Tumor tissue from affected printers exhibited increased mutation rates with a specific mutation pattern and increased strand breakage rates compared to bile duct tumor tissue from unaffected patients. None of the primary risk factors such as primary sclerosing cholangitis, parasitic diseases such as liver fluke or trematode infections, gallstones, fibropolycystic liver disease, viral hepatitis, exposure to Thorotrast, congenital anomalies of the biliary system, excessive consumption of alcohol or smoking were found to apply to the printing workers with CCA.

Of the 37 cases with occupational CCA reported up to the year 2016, 22 underwent surgical treatment. As the available data for one patient were incomplete and the primary tumour of another patient was suspected to be pancreatic cancer, the clinical findings, the laboratory results and the pathology of the tumour tissue were examined for 20 patients. All of the patients were exposed to 1,2-DCP, but many of them were co-exposed to other chemicals: more precisely, five of the patients were exposed only to 1,2-DCP, 8 to 1,2-DCP and dichloromethane, 6 to 1,2-DCP, 1,1,1-trichloroethane and dichloromethane and one patient was exposed to 1,2-DCP and 1,1-dichloro-1-fluoroethane. These co-exposures occurring in many but not all patients make the interpretation of these studies somehow difficult, but altogether, RAC – in agreement with other evaluations e.g. by IARC and the German MAK commission- considers the epidemiological evidence sufficient to consider 1,2-DCP as a human carcinogen. Exposure estimated in those studies was mainly based on indirect information, like amount of solvent use, instead of direct industrial hygiene measurements.

Studies outside Japan have identified an increased risk of intra- and extrahepatic CCA in the printing industry as well, without evaluating the risk with respect to specific exposures. (For more detailed descriptions and discussions, see also Hartwig and MAK Commission, 2022).

Animal carcinogenicity studies

1,2-DCP is carcinogenic in experimental animals following both chronic inhalation and oral exposure. Nevertheless, the target organs are different when compared to exposed workers.

In experimental animals, there is evidence for respiratory tract carcinogenesis following inhalation exposure (nasal tumours in rats, lung tumours in mice) and some evidence for neoplastic lesions in the Harderian gland and spleen in male mice (see Annex 1 for details). The 2-year **mouse inhalation** study by Matsumoto et al. (2013) was identified as the key study since here lowest doses leading to increased tumour formation were identified, used also for ERR calculation (see below). Within this study, bronchiolo-alveolar adenomas and carcinomas were observed in female mice, with a dose-dependent increase in incidences. At 200 ppm, incidences were significantly higher and exceeded the maximum of the historical control data. The combined bronchiolo-alveolar lesions were also significantly increased in males, but with no dose-dependency. However, incidences were significantly increased at 32 and 200 ppm, compared to control animals and exceeding the maximum incidences of historical controls. The data from the lowest dose were used for the T25

derivation. Further substance-related effects included Harderian gland adenomas in male mice (for more details see Annex 1).

Following oral administration, there is equivocal evidence of mammary tumours in female rats and some evidence on hepatocellular neoplasms in male and female mice. Nevertheless, cholangiocarcinogenicity was not observed in rats or mice.

Mode of action

Animal studies show that 1,2-DCP is rapidly and nearly completely absorbed after oral and inhalation exposure and distributed to the whole body. Regarding the generation of potentially toxic metabolites, the CYP2E1-catalysed metabolism of 1,2-dichloropropane must occur as the first step. The combined study findings further indicate that GSH is involved in the metabolism, but that glutathione S-transferase type T1 (GST-T1) plays only a subordinate role in the development of potentially carcinogenic metabolites.

In vitro, 1,2-DCP induced base substitutions in *Salmonella typhimurium* with and without metabolic activation. In mammalian cells in culture, 1,2-DCP is clastogenic, inducing DNA double-strand breaks (DSB), sister-chromatid exchanges and chromosomal aberrations. Mutations were induced at the *hprt* and *tk* locus in mammalian cells after metabolic activation.

In vivo, 1,2-DCP bound weakly to the DNA in rat liver. While no elevated frequencies of mutations were found in either rats or mice, DNA damage and elevated levels of histone H2AX phosphorylation (g-H2AX) indicative of DSB were observed in mice liver.

In contrast to the missing mutagenicity in experimental animals, the incidence of somatic mutations was markedly increased in tissue samples collected from the biliary tract tumours of printing workers with exposure to 1,2-DCP (and partly also dichloromethane), in comparison with the incidence determined in tissue samples collected from biliary tract tumours in the control group. In addition, a specific mutational pattern was observed in the CCAs induced by 1,2-DCP.

Furthermore, there is evidence for DNA damage amplifying effects. Thus, recent studies employing a co-culture model suggest a cross-talk between cholangiocytes and macrophages upon exposure to 1,2-DCP. Among other effects, inflammatory responses through TNF-α and overexpression of activation-induced cytidine deaminase (AID) may explain the potentiation of DNA damage. AID is involved in inflammation-associated neoplastic transformations. In addition, in tumour tissues, the expression of AID correlated with the occurrence of mutations in proto-oncogenes.

It is assumed that the enzyme AID is involved in the development of CCAs because it was found to be expressed in the samples of CCA tissue collected from printing workers. Not only the findings that C : G to T : A transitions are the predominant mutational pattern determined in the tissues from printing workers, but also the increased occurrence of mutations on the non-coding DNA strand (strand bias) point toward an involvement of AID. The accumulation of the latter at the site of injury following exposure to 1,2-DCP may modulate inflammatory responses, which can potentially create an immune milieu favourable for cholangiocarcinogenesis.

Considering all evidence stated above, and in spite of the missing mutagenicity in experimental animals, 1,2-DCP is considered a genotoxic, non-threshold carcinogen. This is based on the occurrence of defined signature mutations in exposed workers, even though specific underlying DNA lesions have not been identified, and amplifying effects may be important.

Cancer risk assessment (see section 9.1.2 of Annex 1 for full discussion)

There is clear evidence of carcinogenic effects of 1,2-DCP in humans. In particular, increased incidences of bile duct tumours have been reported among exposed workers. According to the current database, a genotoxic, non-threshold mode of action must be assumed, and a unique mutational signature has been found in the CCA tissue of

occupationally exposed workers. However, no robust human exposure data is available, and therefore it is not possible to any derive an exposure-risk relationship (ERR) based on human data.

Instead, the ERR was derived from animal data. The 2-year **mouse inhalation** study by Matsumoto et al. (2013) was identified as the key study, showing carcinogenic effects (bronchoalveolar adenomas/carcinomas) at low dose levels.

Cancer incidences of 18/50 animals in the exposed group (32 ppm) and 9/50 in the control group were reported. However the dose-response correlations reported were not very clear and were not suitable for benchmark dose modelling.

Therefore, T25 was used to identify the point-of-departure for bronchoalveolar adenoma/carcinoma findings (LOAEC=32 ppm). Calculations included the following steps:

1) T25 was calculated as:

$$T25 = C \times \frac{\text{reference incidence}}{(\text{incidence at C} - \text{control group incidence})} \times \frac{(1 - \text{control group incidence})}{1}$$

with C being the LOAEC of 32 ppm for bronchoalveolar adenomas/carcinomas as identified above, incidence at C (18/50), control incidence (9/50), and 0.25 being the reference incidence.

$$T25 = 32 \text{ ppm} \times \frac{0.25}{(18/50 - 9/50)} \times \frac{(1 - 9/50)}{1} = 36.5 \text{ ppm } (171.5 \text{ mg/m}^3)$$

2) The T25 value was adjusted to correspond to worker exposure conditions (40 years, 48 weeks/year, 8 h/day, and correction for the inhalation volume for workers at light physical activity. No allometric scaling is needed for inhalation exposure.

$$T25 \text{ (worker)} = 171.5 \text{ mg/m}^3 \times (75/40 \text{ years}) \times (52/48 \text{ weeks}) \times (6/8 \text{ h}) \times (6.7/10 \text{ m}^3) = 175 \text{ mg/m}^3$$

3) Additional lifetime cancer risks were calculated as follows according to a linearised approach (high to low dose extrapolation):

Exposure concentration representing a $1x10^{-5}$ risk:

$175 \text{ mg/m}^3 / 25.000 = 0.007 \text{ mg/m}^3$ (0.0015 ppm).

Assuming linearity, **excess life-time cancer risks were calculated and are presented below.**

Uncertainties

Reports of exposed workers clearly indicate that exposure to 1,2-DCP is associated with a rare type of bile duct /biliary tract cancer (CCA). As there is no information on exposure levels, this data cannot be used to set an OEL or to derive an ERR. Bile duct tumours were not reported in chronic animal inhalation or oral studies.

RAC considers that there may be a significant level of uncertainty for the human cancer risk within the ERR that was calculated on the basis of lung adenoma/carcinoma findings in rats derived from a single study. Especially, cancer risk to humans may be underestimated since target organs are different and CCA are not reflected in the animal experiments.

One further uncertainty consists in co-exposure towards 1,2-dichloromethane and other solvents in many, but not all, cases of CCA. Nonetheless, some of reported cases were solely related to 1,2-DCP exposure.

Chronic toxicity

Besides some case reports with largely unknown exposure, there are no quantitative human data on longer-term 1,2-DCP exposure and non-cancer chronic disease.

Repeated dose toxicity of 1,2-DCP in animals has been examined in oral and inhalation studies of duration from a few days to 2 years. Effects were observed in the liver (increased weight, hypertrophy, fatty changes, central necrosis, vacuolisation), in the respiratory tract (respiratory epithelium hyperplasia, olfactory mucosa degeneration or atrophy, inflammation of the respiratory epithelium in the nasal cavity, larynx) in the majority of the studies, whereas effects in the spleen (increased extramedullary haematopoiesis, megakaryocyte, haemosiderin deposition, atrophy), in the adrenal glands (fatty changes), in the bone marrow (increased erythropoiesis), and depression of the CNS were reported in some but not all studies. Lastly, in some studies haematology and clinical chemistry alterations were also observed. The most sensitive endpoint was nasal hyperplasia, starting at 15 ppm (70.5 mg/m^3) in a 13-week rat inhalation study:

Cancer risk values can be compared to an **8h TWA on non-cancer effects**, which would protect from chronic toxicity other than carcinogenicity. The lowest LOAEC was observed for nasal hyperplasia occuring at 15 ppm (70.5 mg/m^3) in a 13-week rat study (inhalation exposure 6 h /day, 5 days/week). Other studies had higher NOAEC/LOAEC values.

The derivation of an 8h TWA would comprise the following steps:

Correction of the starting point to correspond to worker exposure conditions:

70.5 mg/m^3 x 6h/8h x 6.7/10 mg/m^3= 35 mg/m^3.

Assessment factors to be applied include a factor of 3 for LOAEC to NOAEC extrapolation, a factor of 2 for subchronic to chronic exposure, 2.5 to cover interspecies differences, and 5 for worker intraspecies differences. Application of these factors would lead to an **8h TWA based on chronic toxicity**:

8h TWA: 35 mg/m^3 / 3 x 2 x 2.5 x 5 ≈ 0.5 mg/m^3 (0.11 ppm)

This would correspond to an excess life cancer risk of about 70 cases per 100.000 exposed workers. As a consequence, the BOEL based on cancer risk will also protect from non-cancer effects, provided that the value will not exceed 0.5 mg/m^3.

Reproductive toxicity

1,2-DCP is not classified as reprotoxic under the CLP regulation; only carcinogenicity was considerd by RAC (2014).

In a teratogenicity study with female Sprague Dawley rats, exposed via gavage, from day 6 to 15 of gestation, delays in skeletal development were observed at the highest dose level of 125 mg/kg body weight/ day.

Similar observations were described for New Zealand White rabbits at 150 mg/kg body weight/ day administered via gavage on gestation days day 7 to 19.

However, effects occurred at dose levels with concurrent maternal toxicity. Teratogenic effects were not detected in either species.

No effects on sexual function and fertility were observed in a 2-generation study in rats.

Derived limit values (see section 9 of Annex 1 for full discussion)

1,2-DCP is considered to be an non-threshold carcinogen. Consequently, **no health-based occupational exposure limit (OEL) nor a STEL can be identified.**

Instead, an exposure-risk-relationship has been established, as described above and presented in the table below.

Cancer exposure-risk relationship (bronchoalveolar adenomas/carcinomas)*

1,2-DCP concentration in air (mg/m³)	1,2-DCP concentration in air (ppm)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.028	0.0059	4
0.28	0.059	40
2.8	0.59	400
28	5.9	4000

* Assuming an 8-hour exposure per day and 5 days per week, over a 40-year working life

Analytical feasibility

The only validated method for measuring **1,2-DCP in air** has a LOD of 0.1 µg per sample, with an estimated working range from 0.05 to 130 ppm (0.25 to 600 mg/m³) (NIOSH 1994 and 2013). Since then, a more sensitive method has been described in literature, with a LOQ of 0.001 mg/m³ (about 0.0002 ppm) (see Annex section 6.2 for details). Thus, no analytical problems are foreseen.

Short Term Exposure Limit (STEL)

Even though some cases of acute poisoning at levels around or above 50 ppm have been reported, the 8h TWA BOEL is likely to be low enough to cover also potential peak exposures. Therefore, **no STEL** is proposed.

(Bio) monitoring of exposure (see section 6 of Annex 1 for full discussion)

Biomonitoring methods are described within the Annex 1 and stated with LOQ. **Available parameters discussed for biomonitoring of exposure to 1,2-DCP** are urinary levels of 1,2-DCP or of N-Acetyl-S-(2-hydroxypropyl)-L-cysteine (2-HPMA), but **none of them appears suitable at present.** Regarding 1,2-DCP, background levels are close to zero, but two studies in the printing industry showed a positive correlation between air and urinary levels of 1,2-DCP, with a better correlation when not corrected for creatinine. However, respective correlations have been reported only for higher air concentrations of 1,2-DCP (> 1 ppm), which would correspond to a cancer risk of > 1% (for details see Annex 1, section 6.2.2). Concerning 2-HPMA, this parameter is not specific for 1,2-DCP exposure, since it is also a metabolite of several other compounds such as 1,2-epoxypropane (propylene oxide), propylene, and other halogenated propanes, and the metabolism of 1,2-DCP to 2-HPMA has not been shown in human studies (Eckert et al., 2021).

No relevant human data on internal exposure are currently available to indicate that other metabolites can be measured in urine.

Technical aspects of the (bio)monitoring methods and related health surveillance are discussed in Chapters 6.2. of the Annex of this opinion.

Biological limit value (BLV) (see sections 7.1, 7.3 and 8.2.3 of Annex 1 for full discussion)

Since 1,2-DCP is considered a non-threshold carcinogen, it is **not possible to derive a health-based BLV**. Also, no correlations between biological and air levels can be derived at present.

Biological guidance value (BGV)

No BGV can be stated. Even though the background level of 2-HPMA in human urine is sufficiently well known, due to the non-specificity of this parameter, a BGV for 1,2-DCP is not proposed.

Notations

Accidental dermal exposure to a paint containing 1,2-DCP caused significant renal and hepatic function effects in the exposed person. Therefore, marked systemic uptake via the skin needs to be considered, and a **'skin' notation** is proposed. This is also supported by the predicted absorption potential based on physico-chemical properties.

There are occasional case reports on skin sensitisation effects of 1,2-DCP. However, the exposure concerned usually multiple chemicals. There is no human data on respiratory sensitisation. 1,2-DCP is considered non-sensitiser based on a negative LLNA study and absence of structural alerts. Thus, **no notation for "Sensitisation"** is proposed.

Groups at extra risk

Due to the potential role of glutathione depletion in the toxicity of 1,2-DCP individuals with genetic G6PDH deficiency may be more susceptible to 1,2-DCP toxicity, particularly hemolytic anemia.

Reproductive toxicity does not appear to be relevant, since no adverse effects were found at exposure levels below maternal toxicity in experimental animals.

ANNEXES:

Annex 1 gives the scientific background for the opinion.