EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Institute for Health and Consumer Protection
European Chemicals Bureau
I-21020 Ispra (VA) Italy

1,4-DICHLOROBENZENE

CAS No: 106-46-7

EINECS No: 203-400-5

Summary Risk Assessment Report

2004 **Special Publication I.04.218**

1,4-DICHLOROBENZENE

CAS No: 106-46-7

EINECS No: 203-400-5

SUMMARY RISK ASSESSMENT REPORT

Final report, February 2004

France

Rapporteur for the risk assessment of 1,4-dichlorobenzene is The French rapporteur for the risk evaluation of 1,4-dichlorobenzene is the Ministry of the Environment with the Ministry of Health and the Ministry of Work.

The scientific work on this report has been prepared by:

Institut National de l'Environnement Industriel et des Risques (INERIS)
DRC
Parc Technologique ALATA
BP N° 2
60550 Verneuil en Halatte
France

Institut National de Recherche et de Sécurité (INRS)
Département Risques Chimiques et Biologiques
Département Etudes et Assistances Médicales
30 rue Olivier Noyer
75680 Paris Cedex 14
France

Centre Antipoison et de Toxicovigilance de Paris
Hôpital Fernand Widal
200 rue du Faubourg Saint Denis
75475 Paris Cedex 10
France

Date of Last Literature Search:	**2002**
Review of report by MS Technical Experts finalised:	**2003**
Final report:	**2004**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance 1,4-dichlorobenzene that has been prepared by France in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

CONTENTS

1 GENERAL SUBSTANCE INFORMATION 3

1.1 IDENTIFICATION OF THE SUBSTANCE 3

1.2 PURITY/IMPURITIES, ADDITIVES 3

1.3 PHYSICO-CHEMICAL PROPERTIES 4

1.4 CLASSIFICATION 4

2 GENERAL INFORMATION ON EXPOSURE 5

3 ENVIRONMENT 6

3.1 ENVIRONMENTAL EXPOSURE 6

3.2 EFFECTS ASSESSMENT 6

3.3 RISK CHARACTERISATION 7

4 HUMAN HEALTH 8

4.1 HUMAN HEALTH (TOXICITY) 8
4.1.1 Exposure assessment 8
4.1.2 Effects assessment 10
4.1.3 Risk characterisation 13

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES) 16

5 RESULTS 17

5**.1 ENVIRONMENT** 17

5**.2 HUMAN HEALTH** 17
5.2.1 Human health (toxicity) 17

TABLES

Table 1.1 Summary of physico-chemical properties 4
Table 2.1 Use pattern of 1,4-dichlorobenzene in Europe 5
Table 3.1 Highest estimated PEC/PNEC-ratios for the surface water 7
Table 4.1 Occupational exposure 8
Table 4.2 Risk characterisation for ocular and nasal irritations 13
Table 4.3 Risk characterisation for repeated dose toxicity (inhalation exposure) 13
Table 4.4 Risk characterisation for carcinogenicity (inhalation exposure) 14
Table 4.5 Risk characterisation for developmental toxicity (inhalation exposure) 15

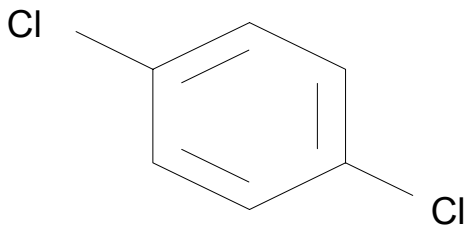
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 106-46-7
EINECS Number: 203-400-5
IUPAC Name: 1,4-Dichlorobenzene
Synonyms: p-Dichlorobenzene
Paradichlorobenzene
p-chlorophenyl chloride

Dichlorocide

Molecular weight: 147.01
Molecular formula: Dichlorocide
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Degree of purity of the produced/imported products within the EU: 99.7 - 99.9%
Impurities:

1,2-dichlorobenzene	<= 0.1%
1,3-dichlorobenzene	<= 0.1%
chlorobenzene	<= 0.05%
trichlorobenzene	<= 0.05%

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value/remark
Physical state	solid, colourless or white crystals (flakes/granular)
Melting point	52.8 - 53.5°C
Boiling point	173 - 174°C
Density	1.25 - 1.46 g/cm^3 at 20°C 1.23 g/cm^3 at 70°C
Bulk density	0.65 g/cm^3 (granular form) 0.788 g/cm^3 (scale form)
Vapour pressure	160 - 170 Pa at 20°C
Water solubility	60 - 70 mg/l at 20°C
Henry's law constant: partition coefficient	262 Pa · m3/mol (at 20°C)
n-octanol/water	log Pow = 3.4
Flash point	65-66°C (closed cup)
Autoflammability	no autoflammability up to 500°C
Flammability limits in air at 20 °C, 1 atm	lower = 1.7 (%V) upper = 5.9 (%V)

A test on flammability according to method A10 (directive 92/32/EC) was negative.

1.4 CLASSIFICATION

Classification:	Xi; R36	Irritating to eyes
	N; R50-53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
	Carc. Cat 3 R40	Limited evidence of a carcinogenic effect
Labelling:	Xn; N R: 36-40-50/53 S: (2-)36/37-46-60-61	

2 GENERAL INFORMATION ON EXPOSURE

The overall 1,4-dichlorobenzene consumption in the EU was estimated to be at most 15,000 tonnes/annum in 1994.

Most of the amount produced is processed to 1,4-dichloro-2-nitrobenzene, a precursor for dyes and pigments. Otherwise, 1,4-dichlorobenzene is formulated to moth repellents, air fresheners and toilet blocks. 1,4-Dichlorobenzene acts mainly to disguise odours. The toilet blocks are used in standing urinals and urinal drains and are not hung in flushing tanks or toilet bowls.

A minor use of 1,4-dichlorobenzene is as a processing aid in the production of grinding wheels.

In **Table 2.1**, the quantitative use pattern is described.

Table 2.1 Use pattern of 1,4-dichlorobenzene in Europe

Industrial category	Use category	Quantity [t/a]	[%]
3: Chemical industry: chemicals used in synthesis	33: Intermediate	7,154	49.3
5: Personal / Domestic	36: Odour agents	3,170	21.9
5: Personal / Domestic	39: Biocides, non-agricultural (moth repellents)	4,070	28.1
2: Chemical industry: basic chemicals	43: Process regulators (grinding wheels)	100	0.7

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

1,4-Dichlorobenzene may be released into the environment during its production and other life cycle steps. Emission to air is expected to be the most important entry route. General characteristics of 1,4-dichlorobenzene which are relevant for the exposure assessment are: no hydrolisation, an estimated atmospheric half-life between 33 and 50 days, ready biodegradability and a high Henry's law constant. Many results from adsorption-desorption tests are available. An average value of Koc = 450 l/kg is used in the assessment. The results on bioaccumulation are variable. The highest value of BCF = 1,400 has been determined in 23-day old alevins. This value is used for the assessment of secondary poisoning. The highest value of BCF = 296, observed at higher development stages of fish are used for the assessment of man exposed via the environment.

For the environmental exposure assessment of 1,4-dichlorobenzene both site-specific and generic emission scenarios are used for calculating the Predicted Environmental Concentrations (PECs) in the various compartments. Site-specific scenarios are based on actual data from industry on emission patterns etc., whereas generic scenarios are primarily based on model calculations. Generic scenarios are used if no data were obtained from either industry or other bodies. For the releases of 1,4-dichlorobenzene during production, three site-specific scenarios are used. Releases during processing and formulation are subdivided in four subscenarios: use as chemical intermediate, formulation of air fresheners and moth-repellents, use of air fresheners and moth repellents, use in the production of grinding wheels. The exposure assessment is based on the EU-Technical Guidance Document (TGD 1996) applying the European Union System for the Evaluation of Substances EUSES (EC 1996). Predicted Environmental Concentrations (PECs) are calculated for the various environmental compartments. Environmental releases

<u>PECs at production, processing, formulation and private use</u>

Local PEC values for the sewage treatment plant range from 15 to 830 µg/l. Local PEC values for surface water range from 0.03 to12 µg/l. The highest measured concentration in a monitoring programme amounts to 4.05 µg/l. Local estimated sediment concentrations range from 1.35 to 540 µg/kg dw. Based on monitoring data, a reasonable worst case of 430 µg/kg was derived. Estimated concentrations in the air near the emission sources range from 0.8 to 273 µg/m^3. The highest estimated soil concentrations reach 2.3 and 72.5 µg/kg dw. The highest concentration of 1,4-dichlorobenzene in fish was estimated to be 8.4 mg/kg (wet fish).

3.2 EFFECTS ASSESSMENT

Long-term toxicity data are available for fish, daphnia, algae and microorganisms. The PNEC for the aquatic compartment is extrapolated from the NOEC for fish (0.2 mg/l), by using an assessment factor of 10. This extrapolation results in a PNEC of 20 µg/l for the aquatic environment.

The PNEC for microorganisms is extrapolated from the EC50 for *Nitrosomas spec* (86 mg/l), using an extrapolation factor of 10. This leads to a PNEC of 8.6 mg/l.

Since there are no data available for directly deriving a PNEC for the sediment, the PNECsoil was estimated from the PNEC for aquatic organisms using the equilibrium partitioning approach. This results in a PNEC of 900 µg/kg dw.

Short term toxicity tests are available for terrestrial plants and invertebrates. The PNEC for the terrestrial compartment is extrapolated from the LC50 for earthworms (96 mg/kg dw), using an assessment factor of 1,000. This extrapolation results in a PNEC of 96 µg/kg dw for the terrestrial environment.

The PNEC for predators of 10 mg/kg (food) was estimated from the overall NOAEL of 10 mg/kg bw/day.

3.3 RISK CHARACTERISATION

The highest estimated PEC/PNEC ratio for micro-organisms in the STP amounts to 0.1, and therefore no risks to micro-organisms in the STP are to be expected. **Conclusion (ii)**.

In **Table 3.1** the comparison between the highest estimated surface water concentrations and the aquatic PNEC for the different exposure scenarios is presented.

Table 3.1 Highest estimated PEC/PNEC-ratios for the surface water

Scenario	PEC/PNEC
Production	0.60
Use as an intermediate	0.02
Formulation of moth repellents and air fresheners	0.22
Use of toilet blocks	0.17

With the highest single measured concentration in a monitoring programme of 4.05 µg/l, a PEC/PNEC-ratio of 0.2 can be deduced. As all the above calculated PEC/PNEC-ratios are below 1, it can be concluded that there is no risk to aquatic organisms through 1,4-dichlorobenzene. **Conclusion (ii)**.

In the same way, all calculated PEC/PNEC ratios for sediment are below 1. Based on the monitoring data, a reasonable worst case concentration of 430 µg/kg dw was derived. Based upon this value, a PEC/PNEC ratio of 0.5 can be derived. As all estimated PEC/PNEC-ratios are below 1, it can be concluded that there is no risk to sediment dwelling organisms through 1,4-dichlorobenzene. **Conclusion (ii)**.

Similarly all the estimated PEC/PNEC-ratios for the terrestrial compartment as well as for predators are below 1. **Conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Exposure to 1,4-dichlorobenzene may arise during its manufacture, its use in synthesis, its incorporation into various products and from their use: workers and consumers may be exposed to 1,4-dichlorobenzene. The main source of exposure is likely to be vapour emitted by the solid (consumers, workers) or from molten material (workers).

Occupational exposure

Occupational exposure may occur by inhalation, skin contact and oral route. Inhalation of vapour is the predominant route of exposure. Dust exposure may arise but is likely to be minimal because of the physical state of the substance (flake).

Dermal exposure from the solid (flake) is expected to be low. It is also expected to be low when the substance is used as a hot molten material.

Oral exposure is not considered to be a significant route under normal working practices.

Few data are available on the levels of 1,4-dichlorobenzene in the workplace and consequently, the model for the Estimation and Assessment of Substance Exposure (EASE) and industry exposure data have mainly been used to estimate occupational exposure within the following various use sectors:

Exposure during manufacture and use as synthesis intermediate

Exposure during formulation of household products (moth repellents, toilet blocks, air fresheners)

Exposure during abrasive manufacturing (production of grinding wheels)

For occupational exposure, we will consider the two following scenarios:

- Scenario 1: manufacture and use as synthesis intermediate
- Scenario 2: formulation of moth repellents, toilet blocks, air fresheners and use in the production of grinding wheels

The potential exposure scenarios and resulting exposures are summarised in **Table 4.1**.

Table 4.1 Occupational exposure

Scenario		Estimated inhalation exposure level (8-hour TWA) (Data industry and Ease)		Estimated skin exposure level (Ease and expert)
		mg/m³	ppm	mg/day
Scenario 1	- Production of 1,4-dichlorobenzene - Synthesis intermediate	42	7	80
Scenario 2	- Formulation of household products - Abrasive manufacturing	300	50	80

Consumer exposure

1,4-dichlorobenzene is used in moth repellents, air fresheners or toilet blocks Consumer exposure occurs both at home and in public lavatories. Vapour inhalation is the predominant route of exposure.

Measured exposure data from experimental use and monitoring studies are available.

The results of the monitoring studies show that the distribution of personal air exposure levels is very large, with a few measurements having a very high value.

The results of the TEAM study reported by Wallace et al. have been used to define a realistic pessimistic long-term exposure level to 1,4-dichlorobenzene. This study is the largest study on personal exposure and is also characterised by a large program of quality assurance. A value of 850 $\mu g/m^3$ (personal air exposure level exceeded by less than 1% of the population studied by Wallace and al., in New Jersey) has been defined for long-term exposure. This value is consistent with the daily exposure level which can be calculated using the concentration measured and the time spent per day in a room containing mothballs and a bathroom containing an air freshener tablet.

For acute exposures, the most elevated concentration that has been measured in exposure places has been considered. It is equal to 23, 8 mg/m^3, value measured in a lavatory with an air refreshener.

Humans exposed via the environment

The total daily intake for humans based on the local environmental concentrations due to the different uses is $3.8.10^{-5}$ mg/kg bw/day and the highest indirect exposure is estimated for production processes.

The highest exposures are to be expected through intake of fish and through inhalation.

Furthermore, 1,4-dichlorobenzene has been detected in honey samples (BUA, 1994). The highest measured concentration was 0.06 mg/kg. Using this concentration and assuming a worst case-consumption of 50 g honey per capita per day, an additional dose of 0.00004 mg/kg bw/day can be calculated. This would represent a negligible addition to the total daily intake.

Combined exposure

The indirect exposure via the environment can be considered as negligible. Combined exposure is mainly occupational and consumer exposure, taking into account that a person may be daily exposed at work during 8 hours and at home during 16 hours.

- Occupational exposure: the relevant values for this section are an estimated (8 hour TWA) inhalation exposure of 50 ppm (300 mg/m^3) and an estimated dermal exposure of 80 mg/day which result in a total body burden of 33.2 mg/kg/day.
- Consumer exposure: considering an exposure concentration of 0.142 ppm (850 $\mu g/m^3$) for 16 hours per day (with a breathing rate of 0.7 m^3/h, and a body weight of 60 kg) is equivalent to an internal dose of 0.119 mg/kg/day.
- Combined exposure corresponds to 33.3 mg/kg/day. This result confirms that combined exposure results mainly from occupational exposure.

4.1.2 Effects assessment

In animals, absorption takes place through the digestive and respiratory tracts rapidly but not completely, and subcutaneously. Absorption after inhalation exposure was poor compared to oral exposure; as no data is available, significant dermal absorption cannot be evaluated even if suspected to be low.

In vivo, 1,4-DCB is distributed primarily in the fatty tissues, the kidneys, the liver, the lungs, the gonads and muscle tissues and is principally metabolised to the sulphate and glucuronide conjugates of 2,5-dichlorophenol but also to free 2,5-dichlorophenol and 2,5-dichlorohydroquinone (in rats). The hydroxylation of the aromatic ring seems to result in the formation of intermediate epoxides: the metabolic fate of epoxide appears species dependant *In vitro*, qualitative differences in the metabolic pathway between rat and mice (with mice liver microsomes producing more hydroquinones metabolites than rats) and quantitative differences (conversion much higher in mouse than in rats or human microsomes) were shown. Elimination is principally via the urine (> 80%).

In human, absorption occurs via the digestive and respiratory tracts (no quantitative data on human absorption are available). 1,4-dichlorobenzene is essentially distributed to the fatty tissue. Elimination occurs essentially through the urine in the form of 2,5-dichlorophenol and via the respiratory tract with a maximum at the 8th hour, and continues for several days.

In vivo, 1,4-dichlorobenzene covalently binds with proteins after oral or ip administrations in rats and mice; there is some evidence for association (adducts not having been isolated) of 1,4-dichlorobenzene with DNA in mice, whereas there is no evidence for the association of 1,4-dichlorobenzene with DNA in rats.

In vitro, covalent binding to protein was higher in mice than rats and human liver microsomes. Detection of DNA adducts after incubation with liver microsomes from rat, mouse or man gave contradictory results.

Given the available animal data, the acute oral, dermal or inhalation toxicity of 1,4-dichlorobenzene is judged to be rather low and do not justify the classification for acute toxicity endpoints.

1,4-dichlorobenzene is a slight irritant for the skin and eyes based on the available data on rabbits. Human data show that 1,4-dichlorobenzene is a slight irritant upon repeated skin exposure.

Workers experienced ocular and nasal irritations from 50 ppm onwards and respiratory irritation from 160 ppm in an old study in which peak exposure concentrations cannot be excluded. These data do not justify the current classification R38 “irritating to skin” or R37 “irritating to respiratory tract” but justify the current classification R36 “irritating to eyes”.

1,4-dichlorobenzene has a low sensitisation potential given the animal data (*in vitro* study and open epicutaneous test negatives, maximisation study difficult to interpret) and only one questionable case reported in human despite the widespread use of 1,4-dichlorobenzene.These data do not justify the classification Xi R43 “May cause sensitisation by skin contact”.

With respect to repeated dose toxicity, the most relevant inhalation NOAEC for non carcinogenic effects was estimated at 75 ppm in rats and mice (104-week inhalation studies in rats and mice, 76-week inhalation studies in rats), with abnormalities of the liver from 158 ppm and of the kidney from 300 ppm.

After oral administration, hyaline droplet nephropathy is observed only in male rats from 75 mg/kg/day (species- and sex -specific). The oral NOAEL for female rats is established at 150 mg/kg/day and the oral LOAEL for renal effects in male is 75 mg/kg/day.

In a one-year dog study, the NOAEL was of 10 mg/kg/day, with liver effects observed from 50 mg/kg/day; although the oral route is not the human route of exposure, this NOAEL will be taken into account for risk assessment because there is no evidence that dog is a less appropriate model for human than rodents; the high sensitivity of this species will have to be taken into account in the assessment of margin of safety.

A NOAEL via dermal route identified in a 21-day study in rat was higher than 300 mg/kg/day.

No epidemiological study of humans and only case reports difficult to take in consideration for risk assessment are available at the current time.

For risk assessment purpose, a NOAEC of 75 ppm has been determined via inhalation. Moreover, the more conservative NOAEL of 10 mg/kg/day from a dog oral study has also to be considered. Classification Xn R48/22 is not indicated.

With regard to mutagenicity, even if 1,4-dichlorobenzene has been investigated in a large number of *in vitro* and *in vivo* tests, data do not provide a coherent view of the genotoxicity of 1,4-dichlorobenzene. The so-called standard tests for genotoxicity do not suggest that 1,4-dichlorobenzene has any such potential; the evidence pointing in this direction comes from non-standard tests that may not be fully recognised by regulatory authorities (*in vitro* and *in vivo* Comet assays in rat, mice or human).

The overall weight of evidence from the most reliable studies indicates that it does not have any significant genotoxic potential. According to the EEC criteria for classification and labelling of dangerous substances and following the CMR meeting of May 2003, 1,4-dichlorobenzene does not need to be classified in Category 3 mutagen (R68) and is not considered as a genotoxic agent.

Studies on the carcinogenicity of 1,4-dichlorobenzene in a two years oral administration revealed renal tubular cell adenocarcinoma tumours in F344 male rats from 150 mg/kg/day; the formation of the renal tumours appears to be species- and sex-specific by a mechanism of hyaline droplet nephropathy which cannot be extrapolated to humans.

Hepatocellular adenocarcinomas appear in B6C3F1 mice via oral route at 600 mg/kg/day and in BDF1 mice via inhalation exposure at 300 ppm. A NOAEL of 300 mg/kg/day and a NOAEC of 75 ppm were clearly determined for carcinogenicity in these studies. No hepatocarcinomas were observed in the two carcinogenicity studies in rats (via inhalation and oral exposure~~).~~ In some animals, hepatocarcinomas were associated with hepatoblastomas and/or histiocytosarcomas; hepatoblastomas appear in B6C3F1 mice via oral route at 600 mg/kg/day and in BDF1 mice via inhalation exposure at 300 ppm and histiocytosarcomas in BDF1 male mice via inhalation exposure at 300 ppm; these two types of tumours (hepatoblastomas and histiocytosarcomas) are rare in mice.

In the absence of any clear genotoxic effect, other mechanisms (than genotoxic) of tumour formation and their possible relevance to man should be considered. Hepatocellular carcinomas appear in mice at doses where hepatotoxicity was observed; in contrast, in rats only slight hepatotoxicity was observed at 600 mg/kg/day in a two year study without liver tumours. Cellular proliferation was observed in the liver of F344 rats at the same dose than

the carcinogenicity study but rats did not develop any cancer of the liver and hepatocyte cell proliferation has been seen in mice and rat in spite of the lack of hepatotoxicity as a result of mitogenic stimulation. Therefore the relationship between cellular proliferation, hepatotoxicity and liver tumours is thus not clear.

The carcinogenic effect on the mouse liver is probably not the result of a peroxisomal proliferation

The role of the hepatic metabolism of 1,4-DCB in the mechanism of carcinogenicity can also be discussed in view of differences between rat, mice and human. These differences in hepatic metabolism cannot at the moment completely explain the results of the carcinogenicity studies.

The carcinogenic potential of 1,4-dichlorobenzene for the liver has been clearly demonstrated in B6C3F1 and BDF1 mice; A NOAEL for carcinogenic liver effects of 300 mg/kg/day via oral route in B6C3F1 mice and a NOAEC of 75 ppm via inhalation route in BDF1 mice can be determined

For kidney adenocarcinoma a LOAEL of 150 mg/kg/day via oral route in F344 rats is noted; the kidney tumours in male rats have no relevance to humans because the underlying mechanism is male rat specific hyaline droplet nephropathy, which cannot be extrapolated to human.

The mechanism of the liver tumours in mice is not clear; as no tumour in excess was observed at 75 ppm and 300 mg/kg/day, a threshold mechanism for carcinogenicity of 1,4-dichlorobenzene has to be considered.

New genotoxicity data (even if 1,4-DCB is not considered as a genotoxic), associated with animal data justify to reconsider the classification for carcinogenicity of 1,4-dichlorobenzene; The classification Carc. Cat 3 was agreed at the CMR meeting in May 2003 and proposed to the 29th ATP of Directive 67/548/EEC.

1,4-dichlorobenzene has no adverse effects on fertility in the absence of maternal toxicity (oral and inhalation exposure in rats).

Considering the two-generation study in rats via gavage, developmental toxicity in pups (isolated reduced mean body weight only at birth, reversible after in F0/F1 generation and increased total number of pups deceased between day 1 and 4 in F1/F2 generation and not between day 4 and 21, not in generation F0/F1, not if number of pups per litter is considered) appears from 90 mg/kg/day associated at the same dose with slight behavioural anomalies (reduced percentage of pups with positive draw up test in F1/F2 generation) Toxic effects were seen in parents at 270 mg/kg/day. The NOAEL for these developmental effects is estimated at 30 mg/kg/day. In the two-generation study in rats via inhalation, similar signs of toxicity (weight loss, increased perinatal mortality, reduced litter size, reduction in number of live foetuses per litter) than those observed at the high dose tested via oral route (270 mg/kg/day) were observed in the offspring at 538 ppm, concentration where parental toxicity was noted. A NOAEC of 211 ppm for the two generation study through inhalation in rats is established.

Three teratogenicity studies (rats and rabbits via oral and inhalation exposures) did not reveal any evidence of teratogenic effects in the absence of parental toxicity.

The available human data do not provide relevant information for risk assessment in humans. These data do not justify the classification for reproductive endpoints.

4.1.3 Risk characterisation

Workers

Acute toxicity, sensitisation

Given the effects observed in the acute toxicity studies via oral, dermal and inhalation routes, and the sensitisation studies and the anticipated occupational exposure levels, it is concluded that 1,4-dichlorobenzene is of no concern for workers. **Conclusion (ii)**

Irritation

Considering the exposure data and the LOAEC for ocular and nasal irritation in human, the following MOS's can be calculated:

Table 4.2 Risk characterisation for ocular and nasal irritations

Scenario	Airbone exposure (ppm)	LOAEL (ppm)	MOS	Conclusion
1	7	50	7.1	(ii)
2	50	50	1	(iii)

Irritation does lead to concern for scenario 2 because a minimal MOS of 6 is required. Therefore risk reduction measures are necessary during use (formulation of household products and production of grinding wheels).

Conclusion (iii) for Scenario 2.

Repeated dose toxicity

The rat and mice inhalation studies are preferred over the dog feeding study, as the route of exposure in the rodent studies is the same as the exposed workers; moreover, when using the dog feeding study, there is a need for route to route extrapolation that increases the uncertainty.

Considering the exposure data, the NOAEC of 75 ppm determined in rats and mice (104 weeks, 76 weeks) and the more conservative NOAEL of 10 mg/kg/day (one year), the following MOS's can be calculated :

Table 4.3 Risk characterisation for repeated dose toxicity (inhalation exposure)

Scenario	External exposure (inhalation) ppm	NOAEL Inhalation (rat, mice) ppm	MOS	Internal exposure (dermal and inhalation) mg/kg/day	NOAEL oral (dog) mg/kg/day	MOS	Conclusion
1	7	75	10.7	4.5	10	2.1	(iii)
2	50	75	1.5	32.1	10	0.31	(iii)

Margins of safety of 0.31, 1.5 and 2.1 are considered insufficient for worker health protection compared to the minimal MOS of 9 (inhalation studies) and 18 (oral study) required. Further risk reduction measures during manufacture and use (intermediates, formulation and production of grinding wheels) are necessary.

With regard to dermal route, no repeated dose toxicity data are available; therefore the oral NOAEL (10 mg/kg/day) will be used and the same conclusion (iii) required (margins of safety of calculated 9 for scenarios 1 and 2 considered insufficient for worker health protection compared to the minimal MOS of 18 required).

Conclusion (iii) for scenarios 1 and 2.

Mutagenicity

With regards to mutagenicity, 1,4-DCB has not any significant such potential and this point needs not to be discussed

Conclusion (ii) for scenarios 1 and 2.

Carcinogenicity

The carcinogenic potential of 1,4-dichlorobenzene has been demonstrated in mice which are of very high sensitivity towards hepatotoxic chemicals but the mechanism by which these hepatic tumours form, has not been clearly identified A threshold mechanism for carcinogenicity of 1,4-dichlorobenzene is proposed in view of the liver tumours from the highest doses tested (oral and inhalation route in two species of mice).

For carcinogenicity, a NOAEC of 75 ppm following inhalation exposure was obtained in mice and a NOAEL of 300 mg/kg/day was identified in mice following oral administration. Since route of worker exposure is mainly by inhalation, the NOAEC of 75 ppm in mice is preferred.

Considering the exposure data, the NOAEC of 75 ppm in mice and the NOAEL of 300 mg/kg/day in mice (liver tumours, 104 weeks), the following MOS's can be calculated:

Table 4.4 Risk characterisation for carcinogenicity (inhalation exposure)

Scenario	External exposure (inhalation) Ppm	NOAEC inhalation (mice) ppm	MOS	Internal body burden (inhalation) mg/kg/day	NOAEL oral (mice) mg/kg/day	MOS	Conclusion
1	7	75	10.7	4.5	300	66.7	(iii)
2	50	75	1.5	32.1	300	9.3	(iii)

Margins of safety (MOSs) of 10.7 and 1.5 are considered insufficient for worker health protection compared to the minimal MOS of 45 required.

Starting with an oral study in mice, a minimal MOS of 315 is required and the margins of safety (MOSs) of 66.7 and 9.3 are considered insufficient for worker health protection.

With regard to dermal route, no carcinogenicity data are available. Therefore the oral NOAEL of 300 mg/kg/day in mice (104 weeks) will be used and the following MOSs of 272 can be calculated and are considered insufficient for worker health protection compared to the minimal MOS of 315 required.

Conclusion (iii) for scenarios 1 and 2.

Developmental toxicity

For developmental toxicity, the NOAEL of 30 mg/kg/day in rat following oral administration is preferred to the NOAEL of 211 ppm in rat following inhalation exposure because developmental effects were observed in the oral study (even if it is not the main route of exposure for workers).

Considering the exposure data, the NOAEL of 30 mg/kg/day in rats, the following MOS's can be calculated:

Table 4.5 Risk characterisation for developmental toxicity (inhalation exposure)

Scenario	Internal exposure (inhalation) mg/kg/day	NOAEL oral (rat, primary effects) mg/kg/day	MOS	Conclusion
1	4.5	30	6.6	(iii)
2	32.1	30	0.9	(iii)

The NOAEL of 30 mg/kg/day compared with the total body burden gives margins of safety of 6.6 and 0.9 for scenario 1 and 2 which are considered insufficient for worker health protection compared to the minimal MOS of 180 required. Further risk reduction measures are necessary.

With regard to dermal route, no developmental toxicity data are available; therefore the oral NOAEL of 30 mg/kg/day will be used and the same Conclusion (iii) required; calculated margins of safety of 27 for scenarios 1 and 2 are considered insufficient for worker health protection compared to the minimal MOS of 180 required).

Conclusion (iii) for scenarios 1 and 2.

Consumers

Given the effects observed in the acute toxicity studies, the sensitisation studies and the mutagenicity tests, and the maximum concentration measured in a room containing a product dedicated to consumers (23.8 mg/m^3), it is concluded that 1,4-dichlorobenzene is of no concern for consumers. **Conclusion (ii)**.

Irritation

Irritation of the eyes and upper airways may occur when air concentration of 1,4-dichlorobenzene exceeds 50 ppm (300 mg/m^3). When compared to the highest measured consumer exposure (23.8 mg/m^3), a margin of safety of 13 is obtained. As no complaint has been recorded below 50 ppm, as the exposure levels used to calculate the margin of security corresponds to the maximum air concentration ever reported in a room, in consumer exposure conditions, this endpoint does not lead to concern. **Conclusion (ii)**.

Repeated-dose toxicity

The NOAEL of 75 ppm, 6 hours per day, 5 days per week reported in rats and mice, by inhalation, is equivalent to 13 ppm or 80 mg /m^3, for continuous exposure. Compared to 0.85 [0.60-1.15] mg/m^3, it gives a margin of safety of 95 [70-134]. As the minimum margin of safety corresponds to the average between the 99th percentile of the personal exposures measured during one day and during one night, as such levels must be higher than the average

exposure for a long-term (several years) and continuous exposure, the Conclusion (ii) is drawn. **Conclusion (ii)**.

Carcinogenicity

The mechanism by which hepatic tumours form in mice has not been clearly identified, but a threshold for carcinogenicity of 1,4-dichlorobenzene has been proposed in view of the liver tumours from the highest doses tested (oral and inhalation route in two species of mice).

The NOAEL of 75 ppm, 6 hours per day, 5 days per week via inhalation, is equivalent to 13 ppm or 80 mg /m^3, for continuous exposure. Compared to 0.85 [0.60-1.15] mg/m^3, it gives a margin of safety of 95 [70-134]. Considering the severity of the effects, the margin of safety has been judged insufficient. **Conclusion (iii)**.

Toxicity for reproduction

For developmental toxicity, the NOAEL was 211 ppm, in rats, by inhalation. Considering the animals have been exposed 6 hours per day, 7 days per week, the equivalent NOAEL for a continuous exposure by inhalation is equivalent to 317 mg/m^3. Comparing the exposure of 0.85 [0.60-1.15] mg/m^3, it gives a margin of safety of 373 [276-528].

No teratogenic effects were observed and abnormalities reported in foetuses were always minor (weight reduction, minor birth defects). So, the endpoint is of no concern. **Conclusion (ii)**.

Conclusion of the risk assessment for consumers: **Conclusion (iii)**.

Humans exposed via the environment

General systemic repeated-dose toxicity, carcinogenicity and the developmental toxicity are the critical end points for man exposed indirectly via the environment. Comparison of the NOAELs of 10 mg/kg/day (general systemic repeated-dose toxicity), 300 mg/kg/day (carcinogenicity) and 30 mg/kg/day (developmental toxicity) with the highest estimated exposure of 0.0109 mg/kg/day leads to margins of safety of 917, 27,522 and 2,750 which do not lead to concern. **Conclusion (ii)**.

Combined exposure

In the case of combined exposure the highest potential uptake is likely to occur during occupational exposure. Consumer exposure and indirect exposure via the environment can be considered negligible. The same conclusion as for occupational exposure is achieved. **Conclusion (iii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

There are no risks from physico-chemical properties arising out the use of 1,4-dichlorobenzene. **Conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion is reached for the exposure of the aquatic compartment (including the sediment), the atmosphere, and the terrestrial compartment as well as for predators.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Taking into account the currently available toxicological data and the estimated occupational exposure, **conclusion (iii)** is reached because:

- nasal and ocular irritation due to vapour exposure during use for formulation of products containing the substance and production of grinding wheels
- general systemic toxicity, carcinogenicity and reproductive toxicity due to exposure mainly via inhalation and dermal, during manufacture and use (intermediate, formulation of products containing the substance and production of grinding wheels).

Consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Taking into account the currently available toxicological data and the estimated consumer exposure, this conclusion (iii) is reached because:

- carcinogenicity due to inhalation exposure arising from use of moth repellents, air fresheners and toilet blocks

Humans exposed indirectly via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.