1,2-Dibromoethane

Health-based recommendation on occupational exposure limits

To: the State Secretary of Social Affairs and Employment
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Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad het advies over beroepsmatige blootstelling aan de kankerverwekkende stof 1,2-dibroomethaan geactualiseerd. De Gezondheidsraad schat de concentraties van 1,2-dibroomethaan in de lucht die samenhangen met het streefrisiconiveau en het verbodsrisiconiveau op respectievelijk 0,002 en 0,2 milligram (mg) per kubieke meter (m^3), bij 40 jaar beroepsmatige blootstelling. Deze concentraties komen overeen met de waarden die de Gezondheidsraad eerder heeft berekend. Verder adviseert de raad om een huidnotatie toe te passen voor 1,2-dibroomethaan, wat betekent dat maatregelen noodzakelijk zijn om huidcontact met de stof te vermijden. Een huidnotatie wordt geadviseerd als verwacht wordt dat blootstelling via de huid bijdraagt aan gezondheidsschade die optreedt na inademing van de stof.

Dit advies is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Deze vaste commissie van de Gezondheidsraad beoordeelt stoffen waar mensen tijdens hun werk mee in aanraking komen op hun mogelijk schadelijke effecten. Op www.gezondheidsraad.nl staat meer informatie over de taken van de commissie en de samenstelling van de commissie.

Gebruik van 1,2-dibroomethaan

1,2-Dibroomethaan wordt gebruikt als intermediair in de synthese van chemische verbindingen, hoofdzakelijk voor de productie van vinylbromide, en als oplosmiddel voor harsen, gommen en wassen.

Risiconiveaus voor kankerverwekkende stoffen

Voor kankerverwekkende stoffen die geclassificeerd zijn in categorie 1A of 1B en een directe interactie aangaan met het genetisch materiaal (stochastisch genotoxisch werkingsmechanisme) heeft de minister van SZW risiconiveaus vastgelegd. Deze risiconiveaus betreffen het extra risico op kanker door beroepsmatige blootstelling gedurende het arbeidzame leven. De commissie GBBS schat de concentraties van een stof in de lucht die overeenkomen met die risiconiveaus. Dit worden risicogetallen genoemd. Voor de schatting maakt de commissie gebruik van de Leidraad berekening risicogetallen voor carcinogene stoffen van de Gezondheidsraad.[1]

Streefrisiconiveau en verbodsrisiconiveau in Nederland

Het streefrisiconiveau is 4 op 100.000. Dat betekent dat bij blootstelling overeenkomend met 4 of minder extra sterfgevallen op 100.000 beroepsmatig blootgestelde mensen geen extra beschermende maatregelen genomen hoeven te worden.

Het verbodsrisiconiveau is 4 op 1.000. Dat betekent dat blootstelling overeenkomend met 4

extra sterfgevallen op 1.000 beroepsmatig blootgestelde mensen niet overschreden mag worden.
De Gezondheidsraad berekent welke blootstellingniveaus overeenkomen met deze risiconiveaus, uitgaande van iemand die 40 jaar lang, 5 dagen per week en 8 uur per dag werkt.

Geraadpleegde onderzoeken

In 1999 heeft de commissie WGD, de voorganger van de commissie GBBS, risicogetallen afgeleid voor 1,2-dibroomethaan. Er zijn nog steeds geen gegevens beschikbaar over blootstelling aan 1,2-dibroomethaan en kanker bij de mens. De commissie gaat bij haar risicoschatting daarom, net als de WGD destijds, uit van een rattenstudie die is uitgevoerd in het kader van het Amerikaanse ‘National Toxicology Program’. Hoewel de commissie nu andere tumortypen als uitgangspunt gebruikt, komt de nieuwe schatting van het risico overeen met de eerdere schatting uit 1999.

Advies aan de staatssecretaris

De commissie schat de concentratie van 1,2-dibroomethaan in de lucht die samenhangt met een extra risico op kanker van 4 per 100.000 (het streefrisiconiveau) gelijk aan 0,002 mg/m^3. Een extra risico op kanker van 4 per 1.000 (het verbodsrisiconiveau) komt overeen met een concentratie van 0,2 mg/m^3. Beide schattingen gaan uit van een 40 jaar beroepsmatige blootstelling. Verder adviseert de commissie om een huidnotatie toe te passen voor 1,2-dibroomethaan.

executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council has updated its recommendation on occupational exposure to 1,2-dibromoethane and the risk of cancer. The Health Council estimates the concentrations 1,2-dibromoethane in the air that correspond to the target risk level and the prohibitive risk level to be 0.002 en 0.2 milligram (mg) per cubic meter (m^3), respectively, considering 40 years of occupational exposure. These concentrations are similar to those derived by the Health Council previously. In addition, the Health Council recommends to apply a skin notation for 1,2-dibromoethane. This notation means that measures needs to be taken to prevent skin contact with the substance since this could attribute to the adverse health effects that can develop after exposure by inhalation.

This advisory report has been drafted by the Dutch Expert Committee on Occupational Safety (DECOS). This permanent Committee of the Health Council evaluates the adverse health effects of substances to which people can be occupationally exposed. Additional information on the task of the Committee and the members can be found on www.gezondheidsraad.nl.

Use of 1,2-dibromoethane

1,2-Dibromoethane is being used as intermediate in the synthesis of chemical compounds, mainly for the production of vinyl bromide, and as a non-flammable solvent for resins, gums and waxes.

Risk levels for carcinogenic substances

The Minister of Social Affairs and Employment has set risk levels for carcinogenic substances that have been classified in category 1A or 1B and directly interact with the DNA (stochastic genotoxic mechanism). These risk levels relate to the extra risk of cancer due to life time occupational exposure. DECOS estimates the concentrations in the air that correspond to these risk levels. These estimates are referred to as cancer risk values. For this estimation, the Committee follows the Guideline for the calculation of occupational cancer risk values.[1]

Target risk level and prohibitive risk level applied in the Netherlands

The target risk level is 4 per 100,000. This means that for concentrations leading up to 4 extra cancer cases per 100,000 occupationally exposed people, no additional measures need to be taken.

The prohibitive risk level is 4 per 1,000. This means that the concentration leading to 4 extra cancer cases per 1,000 occupationally exposed people, cannot be exceeded.

The Health Council estimates which exposure levels correspond to these risk levels, considering someone is exposed for 40 years, 5 days a week and 8 hours a day.

Consulted research

In 1999, the Committee WGD (the predecessor of DECOS) has derived cancer risk values for 1,2-dibromoethane. Like in 1999, no data are available on exposure to 1,2-dibromoethane and cancer in humans. Again, the Committee has based its estimation on a study in rats that was conducted within the US National Toxicology Program. The new estimation corresponds to the previous estimation of 1999, although the Committee used different tumor types as starting point.

Recommendation to the State Secretary

The Committee estimates the concentration of 1,2-dibromoethane in the air that corresponds to an extra cancer risk of 4 per 100,000 (the target risk level) equal to 0.002 mg/m^3. An extra risk of cancer of 4 per 1,000 (the prohibitive risk level) corresponds to a concentration of 0.2 mg/m^3. Both estimates are based on 40 years of occupational exposure. In addition, the Committee recommends to apply a skin notation for 1,2-dibromoethane.

01 scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment. This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with stochastic genotoxic carcinogenic properties. In that case, an exposure-response relationship is recommended for use in regulatory standard setting, i.e., the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The Committee calculates HBC-OCRVs for compounds, which are classified by the European Union or by the Committee as carcinogens in category 1A or 1B.

For the establishment of the HBC-OCRVs, the Committee generally uses a linear extrapolation method, as described in the Committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens'.[1] The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure, the Minister sets the official occupational exposure limits.

In 1999, the Committee WGD (the predecessor of DECOS) derived cancer risk values for 1,2-dibromoethane.[2] In this report, the Committee provides an update.

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee.

In 2017, the president of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the advisory report. The individuals and organizations that commented on the draft, the comments and the replies by the Committee can be found on the website of the Health Council.

1.3 Data

The Committee's recommendation has been based on scientific data, which are publicly available. Data were obtained from the online databases Toxline and Medline, using carcinogenic properties, carcino*, cancer, neoplastic, 1,2-dibromoethane and CAS registry number as key

words. In addition, in preparing this report the following reviews were consulted:

- Agency for Toxic Substances and Disease Registry (ATSDR)[3]
- International Agency for Research on Cancer (IARC)[4]
- US Environmental Protection Agency (US EPA)[5]
- European Commission: Scientific Committee on Occupational Exposure Limits (SCOEL)[6]
- National Toxicology Program (NTP)[7].

The last literature search was performed in May 2017.

02 identity, toxicity profile and classification

2.1 Identity, and physical and chemical properties

1,2-dibromoethane is being used as a chemical intermediate in synthesis, mainly in the production of vinyl bromide, and as a non-flammable solvent for resins, gums and waxes. A primary use of 1,2-dibromoethane in the past has been as a lead scavenger in antiknock mixtures added to gasoline. This use has decreased with banning the use of lead-containing fuels in nearly all countries. Another major use in the past was as a pesticide and ingredient in soil and grain fumigant formulations.[6] Many of the uses of 1,2-dibromoethane as pesticide have also been discontinued. Physical and chemical data shown below are from http://toxnet.nlm.nih.gov (HSDB), ATSDR[3] and IARC[4].

Chemical name	:	1,2-dibromoethane
CAS number	:	106-93-4
EC number	:	203-444-5
IUPAC name	:	1,2-dibromoethane
Synonyms	:	Ethylene dibromide; 1,2-ethylene dibromide; dibromoethane, ethylene bromide; EDB; glycol bromide; glycol dibromide
Physical description and colour	:	Colourless liquid
Molecular formula	:	$C_2H_4Br_2$
Structure	:	
Molecular weight	:	187.86
Melting point	:	9.9°C
Boiling point (101.3 kPa)	:	131.6°C
Density (20°C)	:	2.172 g/cm^3
Solubility	:	Solubility in water (30°C) = 4.3 g/L; Miscible with acetone, benzene, diethyl ether and ethanol
Octanol/water partition coefficient, Log $P_{oct/w}$	:	1.96
Vapour pressure (25°C)	:	11.2 mmHg (1.5 kPa)
Relative vapour density (air = 1)	:	6.5
Flash point	:	Not flammable
Odour threshold	:	62.50 - 76.80 mg/m^3
Conversion factor (20°C, 101.3 kPa) (mg/m^3 = molecular weight / 24.45 * ppm)	:	1 mg/m^3 = 0.13 ppm 1 ppm = 7.69 mg/m^3
EU classification (EC No 790/2009 of 10 August 2009)	:	Acute Tox. 3: H331, H311, H301; Eye Irrit. 2: H319 ; Skin Irrit. 2: H315; STOT SE 3: H335; Carc. 1B: H350

2.2 Classification as a carcinogenic substance

In the European Union, 1,2-dibromoethane is classified as a category 1B carcinogen (presumed to have carcinogenic potential for humans).[8] IARC has classified the compound as a group 2A carcinogen (Probably carcinogenic to humans).[4] This evaluation was based on sufficient evidence in animals but inadequate evidence in humans. However, IARC considered that 1,2-dibromoethane is genotoxic in a broad range of in vitro and in vivo assays and binds covalently with DNA in vivo to elevate the overall evaluation from 2B (possibly carcinogenic to humans) to 2A.

2.3 Toxicity profile

2.3.1 Human studies

Five reports on acute toxicity following accidental or suicidal poisoning and three epidemiological studies on human reproduction toxicity have been summarised by the IARC, ATSDR, EPA and European commission.[3-6] A compilation hereof is given below.

Acute toxicity

Letz et al. (1984) reported on two workers who collapsed shortly after entering a pesticide storage tank containing residues of 1,2-dibromo-ethane.[9] These workers were exposed for about 45 minutes or 20-30 minutes, and died 12 and 64 hours after collapse, respectively. Neither worker had respiratory or skin protection. Air samples from the tank, taken about 20 hours after the accident, contained 1,2-dibromoethane at concentrations between 15-41 ppm (115-315 mg/m^3, average 28 ppm (215 mg/m^3)). The other reports concern cases of suicidal poisoning via ingestion of 1,2-dibromoethane. Saraswat et al. (1986) reported on six young individuals who ingested an ampule of commercial 1,2-dibromo-ethane, two of which died 1-2 days after hospital admission.[10] Another fatal poisoning occurred in a woman who ingested about 9 capsules containing 1.5 mL of 1,2-dibromoethane each (140 mg/kg body weight), and died 54 hours later (Olmstead et al. (1960).[11] A woman who intentionally ingested a capsule containing 6.5 g of 1,2-dibromoethane died 8 days later (Singh et al. (1993).[12] More recently, Singh et al. (2007) reported on 64 patients with 1,2-dibromoethane poisoning.[13] Death occurred between 12 hours and 5 days in 38 of these patients. About half an ampule (1.5 ml) of 1,2-dibromoethane was fatal.

Common clinical symptoms in the above studies included nausea, vomiting, abdominal pain and diarrhea. Neurological and respiratory symptoms and urinary changes were also observed. Pathological examination consistently showed hepatic and renal damage (including necrosis), and gastrointestinal toxicity (erosion and ulceration). Cardiotoxicity occurred in the accidentally exposed workers and in patients examined by Singh et al. (2007).[13] Hypoglycaemia was another symptom observed in these patients.

Reproduction toxicity

The epidemiological studies summarized below have significant shortcomings (including small sample size, inadequate exposure data, inappropriate control groups, and general methodological weakness in assessing fertility status and antispermatogenic effects), but provide some indication of potential adverse effects of 1,2-dibromoethane on male fertility and sperm production.[3]

Wong et al. (1979) observed a decrease in male fertility in workers from four plants manufacturing 1,2-dibromoethane.[14] Two exposures categories were distinguished: <0.5 ppm (<3.8 mg/m^3) and 0.5-5 ppm (3.8-38 mg/m^3). Based on the men's reproductive histories subsequent to their occupational exposure, the number of live births to their wives was 29% below expected values (this difference was not statistically significant at p = 0.05).

The effect of long-term exposure, with an average of five years, to 1,2-dibromoethane (8-hr time-weighted average 88 ppb [0.68 mg/m^3]) on semen quality was studied by Ratcliffe et al. (1987) among 46 men employed in the papaya fumigation industry.[15] The comparison group consisted of 43 unexposed men from a sugar refinery. Significant decreases in sperm count, viability and motility, and increases in sperm with morphological abnormalities were observed among exposed men.

Schrader et al. (1988) conducted a longitudinal study in 10 forestry employees exposed for about six weeks (8-hr time-weighted average 60 ppb [0.46 mg/m^3]) and six unexposed men.[16] Sperm velocity decreased in all 10 exposed men and in only two unexposed men.

2.3.2 Animal studies

Acute toxicity

Experimental data on acute toxicity of 1,2-dibromoethane have been compiled by the European Commission[6] and on the ECHA website[8]. A compilation is given below.

In acute oral toxicity studies (following OECD guideline 401) in different species the following LD_{50} values were obtained: rat (male, female) 140, rat (male) 146, rat (female) 117, mouse (female) 420, rabbit (female) 55, chick (male, female) 79, and guinea pig (male, female) 110 mg/kg body weight.

In an acute inhalation study (predating OECD guidelines) rats were exposed (whole body) to concentrations of 1,2-dibromoethane (vapour) between 100 and 10,000 ppm (769 and 76,900 mg/m^3) for 0.02 to 16 hours. The LC_{50} (4-hours) was >200 ppm (>1,538 mg/m^3). At 400 ppm (3,076 mg/m^3) exposure for 2 hours or longer resulted in 64-100% mortality. The most sensitive non-lethal effects consisted of an increase in liver weight and slight histopathological changes in this organ. In the same study guinea pigs were exposed to 200 ppm (for 7 hours) and 400 ppm (for 2-7 hours) (1,538 and 3,076 mg/m^3, respectively). Fifty per cent of the guinea pigs exposed to 400 ppm (3,076 mg/m^3) for 3 hours died while no mortality occurred at 200 ppm (1,538 mg/m^3).

In rats, a dermal application of 0.25 ml of neat 1,2-dibromoethane was lethal.

Skin and eye irritation and corrosion

In vitro, 1,2-dibromoethane was negative in a human epidermis model for skin corrosion. In vivo, the substance caused slight irritation, characterized by erythema and exfoliation, upon repeated application to rabbit ear. The undiluted substance was irritating to the rabbit eye, causing reversible conjunctival irritation and slight superficial necrosis of the cornea, in a study similar to OECD 405. In the same study, a 10% dilution of 1,2-dibromoethane in propylene glycol caused more severe (but still reversible) conjunctival and corneal irritation than the undiluted material.[8]

Skin sensitisation

1,2-Dibromoethane was negative in a mouse local lymph node assay (OECD 429) in which the substance was tested at concentrations of 25, 50 and 100% in acetone/olive oil (4:1). The stimulation index values for these concentrations were 0.7, 0.63 and 1.39, respectively.[8]

Repeated dose toxicity

Effects on non-cancer endpoints upon chronic exposure to 1,2-dibromoethane were reported for several of the carcinogenicity studies summarized in Table 3.

The NTP conducted carcinogenicity studies in rats and mice. Long-term exposure by inhalation 1,2-dibromoethane (10 and 40 ppm (77 and 308 mg/m^3)) caused mortality and growth retardation at the highest concentration in rats.[17] Clinical symptoms consisted of weakness of limbs or body at 40 ppm (308 mg/m^3). In male mice (all groups), early mortality occurred due to urinary tract infection. Increased mortality was observed at 10 ppm (77 mg/m^3) and for females only, at 40 ppm (308 mg/m^3). Growth retardation was observed only at the highest concentration.[17] Histopathological examination of animals exposed by inhalation revealed treatment-related non-neoplastic lesions in the respiratory system (including epithelial hyperplasia and inflammation) of rats and mice, and hepatic necrosis, toxic nephropathy, degeneration of the testis, retina and adrenal cortex, and atrophy of the spleen in rats.[17,18]

In another inhalation carcinogenicity study in rats, exposure to 20 ppm 1,2-dibromoethane (154 mg/m^3) resulted in an increased mortality.[19] Effects unrelated to the carcinogenicity of 1,2-dibromoethane were not reported.

The oral (gavage) carcinogenicity studies by NCI in rats and mice (doses reported of 41 and 38 mg/kg/day for male rats, 39 and 37 mg/kg/day for female rats and 107 and 62 mg/kg/day for mice of both sexes) showed treatment-related mortality, reduced weight gain and various clinical symptoms.[20,21]

In studies by Van Duuren et al., mice given 1,2-dibromoethane in their drinking water (equivalent doses of 50 and 110 mg/kg, for males and females combined) showed reduced water consumption, growth

retardation and increased mortality (the authors did not report on clinical signs or non-neoplastic histopathological changes).[22,23]
Full histopathological examination was conducted only in the oral (gavage) carcinogenicity studies conducted by NCI.[20] This examination showed that acanthosis and hyperkeratosis in the forestomach were the main non-neoplastic changes in both rats and mice (at both dose levels). In addition, rats showed testicular atrophy and degenerative changes in the liver and adrenals.

The toxicity of 1,2-dibromoethane after sub-chronic repeated exposure was examined in several animal studies. These studies have been summarised by the IARC in 1999.[4] A short compilation hereof is given below.
Male and female Fischer 344 rats were exposed by inhalation to 0, 3, 10 or 40 ppm (0, 23, 77 or 308 mg/m^3) of 1,2-dibromoethane for 13 weeks (6 hours/day, 5 days/week).[24] The lowest concentration (3 ppm (23 mg/m^3)) was a No-Observed-Adverse-Effect concentration. At 10 ppm (77 mg/m^3) slight epithelial hyperplasia of the nasal turbinates was seen in animals examined after one, six or 13 weeks of exposure. At 40 ppm (308 mg/m^3) the substance induced hyperplasia and non-keratinizing squamous metaplasia of the respiratory epithelium of the nasal turbinates and increases in liver and kidney weights. The nasal lesions at 10 and 40 ppm (77 and 308 mg/m^3) were no longer observed after a recovery period of 88 days.

In another 13-week inhalation study, conducted to estimate the maximum tolerated exposure levels for carcinogenicity studies, male and female Fischer 344 rats and B6C3F$_1$ mice were exposed to 3, 15 or 75 ppm (23, 115 or 577 mg/m^3) of 1,2-dibromoethane (6 hours/day, 5 days/week).[17,25] All rats survived whereas 4 male mice exposed to 3 ppm (23 mg/m^3) and one female mouse exposed to 75 ppm (577 mg/m^3) died. Growth was retarded (dose-dependently) in all dosed groups except in high-dose females. Treatment-related histopathological changes were observed in the nasal cavity at 15 ppm (115 mg/m^3; squamous cell metaplasia, focal hyperplasia, cytomegaly and loss of cila in rats) and 75 ppm (577 mg/m^3; severe necrosis and atrophy of the olfactory epithelium in rats and mice).
In a sub-acute study on systemic and immunologic toxicity, female B6C3F$_1$ mice received 1,2-dibromoethane by daily oral gavage at 100, 125, 160 or 200 mg/kg body weight (vehicle corn oil) for 14 days.[26] Decreases were seen in relative thymus and spleen weights, red blood cells, haemoglobin, haematocrit and responses of immunological cells in culture. Relative weights of liver and kidney were increased.
In another sub-acute study, male Fischer 344 rats were treated by daily (5 days/week) oral gavage with 1,2-dibromoethane (40 and 80 mg/kg body weight/day) to identify early forestomach lesions following gavage administration of known stomach carcinogens.[27] At 80 mg/kg the substance caused epithelial cell proliferation and hyperkeratosis in the forestomach (in 4/8 and 6/8 rats, respectively). The only finding at 40 mg/kg was hyperkeratosis in 1/8 rats.

Following short-term intraperitoneal administration (40 mg/kg body weight in corn oil; twice daily for two consecutive days) 1,2-dibromoethane induced impairment of renal function in male but not in female Fischer 344 rats. Hepatotoxicity was not observed.[28]

Reproduction toxicity

The effect of 1,2-dibromoethane on reproduction was studied in male and female CD rats exposed by inhalation to 0, 19, 39 or 89 ppm (0, 146, 300, 684 mg/m^3) for 10 weeks (7 hours/day, 5 days/week).[29] At 89 ppm (684 mg/m^3) morbidity and mortality occurred and males of this group had reduced testicular weight, reduced serum testosterone concentration and failed to impregnate any females during a 2-week mating period. Atrophy of the testes, epididymis, prostate and seminal vesicles was also observed. Females exposed to 89 ppm (684 mg/m^3) did not cycle normally until several days after termination of exposure.

Male New Zealand white rabbits were given subcutaneous injections of 15, 30 or 45 mg/kg body weight of 1,2-dibromoethane per day for five days.[30] Semen samples were taken before exposure, during treatment and during 12 weeks after exposure and analysed. Mortality, hepatotoxicity and alterations in measured semen parameters (velocity, percentage motility, amplitude of lateral head displacement) were observed in the highest-dose group.

Female B6C3F$_1$ mice were given 31.25, 62.5 or 125 mg/kg body weight of 1,2-dibromoethane by gavage for 12 weeks (5 days/week).[31] Vaginal smears showed that the oestrous cycle was significantly prolonged at the highest dose.

Pregnant CD rats and CD-1 mice were exposed by inhalation to 20, 38 and 80 ppm (154, 292, and 615 mg/m^3) of the substance for 23 hours per day over 10 days, beginning on day 6 of gestation.[29] The animals were killed on gestational days 20 (rats) and 18 (mice). Significant adult mortality occurred in rats at 80 ppm (615 mg/m^3) and in mice at 38 and 80 ppm (292 and 615 mg/m^3; at the highest dose all mice died untimely). Adverse effects on maternal welfare, as assessed from weight change, feed consumption and survival, occurred at all concentrations in both species. Fetal mortality was increased in rats at 80 ppm (615 mg/m^3) and in mice at 38 ppm (292 mg/m^3). Fetal body weights were reduced in rats at 38 ppm (292 mg/mg^3) and in mice at 20 and 38 ppm (154 and 292 mg/m^3).

Male Fischer 344 rats were treated by sub-acute intraperitoneal injection of a daily dose of 1.25, 2.5, 5 or 10 mg/kg body weight 1,2-dibromoethane on five successive days.[32] Four or nine weeks after the last injection, males were crossed with virgin females. Significant differences in the development of motor coordination and motor activity were observed in the F1 progeny.

2.3.3 Genotoxicity

Studies investigating the genotoxicity of 1,2-dibromoethane have been reviewed by the IARC4 and the EPA.[5] A summary of the most relevant

data is given below. Additional literature is noted where appropriate.

Gene mutation tests

1,2-Dibromoethane has been tested for mutagenicity in vivo in the transgenic Big Blue® mice assay (utilizing the cII gene).[33] Male mice (5/group) were treated with 1,2-dibromoethane (30 mg/kg bw i.p. in corn oil), whereas control animals were treated with corn oil only. Dibromoethane treatment increased the cII mutant frequency in the liver 6-fold at 6 hours after treatment.

1,2-Dibromoethane was mutagenic in *Eschericia* coli and in the *Salmonella typhimurium* strains TA98, TA100 and TA1535 both in the absence and the presence of an exogenous metabolic system, and in *Streptomyces coelicolor* and *Aspergillus nidulans* (the fungal strains were not tested with metabolic activation). The substance was negative, with and without metabolic activation, in *Salmonella typhimurium* strains TA1537 and TA1538. Mutations were also induced in cultured mammalian cells: Chinese hamster ovary cells and mouse lymphoma L5178Y cells, tk-locus (with and without metabolic activation); two human lymphoblastoid cell lines (AHH-1 and TK6; tested without metabolic activation).

In vivo, the substance induced somatic mutations and sex-linked recessive lethal mutations in *Drosophila melanogaster*.

Cytogenetic tests

1,2-Dibromoethane has been tested in an in vivo rat alkaline comet assay.[34] 1,2-Dibromoethane was administered to 5 male Sprague-Dawley rats per group (25, 50, and 100 mg/kg/day) by oral gavage at 48, 24, and 3 h before analysis. Single cells were collected from the liver and glandular stomach at 3 h after the final dosing. From the same animals also bone marrow cells were collected for measuring the induction of micronuclei. 1,2-Dibromoethane tested positive in the comet assay, and negative in the micronucleus assay.

In addition, 1,2-dibromoethane has been shown to induce DNA strand breaks in vivo in liver cells of rats treated orally; in testicular germ cells of rats treated intraperitoneally; in the stomach, kidney, liver, lung and bladder of mice treated intraperitoneally. 1,2-Dibromoethane was negative in dominant lethal tests in rats treated orally and in mice treated orally or intraperitoneally. The substance was also negative when tested for micronuclei in bone marrow or peripheral erythrocytes of mice treated intraperitoneally.

In vitro, sister chromatid exchanges and chromosomal aberrations were induced in Chinese hamster lung V79 cells (tested only without metabolic activation) and in Chinese hamster ovary cells (with and without metabolic activation). Sister chromatid exchanges were also induced in human peripheral lymphocyte cultures (tested only without metabolic activation). The substance was positive in unscheduled DNA synthesis assays in rat spermatocytes and primary hepatocytes (tested only without metabolic

activation). Micronuclei were induced in cultured human lymphocytes (tested only without metabolic activation). Transformations were induced in BALB/c-3T3 cells in the absence and presence of a metabolic activation system. The substance induced DNA strand breaks in vitro in hepatocytes and testicular germ cells of rats (tested only without metabolic activation), and in testicular cells isolated from human organ transplant donors.

Miscellaneous

In vivo, treatment with 1,2-dibromoethane (30 mg/kg bw i.p. in corn oil) increased dibromoethane-GSH DNA adducts (N7-guanyl) in a transgenic mouse model.[33]

In vitro, 1,2-dibromoethane produced DNA-adducts in calf thymus DNA (tested with metabolic activation system) and in human and rat hepatocytes (tested without metabolic activation). Intraperitoneal administration of the substance to rats and mice resulted in binding to DNA, RNA and proteins in various organs (liver, kidney, stomach, lung).

In 1987, DECOS concluded that 1,2-dibromoethane should be considered a genotoxic carcinogen.[35] In 2011, SCOEL concluded that 1,2-dibromoethane should be regarded as a genotoxic carcinogen with no threshold.[6]

2.4 Existing occupational exposure limits

Table 1 presents the occupational exposure limits established by the regulatory authorities of the Netherlands, the United Kingdom, Denmark, and by the USA-NIOSH and USA-OSHA. The European Union did not assign occupational exposure limits because the Scientific Committee on Occupational Exposure Limits (SCOEL) concluded that the quantitative data on carcinogenicity and the present state of toxicokinetic interspecies modelling do not permit a reasonable and reliable quantitative cancer risk assessment for humans.[6]

Table 1. Occupational exposure limits of 1,2-dibromoethane[a]

Country (Organization)	OEL (ppm)	OEL (mg/m³)	TWA	Type of exposure limit
The Netherlands[b]	-	0.002	8h	OEL
European Union	-[d]	-[d]	-	-
Germany (DFG)	-	-	-	-
Germany (AGS)	-	-	-	-
France	-	-	-	-
UK (HSE)[b]	0.5[d]	3.9[d]	8h	WEL
Denmark[b]	0.1[d]	1[d]	8h	OEL
Sweden	-	-	-	-
USA (NIOSH)[c]	0.045	-	8h	REL
USA (OSHA)[c]	20	-	8h	PEL

[a] http://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx [accessed May 3rd, 2017]; WEL: workplace exposure limit; PEL: permissible exposure limit; REL: recommended exposure limit; TWA: time-weighted average

[b] www.ser.nl,

[c] www.osha.gov

[d] skin notation

03 carcinogenicity studies

3.1 Human studies

The Committee identified four epidemiological studies investigating mortality among workers (potentially) exposed to 1,2-dibromoethane. Two studies examined the mortality of grain workers/chemical production workers, in order to relate occupational exposure to multiple chemicals with specific causes of death. In these studies workers were exposed to multiple substances, making it impossible to determine the effect of exposure to solely 1,2-dibromoethane on mortality.[36,37] The studies were therefore excluded from further evaluation.

In a retrospective cohort study by Ott et al. (1980), a total of 161 1,2-dibromoethane exposed male workers from two production units were studied.[38] However, exposure to multiple other (potentially carcinogenic) substances at various times in the past made it impossible to determine the specific effect of 1,2-dibromoethane on mortality. This study was, therefore, also excluded from further evaluation.

Turner et al. (1979) examined mortality data for individuals who had been employed in two factories producing halogenated hydrocarbons.[39] Both factories were situated remotely from any other chemical industry. A summary of this study is presented in Table 2. In this study, 117 men from factory A and 195 men from factory B were identified as potentially exposed workers. The workers were exposed to 1,2-dibromoethane for at least four years during the periods 1940-1970 (factory A) and 1954-1975

Table 2. Epidemiological studies

Study design and population (Reference)	Data on exposure and health assessment	Results	Remarks
Type of study: Retrospective cohort study Country: UK Follow-up period: unknown Participants: 117 exposed male workers (factory A) and 195 exposed workers (factory B) Control: local population (Turner et al. (1979)[39])	No information on exposure levels and duration. No statistical analysis	Mortality death rate due to cancer per 1000 man years (workers/controls): Factory A: 25-44 y: 0/0.32; 45-64 y: 0.69/3.44; 65-74 y: 11.30/11.65; ≥75 y: 21.28/16.99 Factory B: 25-44 y: 0.6/0.3; 45-64 y: 4.2/4.0; 65-74 y: 12.3/12.9; ≥75 y: not reported/21.5	Study contains several flaws. No data on exposure levels and duration, no follow-up time reported, small number of participants, no statistical analysis performed

y: year of age

(factory B). Workers were divided in four age groups (25-44, 45-64, 65-74, ≥75). The death rates from all causes, including cancer, within each age group were compared with the values for the general population in the same part of the country over a similar period. The death rates due to cancer for the workers were comparable to, or lower than those for the local population in both factories, except for the ≥75 age group in plant A which was higher for the workers. Also this study has several limitations (i.e. no information on exposure levels and duration, small number of participants, no follow-up time, no statistical analysis performed).

The Committee considers the epidemiological studies on 1,2-dibromoethane exposure and cancer not suitable for risk calculation.

3.2 Animal experiments

In Table 3, the carcinogenicity studies in experimental animals are summarised. These studies comprise five inhalation studies (three in rats, two in mice), five oral studies (one in rats, four in mice), and one intraperitoneal study and one dermal study in mice. The carcinogenicity results of these studies are presented below, starting with the most reliable studies. Results on non-cancer endpoints seen in these studies (body weight, mortality and other) are presented in Section 2.3 'Toxicity profile'.

Inhalation exposure

The National Toxicology Program (NTP) performed inhalation carcinogenicity bioassays in rats and mice.[17] Male and female Fisher 344 rats and B6C3F$_1$ mice (50 animals/sex/group) were exposed to concentrations 10 or 40 ppm (77 or 308 mg/m^3) 1,2-dibromoethane for 6 hours/day, 5 days/week for a maximum of 103 weeks. Due to high mortality, high dose male and female rats, all male mice and high dose female mice were sacrificed about 3-6 months before the scheduled termination. In rats 1,2-dibromoethane caused increased incidences of tumours in the nasal cavity (carcinomas, adenocarcinomas, adenomas and adenomatous polyps) in both sexes, of hemangiosarcomas of the circulatory system in both sexes, of mesotheliomas of the tunica vaginalis in male rats, and of mammary gland fibroadenomas and lung tumours (predominantly alveolar/bronchiolar carcinomas) in female rats. The incidences of the tumours in the nasal cavity, tunica vaginalis and mammary gland were increased statistically significantly at 10 and 40 ppm (77 and 308 mg/m^3), whereas the incidences of the pulmonary and circulatory system tumours reached statistical significance at 40 ppm (308 mg/m^3) only. In mice, 1,2-dibromoethane induced lung tumours (alveolar/bronchiolar carcinomas and adenomas) in both sexes, and tumours of the nasal cavity (predominantly carcinomas), of hemangiosarcomas of the circulatory system, of mammary gland adenocarcinomas, and of fibrosarcomas in subcutaneous tissue or rib in female mice. The incidences of the tumours in the circulatory system, mammary gland and subcutaneous tissue/rib were statistically significantly increased at 10 and 40 ppm (77 and 308 mg/m^3) whereas the nasal and pulmonary tumours reached statistical significance at 40 ppm (308 mg/m^3) only. See Table 3 for incidences and statistical significances of the above tumours in rats and mice.

Adkins et al. (1986) used 1,2-dibromoethane as a model compound to validate a short-term (6 months) in vivo model, using strain A/J mice exposed by inhalation, for predicting the carcinogenic potential of chemicals.[40] Examination for tumours was limited to the lungs. At the concentrations tested (20 and 50 ppm, 154 and 385 mg/m^3) 1,2-dibromoethane induced a dose-related increase in grossly visible lung adenomas.

Table 3. Animal carcinogenicity studies

Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Inhalation exposure			
F344 rats Control and exposed groups: 50 rats/sex/group (NTP (1982)[17])	Inhalation exposure (whole body), 6 hr/day, 5 days/wk Purity: 99.3-99.4% Target concentrations: 10 and 40 ppm (77 and 308 mg/m^3, actual resp. 10.02±0.84 and 38.93±2.55 ppm) X_{po}=103 wk (control, low), 88 wk (males high), 91 wk (females high) X_{pe}=104-106 wk (control, low), 89 wk (males high), 91 wk (females high) Statistical analysis tumour incidences: one-tailed Fisher exact test to compare dosed groups with control; Cochran-Armitage test for linear trend; approximate 95% confidence interval for relative risk of each dosed group compared with its control	Survival: decreased at 40 ppm in both sexes (resulting in early termination at wk 89/91 for males/females). Survivors at termination at 0, 10 and 40 ppm: males 38/50, 35/50, 5/50; females 38/50, 39/50, 8/50 Adverse effects: weakness of limbs or body at 40 ppm from wk 52; lower body weight at 40 ppm throughout study; hepatic necrosis, toxic nephropathy, testicular degeneration, retinal degeneration, adrenal cortex degeneration at 10 and 40 ppm (incidence generally decreased with dose); epithelial hyperplasia, squamous metaplasia and suppurative inflammation were prominent in respiratory system Tumours: at 0, 10, 40 ppm, resp **(m / f = males / females):** *Nasal cavity:* • carcinoma: m 0/50, 0/50, 21/50 (p<0.001) ; f 0/50, 0/50, 25/50 (p<0.001) • adenocarcinoma: m 0/50, 20/50 (p<0.001), 28/50 (p<0.001) ; f 0/50, 20/50 (p<0.001), 29/50 (p<0.001) • adenoma: m 0/50, 11/50 (p=0.001), 0/50; f 0/50, 11/50 (p<0.001), 3/50 • adenomatous polyp: m 0/50, 18/50 (p<0.001), 5/50 (p=0.028) ; f 0/50, 5/50 (p=0.028), 5/50 (p=0.028) • squamous cell carcinoma: m 0/50, 3/50, 3/50 ; f 1/50, 1/50, 5/50 • above nasal cavity tumours combined: m 0/50, 39/50 (p<0.001), 41/50 (p<0.001); f 1/50, 34/50 (p<0.001), 43/50 (p<0.001) Hemangiosarcoma (circulatory system): m 0/50, 1/50, 15/50 (p<0.001); f 0/50, 0/50, 5/50 (p=0.028) **Only male:** *Mesothelioma*: • tunica vaginalis: 1/50, 8/50 (p=0.015), 25/50 (p<0.001) • multiple organs: 0/50, 5/50 (p=0.028), 1/50 **Only female:** *Lung:* carcinoma or adenoma: 0/50, 0/48, 5/47 (p=0.024) *Mammary gland:* adenocarcinoma: 1/50, 0/50, 4/50 *Mammary gland:* fibroadenoma: 4/50, 29/50 (p<0.001), 24/50 (p<0.001)	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment and derivation of cancer risk values Deficiencies: maximum tolerated dose exceeded in high-dose group, individual animal data not reported, no statistical analysis conducted on non-neoplastic lesions, no adjustment for intergroup differences in survival in statistical analysis of tumour data

		The above tumours were related to treatment. The incidences of the following tumours showed a dose-related positive linear trend. However, as Fisher's test for differences between dosed groups and controls was not significant the relationship to treatment was not clear *Thyroid:* follicular cell adenomas or carcinomas in males: 0/48, 0/50, 3/46 *Salivary gland:* sarcomas (unspecified or invasive) in males: 0/49, 1/50, 3/48 *Subcutaneous tissue:* fibroma or fibrosarcoma, in females: 0/50, 0/50, 4/50 *Liver:* hepatocellular carcinoma in females: 0/50, 1/49, 3/48	
B6C3F1 mice Control and exposed groups: 50 mice/sex/group (NTP (1982)[17])	Inhalation exposure (whole body), 6 hr/day, 5 days/wk Purity: 99.3-99.4% Target concentrations: 10 and 40 ppm (77 and 308 mg/m^3, actual resp. 10.02±0.84 and 38.93 ±2.55 ppm) X_{po}=78 wk (all males), 103 wk (females control, low), 91 wk (females high) X_{pe}=79 wk (all males), 104-106 wk (females control, low), 90 wk (females high) Statistical analysis tumour incidences: one-tailed Fisher exact test to compare dosed groups with control; Cochran-Armitage test for linear trend; Approximate 95% confidence interval for relative risk of each dosed group compared with its control	Survival: poor survival in control and dosed males due to ascending suppurative urinary tract infection which was not related to treatment (resulting in early termination of all males at wk 79); Compared with controls, survival was decreased at 10 ppm in males and, dose-dependently at 10 and 40 ppm in females. Survivors at termination at 0, 10 and 40 ppm: males 13/50, 11/50, 18/50; females 40/50,19/50, 7/50 Adverse effects: weakness of limbs or body at 40 ppm in 2nd year; lower body weight at 40 ppm throughout study; epithelial hyperplasia throughout respiratory system at 10 and 40 ppm Tumours: at 0, 10, 40 ppm, resp **(m / f = males / females):** *Lung* (alveolar/bronchiolar): • carcinoma: m 0/41, 3/48, 19/46 (p<0.001); f 1/49, 5/49, 37/50 (p<0.001) • adenoma: m 0/41, 0/48, 11/46 (p<0.001); f 3/49, 7/49, 13/50 (p=0.007) *Lung* (bronchus): • adenoma or adenomatous polyp: m 0/41, 0/48, 5/46 (p=0.037); f 0/49, 0/49, 6/50 (p=0.014) *Circulatory system:* • hemangiosarcoma: m 0/45, 0/50, 4/50 (significant positive trend); f 0/50, 11/50 (p<0.001), 23/50 (p<0.001) **Only female:** *Mammary gland adenocarcinoma:* 2/50, 14/50 (p<0.001), 8/50 (0.046) *Subcutaneous tissue or rib:* fibrosarcoma: 0/50, 5/50 (p=0.028), 11/50 (p<0.001)	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment Deficiencies: poor survival in males, maximum tolerated dose exceeded in high-dose females, individual animal data not reported, no statistical analysis conducted on non-neoplastic lesions, no adjustment for intergroup differences in survival in statistical analysis of tumour data

		Nasal cavity: • carcinoma : 0/50, 0/50, 6/50 (p=0.013) • carcinoma or adenoma: 0/50, 0/50, 8/50 (p=0.003) • adenomatous polyp or adenoma: 0/50, 0/50, 5/50 (p=0.028) Circulatory system: hemangioma: 0/50, 1/50, 4/50 (significant positive trend)	
Short-term lung tumour bioassay female A/J mice Control and exposed groups: 30 (study 1) or 60 (study 2) mice/group (Adkins et al. (1986)[40])	Inhalation exposure (whole body), 6 hr/day, 5 days/wk Purity: 98-99% Target concentrations: 20 and 50 ppm (154 and 385 mg/m^3, actual concentrations not reported) X_{po}=X_{pe}=6 months Effect parameter: Number of lung adenomas observed at necropsy Statistical analysis: Kruskal-Wallis analysis of variance followed by Duncan's new multiple-range test for comparison with control	Survival: decreased survival at 20 and 50 ppm in study 1 (number of survivors 30/30 control, 11/30 in both exposed groups) Adverse effects: alveolar epithelial hyperplasia (frequently located parabronchiolar; not seen in controls), multifocal hyperplasia and cellular atypia of bronchiolar epithelium, chronic inflammation (mononuclear cells in bronchiolar lamina propria) Tumours: % of mice with lung adenoma at 0, 20 and 50 ppm, resp: Study 1: 51, 100, 100 Study 2: 26, 68, 100 Mean no. of lung adenoma/mouse ±SD at 0, 20 and 50 ppm, resp: Study 1: 0.97±1.07, 6.51±3.67, 17.0±4.09 Study 2: 0.31±0.54, 1.28±1.18, 15.3±5.01 (p<0.05 at both concentrations in both studies)	Klimisch score: 3 Supportive study Deficiencies: only one sex used, individual animal data not reported, limited information on non-cancer effects, exposure period too short, tumour detection limited to grossly visible lung tumours
B6C3F1 mice Control and exposed groups: 50 mice/sex/ group (Stinson et al. (1981)[18])	Inhalation exposure (whole body), 6 hr/day, 5 days/wk Target concentrations: 10 and 40 ppm (77 and 308 mg/m3, actual concentrations were kept within 10% of target) Purity: 99.3% Xpo = 90 (high), 103 (low) or 104 (control) weeks Xpe = 91 (high), 104 (low, control) weeks Histopathological examination limited to the nasal cavity. Statistical analysis: not performed	Survival: not reported Adverse effects: in nasal cavity: focal epithelial hyperplasia in 2-6% low-dose mice and ca. 20% high-dose mice. Tumours: in nasal cavity, at 0, 10 and 40 ppm resp. **(m / f = males / females)** *Benign neoplasms:* • squamous papilloma: m 0/45, 0/44, 3/46; f 0/50, 0/49, 7/49 • adenoma: m none; f 0/50, 0/49, 2/49 *Carcinoma:* • squamous carcinoma: m none; f 0/50, 0/49, 2/49 • adenocarcinoma: m none; f 0/50, 0/49, 2/49 • mixed carcinoma: m none; f 0/50, 0/49, 3/49 *Sarcoma:* • hemangiosarcoma: m none; f 0/50, 0/49, 2/49 • poorly differentiated: m none; f 0/50, 1/49, 0/49	Klimisch score: 3 Supportive study Deficiencies: tumour detection limited to nasal cavity, no information on non-cancer endpoints (except for non-neoplastic lesions in nasal cavity), individual animal data not reported, no statistical analysis

Sprague-Dawley rats male/ female Control and exposed groups: 48 rats/sex/Group (Wong et al. (1982)[19])	Inhalation exposure (whole body), 7 hr/day, 5 days/wk Purity: 99% Target concentration: 20 ppm (154 mg/m^3, actual 18.6±3.1 ppm) X_{po}=X_{pe}=18 months Statistical analysis tumour incidences: Fisher's exact test	Survival: decreased in exposed rats; ca. 90% of controls and 10% / 23% (male/female) exposed rats alive at 18 months Adverse effects: reduced weight gain (food intake was not affected), spleen atrophy (males only), Tumours: at 0 and 20 ppm resp. **(m / f = males / females)** *Spleen*: • hemangiosarcoma: m 0/48, 10/46 (p<0.05); f 0/48, 6/48 (p<0.05) *Adrenal*: • pheochromocytoma, cortical adenoma or carcinoma: m 2/48, 11/46 (p<0.05); f 1/48, 6/48 (p<0.05) *Subcutaneous:* • mesenchymal tumour: m 3/48, 11/46 (p<0.05); f 0/48, 1/48 *Mammary gland:* • adenoma, fibroadenoma, carcinoma, adenocarcinoma: f 2/48, 25/48 (p<0.05) Number of rats with tumour: m 8/48, 25/46 (p<0.05); f 7/48, 29/48 (p<0.05)	Klimisch score: 3 Supportive study Deficiencies: only one concentration tested, individual animal data not reported, high mortality in exposed rats, exposure period less than life-span, in case of different types of tumours in the same organ only combined incidence is reported, nasal cavity not examined
Oral and intraperitoneal exposure			
B6C3F1 mice Male/female exposed: 50/sex control:100/sex (Van Duuren et al. (1986)[22])	Drinking water Exposure level: 2 mM (0.375 g/L) in drinking water, equivalent to a mean substance intake of ca. 50 mg/kg bw/day in both sexes X_{po}=control 24 months, exposed 18 months X_{pe}=X_{po} Statistical analysis tumour incidences: chi-square analysis	Survival: decreased survival in exposed group Adverse effects: decreased water consumption and body weight Tumours: in control and exposed resp. **(m / f = males / females)** *Forestomach*: • squamous cell carcinomas: m 2/99, 41/48 (p<0.0005); f 0/96, 20/49 (p<0.0005) • papillomas: m 5/99, 6/48; f 9/96, 29/49 (p<0.0005) *Oesophagus:* • squamous cell carcinomas: m 0/99, 4/48(p<0.01); none in females • papillomas: m 0/99, 4/48 (p<0.01); f 0/96, 4/49 *Tongue:* • squamous carcinoma in situ: f 0/96, 1/49 ; none in males	Klimisch score: 3 Supportive study Deficiencies: no data on compound purity, only one dose tested, exposure less than life-span, Xpe and Xpo for exposed mice shorter than for controls, individual animal data not reported, limited information on non-cancer effects, no adjustment for intergroup differences in survival in statistical analysis of tumour data
B6C3F1 mice Male/female exposed: 30/sex control: 50/sex (van Duuren et al. (1985)[23])	Drinking water Purity >99% Exposure level: 4 mM in drinking water, equivalent to a mean substance intake of 103 and 116 mg/kg bw/day in males and females resp. X_{po}=control 18 months, exposed ca. 13 (males) or 15 (females) months	Survival: exposed mice were killed before scheduled termination because of morbidity from stomach tumours Median survival time was 389/465 days in males and females resp. Survival controls: ca. 70% at 18 months Adverse effects: water consumption decreased by 34% / 25% (males/ females); body weight 10-20% lower than control from ca. 9 months Tumours: in control and exposed resp.	Klimisch score: 3 Supportive study Deficiencies: only one dose tested, exposure less than life-span, X_{pe} and X_{po} for exposed mice shorter than for controls, low number of exposed animals, individual animal data not reported, limited number of organs examined, limited information on non-cancer effects, no adjustment for intergroup differences in survival in

	$X_{pe}=X_{po}$ Histopathological examination limited to lung, liver, kidneys, stomach and gross lesions Statistical analysis tumour incidences: chi-square analysis	**(m / f = males / females)** *Forestomach:* • squamous cell carcinomas: m 0/45, 26/28 (p<0.005); f 0/50, 22/29 (p<0.005) • papillomas: m 1/45, 0/28); f 1/50, 5/29 *Glandular stomach:* • quamous cell carcinomas: m 0/45, 8/28 (p<0.005); none in females *Oesophagus:* • papillomas: f 0/50, 3/29 (p<0.0005), none in males	statistical analysis of tumour data
Osborne-Mendal rats Exposed: 50 rats/sex/dose Vehicle control: 20/sex Untreated control: 20/sex (started 15 wk later than vehicle and dosed groups) (NCI (1978)[20])	Oral gavage, 5 days/week Purity: ≥99% Vehicle: corn oil Doses: TWA (mg/kg body weight/day): • male: 38, 41 • female: 37, 39 Initial doses were 40 and 80 mg; high discontinued ≥wk 17 and reduced to 40 ≥wk 30; low & high not dosed in wk 42 Xpo dosed and vehicle control = 48/60 wk (males/females) X_{pe} dosed = 49/61 wk (males/females) X_{pe} vehicle control = 63 wk Untreated controls: 5/sex killed wk 59, remaining wk 107 Statistical analysis tumour incidences: (time-adjusted) one- tailed Fisher exact test to compare dosed groups with control; (time-adjusted) Cochran-Armitage test for linear trend; approximate 95% confidence interval for relative risk of each dosed group compared with its control	Survival: dose related decrease in survival of both sexes. Treated rats terminated in week 49 (males) and 61 (females) due to poor survival associated with early onset of stomach cancer Adverse effects: reduced body weight from wk 10 in all dosed groups; reddened ears, hunched appearance, firm distended abdomen, abdominal urine stains; acanthosis and hyperkeratosis in forestomach, degenerative changes in liver and adrenals, testicular atrophy Tumours: In vehicle control, low- and high-dose, resp **(m / f = males / females)** *Forestomach:* quamous cell carcinoma: m 0/20, 45/50 (p<0.001), 33/50 (p<0.001); f 0/20, 40/50 (p<0.001), 29/50 (p<0.001) *Hemangiosarcoma* (circulatory system): m 0/20, 11/50 (p=0.017), 4/50; f 0/20,1/49, 3/48 *Liver*: • hepatocellular carcinoma: m 0/20, 1/50, 1/50; f 0/20, 1/47, 5/48 (p<0.05 time-adjusted Fisher) • neoplastic nodules: m 0/20, 2/50, 1/50; f 0/20, 0/47, 1/48 *Thyroid follicular-cell* adenoma or carcinoma: m 0/20, 5/50, 8/49 (p<0.05 trend); no increase in females	Klimisch score: 3 Supportive study Deficiencies: early termination because of high mortality, doses changed and discontinued during study, dose per animal based on group mean instead of individual animal body weight, individual animal data not reported, animals housed in room with animals treated with other halogenated hydrocarbons
B6C3F1 mice Exposed: 50 mice/sex/dose Vehicle control: 20/sex Untreated control: 20/sex(1978)[20])	Oral gavage, 5 days/week Purity: ≥99% Vehicle: corn oil Doses: TWA (mg/kg body weight/day): 62, 107 Initial doses were 60 and 120 mg; increased to 100 and 200 wk11-12, next 60, 120; high reduced	Survival: dose related decrease in survival of both sexes, leading to termination before scheduled termination in wk 90. Vehicle controls were terminated before wk 90 because they approached moribund state Adverse effects: reduced body weight from wk 10 in all dosed groups; alopecia, body sores, soft faeces at low and high dose, thin and hunched appearance at high dose; acanthosis and hyper-keratosis in forestomach mainly at high-dose	Klimisch score: 3 Supportive study Deficiencies: early termination because of high mortality, doses changed during the study, dose per animal based on group mean instead of individual animal body weight, individual animal data not reported, animals housed in room with animals treated with other halogenated hydrocarbons

	to 60 ≥wk 40; ≥wk 54 vehicle, low and high no longer gavaged X_{po}=53 wk X_{pe}=59-60 wk (vehicle control), 78 wk (untreated controls, low and high males, high females), 90 wk (low females) Statistical analysis tumour incidences: (time-adjusted) one- tailed Fisher exact test to compare dosed groups with control; (time-adjusted) Cochran-Armitage test for linear trend; approximate 95% confidence interval for relative risk of each dosed group compa-red with its control	Tumours: In untreated, vehicle control, low- and high-dose, resp. **(m / f = males / females)** *Forestomach:* squamous cell carcinoma: m 0/20, 0/20, 45/50 (p<0.001), 29/49 (p<0.001); f 0/20, 0/20, 46/49(p<0.001), 28/50 (p<0.001) *Lung:* alveolar/bronchiolar adenomas: m 0/18, 0/20, 4/45, 10/47 (p=0.029); f 0/20, 0/20, 10/43 (p=0.015), 6/46	
A/J mice exposed: 16/sex/dose/route vehicle control: 16/sex untreated control: 136 males, 131 females (Stoner et al. (1986)[43])	Intraperitoneal (ip) injection or oral gavage, 3 times/wk for 8 weeks Purity: reagent grade Vehicle (both routes): glycerol trioctanoate, 0.1 ml/mouse Doses (total, mg/kg): Ip: 168, 420, 840 (= 0.2, 0.5 and 1 x MTD) Oral: 840 mg/kg (=1xMTD) X_{po}=8 weeks X_{pe}=24weeks Statistical analysis: Wilcoxon nonpara-metric rank test for pairwise comparisons; Jonckheere non-parametric trend test	Survival: all animals survived Adverse effects: not reported Tumours: treatment-related increase observed only in ip-treated females at highest dose; % of mice with lung adenoma: Intraperitoneal injection: untreated, vehicle, 168, 420, 840 mg/kg resp. **(m / f = male / female)** m 38, 30,14, 20, 44;f 25, 30, 24, 56, 88 (p<0.001) *Oral:* untreated, vehicle, 840 mg/kg resp m 38, 20, 44; f 25, 14, 31	Klimisch score: 3 Supportive study Deficiencies: only one dose tested orally, exposure and observation period too short, individual animal data not reported, no information on non-cancer effects, histopathology limited to randomly selected lung nodules, liver and gross lesions in other organs
Dermal exposure			
Ha:ICR Swiss mice Vehicle control and exposed: 30 females/ group (Van Duuren et al. (1977)[44]	Dermal exposure, 3 applications/week in 0.2 ml acetone Purity: determined but not reported Doses: 25 and 50 mg/application/mouse X_{po} and X_{pe} not specified per substance (range 440-594 days) Statistical analysis: Chi-square analysis	Survival: not specified per substance (median ranged from 317 days to >589 days). Adverse effects: not reported Tumours: vehicle control, 25, 50 mg, resp: *Skin* (application site) • papilloma: 0/30, 2/30, 8/30 (p<0.001) • squamous cell carcinoma: 0/30, 2/30, 3/30 Lung: benign papillomas: 11/30, 24/30 (p<0.005), 26/30 (p<0.0005) *Forestomach:* • papillomas: 2/30, 3/30, 3/30 • squamous cell carcinoma: in 1/3 low-dose mice with papillomas	Klimisch score: 3 Supportive study Deficiencies: only sex used, small number of animals used, duration of exposure and observation period not specified and probably too short, individual animal data not reported, no information on non-cancer effects, histopathology limited to gross lesions, skin, liver, stomach and kidney, no information on prevention of oral exposure

X_{po} = duration of exposure; X_{pe} = duration of the experiment; SD = standard deviation; ip = intraperitoneal, TWA = time-weighted average, MTD = maximum tolerated dose. Klimisch scores were based on Klimisch et al.[46]

Stinson et al. (1981) exposed B6C3F1 mice by inhalation to 10 or 40 ppm (77 or 308 mg/m^3) of 1,2-dibromoethane (for 90 and 103 weeks, respectively) to examine the characteristics of chemical-induced proliferative lesions in the nasal cavity.[18] Hence, histopathological examination was limited to the nasal cavity. Exposure to 1,2-dibromoethane was associated with a broad spectrum of proliferative lesions, including carcinomas (in high-dose females only), benign neoplasms, focal epithelial hyperplasia, and hemangiosarcomas.

In a chronic inhalation study performed by Wong et al. (1982) Sprague-Dawley rats exposed to 20 ppm (154 mg/m^3) of 1,2-dibromoethane for 18 months developed tumours in the spleen (hemangiosarcoma), adrenals (pheochromocytoma, cortical adenoma or carcinoma), subcutaneous tissue or mammary gland (adenoma, fibroadenoma, carcinoma, adenocarcinoma).[19]

Oral and intraperitoneal exposure

Van Duuren and colleagues used 1,2-dibromoethane as positive control substance in carcinogenicity studies in B6C3F1 mice.[22,23] The mice received 1,2-dibromoethane via the drinking water, at concentrations of 2 mM or 4 mM until sacrifice at 13-18 months (controls were terminated at 24 months). These concentrations in drinking water provided daily doses of about 50 mg/kg body weight (2 mM, calculated by the Committee from the daily substance intake and the average body weight data reported by the authors) and 100 mg/kg body weight (4 mM, calculated by the authors). In both studies 1,2-dibromoethane induced squamous cell carcinomas in the forestomach in both sexes. Squamous cell carcinomas were also induced in the glandular stomach at 4mM and in the oesophagus at 2 mM, though at lower incidences than in the forestomach. Further, the incidences of papillomas in the forestomach and oesophagus were increased in exposed mice.

In a bioassay performed by the National Cancer Institute (NCI) the carcinogenicity of 1,2-dibromoethane upon oral administration (by gavage) was examined in Osborne-Mendal rats (time-weighted average (TWA) dose: about 40 mg/kg body weight/day in each of two treated groups) and B6C3F1 mice (TWA 62 and 107 mg/kg body weight/day).[20,41,42] In both species treatment was terminated after about one year because of high mortality which was associated with the early onset of stomach cancer. Most of the treated rats and mice developed squamous cell carcinomas in the forestomach. In addition, rats showed treatment-related increases in the incidences of hemangiosarcoma of the circulatory system (males), hepatocellular carcinomas (females) and thyroid follicular-cell adenomas or carcinomas (males), and mice showed a treatment-related increase in lung alveolar/bronchiolar adenomas.

Stoner et al. (1986) used 1,2-dibromoethane as a model compound to examine carcinogens representing different chemical classes for their ability to induce lung tumours in strain A/J mice following administration by oral gavage (840 mg/kg) or intraperitoneal injection (168, 420, 840 mg/kg) for 8 weeks (3 doses/week).[43] A significant increase in lung tumours

(adenomas) was observed only in intraperitoneally treated females at 840 mg/kg.

Dermal exposure

Van Duuren treated female Ha:ICR Swiss mice with thrice-weekly skin applications of 1,2-dibromoethane (25 or 50 mg per animal) for at least 440 days.[44] Upon dermal exposure 1,2-dibromoethane caused a significant increase in the incidence of benign papillomas in the lung at both dose levels. In addition, the incidences of papilloma and, to a lesser extent, squamous cell carcinoma in the skin (application site) were increased.

3.3 Selection of the suitable study for risk estimation in the occupational situation

The Committee considers the epidemiological studies on 1,2-dibromoethane exposure and cancer not suitable for risk calculation.

In 1999, the Committee considered the NTP rat carcinogenicity study[17] to be the most suitable study for the estimation of the potential cancer risk in humans under occupational exposure conditions. In this evaluation, the Committee reaches the same conclusion. The study is well performed, the exposure route (inhalation) is appropriate, the exposure period covered the largest part of the standard lifespan of the experimental animals, and group sizes are adequate.

In the previous report, it was stated that the NTP study report was not available to the Committee. Therefore, the Committee used the carcinogenicity data summarized by Gold et al. (1984)[45], i.e. the total number of animals with tumours. Combining numbers of tumours of different origin is not preferred by the Committee, as the mechanisms of tumourigenesis may not be comparable. Since the NTP report is now available, the Committee can derive cancer risk values based on specific types of tumours.

The Committee considers the tumours in the nose of the rat most critical. In this case, the Committee combined the numbers of benign and malignant nasal tumours (adenomatous polyp, adenoma, adenocarcinoma, carcinoma, squamous-cell carcinoma, papillary adenoma and squamous cell papilloma) as basis for cancer risk derivation, because the simultaneous occurrence suggests that benign nasal tumours can develop into the malignant type. The combined number of nasal tumours has the highest incidence, and is dose-dependently and statistically significantly increased at the lowest exposure concentration tested (10 ppm, 77 mg/m^3). The incidences of tumours at other sites than the nose were increased to a lesser extent. The same is true for the treatment-related tumours observed at 10 ppm (77 mg/m^3) in NTP's inhalation carcinogenicity study in mice.

3.4 Calculation of the health-based occupational cancer risk values

3.4.1 Carcinogenic activity in experimental animals, lifetime exposure

To calculate the carcinogenic activity expressed as the incidence per unit air concentration (mg/m^3) of 1,2-dibromoethane, the number of male rats which developed nasal cavity tumours upon exposure to the lowest concentration (10 ppm, i.e. 77 mg/m^3) tested in the carcinogenicity study performed by NTP was used as a starting point. In this study, male and female rats were exposed to the same concentrations. Since the highest incidence of nasal cavity tumours was observed in male rats (the incidence in female rats was only slightly lower), the incidence in male rats was used to derive the cancer risk levels.

For the calculation of the occupational cancer risk values, the Committee prefers to use the benchmark dose method. Though two doses have been tested (77 and 308 mg/m^3) in the NTP rat study, the highest dose exceeded the maximum tolerated dose. The significantly shortened survival in the highest dose group may have curtailed the number of tumours in this group. Therefore, the Committee considers only the low-dose data from the NTP rat study adequate, and therefore, the benchmark dose method cannot be applied.

The incidence per unit concentration in air (mg/m^3) (lifespan conditions assuming a linear concentration-response relationship) is calculated as follows:

$$I_{concentration} = \frac{I_e - I_c}{C \times \frac{X_{po}}{L} \times \frac{X_{pe}}{L} \times \frac{\text{exposure hours per day}}{24} \times \frac{\text{exposure days per week}}{7}}$$

$$= \frac{\frac{39}{50} - \frac{0}{50}}{77 \times \frac{721}{1000} \times \frac{728}{1000} \times \frac{6}{24} \quad \frac{5}{7}} = 10.8 \times 10^{-2} \text{ per } \frac{mg}{m^3}$$

Where:

$I_{concentration}$ = the carcinogenic activity attributable to the exposure to the substance per unit daily concentration in air expressed per mg/m^3

I_e and I_c = incidence of tumour bearing animals in exposed and control animals, respectively.

C = concentration at which animals were exposed expressed in mg/m^3.

X_{po} and X_{pe} are the exposure and experimental periods, respectively.

L = standard lifespan for the animals in question (L rat is assumed to be 1,000 days).

3.4.2 Health risk to humans, exposure under occupational conditions

For the calculation of cancer risk values on the basis of results from

animal experiments, the Committee does not apply default assessment factors (e.g. for differences between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility). Furthermore, it is assumed that the average man lives 75 years, is exposed 24 hours per day, 7 days per week, 52 weeks per year for lifetime and inhales 18 m^3 air per 24 hours. To estimate the additional lifetime risk of cancer in humans under workplace conditions it is further assumed that the average worker is exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years and inhales 10 m^3 air per 8-hour-working day.

Using as starting point the estimated incidence of 10.8 x 10^{-2} per mg/m^3, the additional life-time cancer risk per mg/m^3 under occupational exposure conditions (= HBC-OCRV) amounts to:

$$\text{HBC - OCRV} = 10.8 \times 10^{-2} \times \frac{40y}{75y} \times \frac{48w}{52w} \times \frac{5d}{7d} \times \frac{10m^3}{18m^3} = 2.1 \times 10^{-2} \text{ per } mg/m^3$$

3.4.3 Occupational cancer risk values

Based on the HBC-OCRV of 2.1 x 10^{-2} per mg/m^3, the Committee estimated that the concentration of 1,2-dibromoethane in the air, which corresponds to an excess cancer risk of:

- 4 per 1,000 (4x10^{-3}), for 40 years of occupational exposure, equals to 0.2 mg/m^3
- 4 per 100,000 (4x10^{-5}), for 40 years of occupational exposure, equals to 0.002 mg/m^3.

The Committee notes that these values are (rounded off) equal to the cancer risk values calculated by the Committee in 1999.[2] Based on the toxicity data as summarized in this report, the Committee concludes that no adverse effects other than carcinogenicity are expected at these concentrations.

04 skin notation

Experimental animal data indicate that 1,2-dibromoethane is absorbed through the skin. In rats, mortality occurred following a single application (see Section 2.3.2) and lung tumours were observed following repeated administration (see Section 3.2). Further, the substance was absorbed rapidly through the skin of guinea pigs as demonstrated by the rapidly increasing blood levels of the substance following dermal exposure.[3]

Based on the mortality in rats following a single dermal application, the SCOEL concluded that a skin notation appears justified.

The Committee considers a skin notation warranted when exposure of 2,000 cm^2 of skin (both hands and forearms) to the substance during one hour could result in an absorbed amount exceeding 10% of the amount that can be absorbed via the lungs on exposure for eight hours to the occupational exposure limit (HBC-OCRV).

For an HBC-OCRV of 0.2 mg/m^3 (see Section 3.4), the estimated systemic exposure on a 8-h working day is 2 mg (0.2 mg/m^3 x 10 m^3; assuming

100% retention in the lungs (worst-case scenario)). Calculations with Skinperm (AIHA version 130), applying a single dermal exposure of 50 mg, result in an estimated uptake of 0.82 mg. This uptake far exceeds an amount 10% of the systemic exposure at a level of the HBC-OCRV. Therefore, the Committee concludes that a skin notation is warranted for 1,2-dibromoethane.

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