



Recommendation from the Scientific Committee on Occupational Exposure Limits for vinyl bromide

SCOEL/SUM/155

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Recommendation from the Scientific Committee on Occupational Exposure Limits: Risk Assessment for Vinyl Bromide

8 hour TWA	:	not feasible to set an OEL
STEL (15 min)	:	not feasible to set an STEL
Additional classification	:	-
SCOEL carcinogen group	:	A (non-threshold carcinogen)

Quantitative risk assessment:

Reference is made to the assessed hepatic angiosarcoma risk of vinyl chloride (SCOEL/SUM/109). This was 3×10^{-4} for exposure to 1 ppm for working lifetime. It is advised to apply this risk assessment also to vinyl bromide, considering a 3-fold higher potency of vinyl bromide compared to vinyl chloride. The resulting angiosarcoma risk for working lifetime exposure to 1 ppm vinyl bromide amounts to 9×10^{-4} .

Substance Identity and Properties:

Vinyl bromide	C ₂ H ₃ Br
Classification:	Carc. Cat. 2; R45
Synonyms:	Bromoethylene
Chemical Name	Bromoethene
Structural Formula:	CH ₂ = CH - Br
CAS Number:	593 - 60 - 2
Molecular Weight:	106.96
Melting point:	-139.5°C
Boiling point:	15.8 °C
Vapour pressure:	119 kPa at 20°C
Conversion factors:	1 ppm = 4.37 mg/m ³
(20°C, 101.3kPa)	1 mg/m ³ = 0.229 ppm



1. Occurrence and Use

Vinyl bromide occurs as an intermediate in organic synthesis and in the manufacture of polymers, copolymers, flame retardants, pharmaceuticals and fumigants. Vinyl bromide is used primarily in polymers as a flame retardant in the production of acrylic fibres for carpet-backing material. It has also been used in small quantities as a co-monomer with acrylonitrile in the production of fabrics and fabric blends to be used in sleepwear and home furnishings. It is also copolymerized with vinyl acetate and maleic anhydride to produce granular products. Vinyl bromide-vinyl chloride copolymers are used for preparing films, for laminating fibres and as rubber substitutes. Vinyl bromide is also used in leather and fabricated metal products (IARC 1985, 1999).

Analysis

NIOSH (1979) has developed a method (OSHA Method 8) to measure vinyl bromide with a detection limit of 0.2 ppm (IARC 2008).

2. Health effects

According to IARC (1985, 1999), the only reported data on toxic effects in humans are as follows: Short-term inhalation of high concentrations of vinyl bromide [levels not given] is reported to cause loss of consciousness. Skin and eye contact with liquid vinyl bromide produced irritation and caused a 'frost-bite' type of burn (Fawcett, 1976; Benya *et al.*, 1982).

The oral LD₅₀ of vinyl bromide, given as a 50% solution in corn oil, was approximately 500 mg/ kg bw in male rats.

In subacute inhalation studies, rats were exposed to 44,000 mg/m³ (10,000 ppm) vinyl bromide in air for 7 h per day on five days a week for four weeks; and rats, rabbits and monkeys were exposed to 1100 or 2200 mg/ m³ (250 or 500 ppm) vinyl bromide for 6 h a day on five days a week for six months. No significant change was detected in food consumption, haematology, gross pathology or histopathology.

The hepatotoxicity of vinyl bromide in rats was enhanced by pretreatment with polychlorinated biphenyls. Aroclor 1254-pretreated rats exposed by inhalation for 4 h to 44,000 mg/ m³ (10,000 ppm) vinyl bromide showed increases in serum alanine-alpha-ketoglutarate transaminase and serum sorbitol dehydrogenase, and histological signs of liver damage. The enhancement was more pronounced in fasted than in fed rats (Conolly & Jaeger, 1977; Conolly *et al.*, 1978). Newborn Wistar rats exposed to 8800 mg/ m³ (2000 ppm) vinyl bromide for 8 h per day on five days per week for 8-15 weeks developed putatively pre-neoplastic ATPase-deficient foci in the liver, but to an extent about ten-fold lower than was seen after similar exposure to vinyl chloride (Bolt *et al.*, 1979, 1982).

No data are reported on effects of vinyl bromide on reproduction and prenatal toxicity.

2.1. Toxicokinetics and metabolism

Because of its low boiling point of 15.8°C, vinyl bromide is present at workplaces as a gas. Skin absorption must not be taken into account, and inhalation exposure is most important.

Inhalation pharmacokinetics of vinyl bromide have been studied in rats (Filser & Bolt, 1979, 1981; Gargas & Andersen, 1982). The compound was readily taken up by the lung and, at equilibrium, showed an 11-fold accumulation in the entire organism compared to the concentration in the gas phase. Cantoreggi and Keller (1997) reported a blood/air partition coefficient in rats of 4.05, which was about 2.5 fold



greater than that for vinyl chloride. Similarly, the tissue solubility of vinyl bromide was greater than of both vinyl chloride and vinyl fluoride. Metabolism was saturable at exposure concentrations of over 250 mg/ m³ (55 ppm) (Filser & Bolt, 1979) and was associated with the release of bromide into the plasma (Gargas & Andersen, 1982). Non-volatile bromide levels in the blood increased with duration of exposure to vinyl bromide in rats, rabbits and monkeys (Leong & Torkelson, 1970).

It was reported in an abstract that pretreatment of rats with phenobarbital accelerated the release of bromide from vinyl bromide in animals exposed to 88,000 mg/ m³ (20,000 ppm) vinyl bromide for 5 h per day, once, twice or for five or ten consecutive days (VanStee *et al.*, 1977).

When a mixture of vinyl bromide in air was passed through a mouse-liver microsomal system, a volatile alkylating metabolite was formed, as demonstrated by trapping with 4-(4-nitrobenzyl)pyridine (Barbin *et al.*, 1975; Bartsch *et al.*, 1976, 1979). Results of experiments *in vitro* indicate that the primary metabolite formed by monooxygenase from vinyl bromide is 2-bromoethylene oxide, while the rearrangement product of the latter, 2-bromoacetaldehyde, might be the major alkylating agent bound to protein (Guengerich *et al.*, 1981). Irreversible protein binding of metabolites of [1,2-¹⁴C]-vinyl bromide has been established both with rat-liver microsomes *in vitro* (Bolt *et al.*, 1978) and in rats *in vivo* (Bolt *et al.*, 1980).

A comparative study using isolated rat hepatocytes and hepatic sinusoidal cells revealed that the metabolism of vinyl bromide to reactive metabolites was confined primarily to hepatocytes (Ottenwälder & Bolt, 1980).

When incubated with liver microsomes from phenobarbital-treated rats, vinyl bromide alkylates the prosthetic group (haem) of cytochrome P-450. The alkylated moiety has been identified as the dimethyl ester of *N*-(2-oxoethyl)protoporphyrin IX (Ortiz de Montellano *et al.*, 1982). Incubation of [1,2-¹⁴C]-vinyl bromide with rat-liver microsomes and RNA resulted in alkylation of RNA and formation of 1,N⁶-ethenoadenosine and 3,N⁴-ethenocytidine. The same alkylation products occurred in the hepatic RNA of rats exposed to the radioactive compound (Ottenwälder *et al.*, 1979). Like other halogenated C₁ and C₂ compounds that are transformed to reactive metabolites, vinyl bromide alters rat intermediary metabolism, leading to increased exhalation of acetone (Filser *et al.*, 1982). Exposure of rats to 87,400 mg/ m³ (20,000 ppm) vinyl bromide for 4 h per day for ten days caused a decrease in hepatic cytochrome P-450 (Drew *et al.*, 1976).

The principal pathways of metabolism of vinyl bromide are compiled in Figure 1.

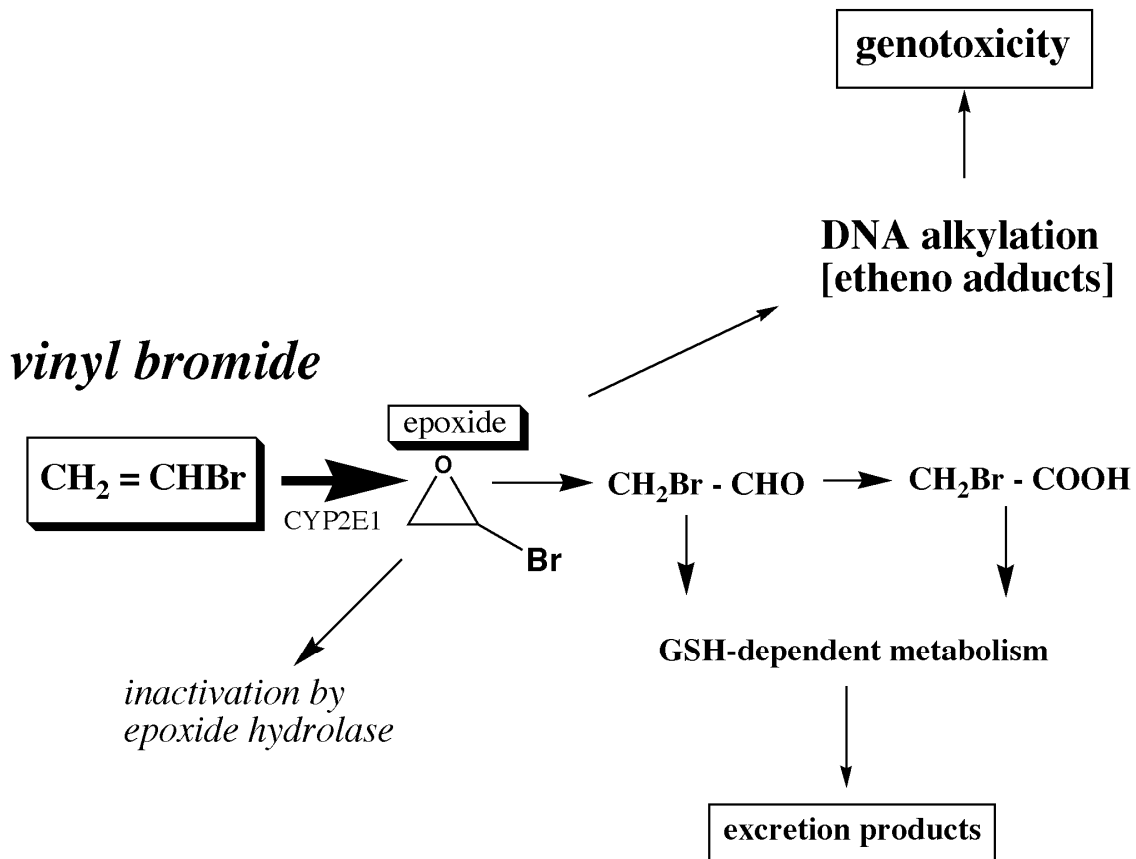


Figure 1: Metabolic activation of vinyl bromide to its genotoxic epoxide intermediate (bromoethylene oxide), and deactivation pathways of the epoxide

2.2. Mutagenicity/genotoxicity

Vinyl bromide (0.2-20% v/v in air for various time periods) was mutagenic to *Salmonella typhimurium* TA1530 and TA100 in the presence or absence of a metabolic System (S9) from the liver of Aroclor-induced rats or phenobarbital-induced mice or humans (Bartsch, 1976; Bartsch *et al.*, 1979; Lijinsky & Andrews, 1980). The compound induced somatic mutations in *Drosophila melanogaster* at airborne concentrations of 2000 or 4000 ppm (compilation: IARC 1999)

2.3. Carcinogenicity

No data in humans are available (IARC 2008).

The experimental carcinogenicity of vinyl bromide has been summarised by IARC (1985) as follows:

Skin application

A group of 30 female ICR/ Ha Swiss mice received topical applications of 15 mg vinyl bromide [purity unspecified] in 0.1 ml acetone thrice weekly for 60 weeks. No skin tumour was observed. In a two-stage skin carcinogenesis study to test for initiating activity, further groups of 30 mice received a single application of vinyl bromide followed by thrice-weekly applications for 60 weeks of 2.5 μg 12-O-tetradecanoylphorbol 13-acetate (TPA) in 0.1 ml acetone, a single application of 7,12-dimethylbenz[a]anthracene followed by treatment with TPA (positive controls), treatment with TPA only, or no treatment at all (160 mice). One of 30 mice treated with vinyl bromide followed by TPA developed a skin papilloma at 412 days; one skin



carcinoma occurred among the 30 TPA-treated controls after 44 days; no skin tumour developed in the 160 untreated controls within 420 days; and the positive-control group showed the expected high number of skin tumours (Van Duuren, 1977). [The Working Group noted that sites other than the skin were not examined, and that the test material was volatile.]

Inhalation exposure

Groups of 120 male and 120 female Sprague-Dawley rats, nine to ten weeks of age, were exposed to 10, 50, 250 or 1250 ppm (44, 219, 1093 or 5875 mg/ m³) vinyl bromide (purity, 99.9%; 0.02% hydroquinone methyl ether as stabilizer, as well as 0.03% ethylene oxide, 0.0007% acetylene, 0.008% aldehydes and ketones) in air for 6 h per day on five days per week for 104 weeks, at which time they were sacrificed. In the group exposed to 1250 ppm, exposure was terminated at 72 weeks because about 50% of animals had died, and the remainder were sacrificed. A group of 144 male and 144 female rats served as untreated controls. Average survival time was not stated. Treatment-related increases in the incidences of liver angiosarcoma were observed in all treated groups: males: 0/ 144 controls, 7/120 at 10 ppm ($p < 0.025$); 36/120 at 50 ppm ($p < 0.001$); 61/120 at 250 ppm ($p < 0.001$) and 43/120 at 1250 ppm ($p < 0.001$); females: 1/144, 10/120, 50/120, 61/120 and 41/120, respectively ($p < 0.001$ for all groups). In addition, increases were observed in the incidences of squamous-cell carcinoma of the Zymbal gland: males, 2/142, 1/99, 1/ 112, 13/ 114 ($p < 0.005$) and 35/ 116 ($p < 0.005$); females, 0/139, 0/99, 3/113, 2/119 and 11/114 ($p < 0.001$), neoplastic nodules and hepatocellular carcinoma: males, 4/143, 5/103, 10/119, 13/120 ($p < 0.025$) and 5/119; females: 7/142, 18/101 ($p < 0.005$), 12/113, 21/118 ($p < 0.005$) and 9/112 in treated animals compared to controls (Benya *et al.*, 1982).

Subcutaneous administration

A group of 30 female ICR/ Ha Swiss mice was injected subcutaneously with 25 mg/ animal vinyl bromide in 0.05 ml trioctanoin once weekly for 48 weeks and observed up to 420 days. No local tumour was seen in treated mice, nor in 30 mice given 48 weekly injections of trioctanoin alone, nor in 60 untreated controls observed up to 420 days (Van Duuren, 1977). [The Working Group noted that examination of the animals for pathological lesions was limited to the injection site.]

2.4. Comparison of carcinogenicity of vinyl bromide and vinyl chloride and assessment of risk

A long-term inhalation bioassay in Sprague-Dawley rats exposed to 0, 10, 50, 250 or 1250 ppm of vinyl bromide (6h/d, 5d/wk for 2 years) has revealed carcinogenic effects at all exposure concentrations (Benya *et al.* 1982; see above). Angiosarcomas, primarily of the liver, were induced in male and female rats. Primary angiosarcomas were also found in lung, spleen, nasal cavity and mesentery. An increase in the number of Zymbal gland neoplasms was found in male and female rats at the 50, 250 and 1250 ppm exposure levels; statistically significant increases were observed in male and female rats exposed at 1250 ppm and male rats at 250 ppm of vinyl chloride. An increased incidence of primary hepatocellular neoplasms was seen in males at 250 ppm and in females exposed at 10, 50 and 250 ppm. Thus, the endpoints of carcinogenicity of vinyl bromide are similar to those of vinyl chloride (see SCOEL/SUM/109). In particular, the unique induction of hepatic angiosarcomas is common to both vinyl halides.

As hepatic angiosarcomas have been observed in humans after occupational vinyl chloride exposure, it is highly plausible that vinyl bromide would also induce angiosarcomas in humans following similar exposure conditions. This analogy is supported by practically identical routes of metabolism and bioactivation of vinyl bromide and vinyl chloride (Barbin *et al.* 1975, Bolt *et al.* 1978, Guengerich *et al.* 1981) via the respective haloethylene oxide and haloacetaldehyde, leading to the formation of identical "etheno"



adducts at the nucleic acid bases (Ottenwalder et al. 1979). Thus, the available data point to a common mode of action for vinyl bromide and vinyl chloride (Bartsch et al. 1979). This parallelism of carcinogenicity of vinyl bromide and vinyl chloride is relevant for risk assessment, as the body of data on vinyl bromide is scarce, compared to that on vinyl chloride, for which a straight line of events has been established (Bolt 2005) from exocyclic "etheno" DNA adducts and pro-mutagenicity of these adducts, via effects of such mutations on protooncogenes/tumour suppressor genes and gene product levels, to the development of preneoplastic hepatic foci and to hepatic tumour development (angiosarcomas and hepatocellular carcinomas). These combined data also supported a linear dose-response relation for vinyl chloride at low doses.

For vinyl chloride, reasonable risk assessments are available (SCOEL/SUM/109). As pointed out by ACHIH (1992), the bioassay of vinyl bromide (Benya et al. 1982) has produced no clearcut dose-response relationship. However, this can be explained on toxicokinetic grounds. Both vinyl halides are primarily metabolised, presumably by CYP2E1, to the DNA-reactive and genotoxic haloethylene oxide (Guengerich et al. 1982; see also *Figure 1*). However, the kinetics of this conversion are different between vinyl chloride and vinyl bromide, as experimentally demonstrated in rats (Filser and Bolt 1979, 1981). At a lower concentration range, vinyl bromide is metabolised slightly (about 1.7 times) faster than vinyl chloride, but a plateau of maximal velocity (v_{max}) is already reached at 55 ppm inhalation exposure. By contrast, a v_{max} for vinyl chloride is reached at concentrations consistently higher than 250 ppm. Hence, up to 50 ppm in ambient air vinyl bromide is transformed to higher amounts of active metabolites per unit time than vinyl chloride is, but above 100 ppm more active metabolites are produced from vinyl chloride (Bolt 1988). Thus, at very high doses the carcinogenic effect of vinyl chloride is much higher than that of vinyl bromide, as also shown in the development of preneoplastic hepatic foci in newborn rats at 2000 ppm vinyl chloride and vinyl bromide exposures, respectively (see above).

A quantitative comparison of the experimental carcinogenicity of vinyl chloride and vinyl bromide, by integration of toxicokinetic elements, can be based on the following long-term studies (Bolt 1988):

1. Maltoni et al. (1974) and Maltoni and Lefemine (1975) exposed Sprague-Dawley rats (aged 11-17 wk) for 1 year (4 h/d; 5 d/wk) to vinyl chloride by *inhalation* and kept the animals then for lifetime without further exposure.
2. Feron et al. (1981) applied *oral* doses of vinyl chloride to Wistar rats (aged 5 wk) for 140 weeks (5 d/wk).
3. As already discussed in detail, Benya et al (1982) exposed rats for 2 years (6h/d; 5 d/wk) by *inhalation*.

When the different ultimately metabolised doses per unit time (day), under the respective dosing conditions, were considered, the resulting hepatic angiosarcoma incidences showed dose-dependencies as demonstrated in *Figure 2*. This comparison shows that the carcinogenic potential of both vinyl halides is quantitatively comparable. The vinyl chloride experiment reported by Maltoni and Lefemine (1975) shows a lower tumour yield, due to its shorter exposure time (1 year only) and a higher age of the animals at the beginning of the test, compared to that of Feron et al. (1981). Also, the integration of kinetic data allows to explain why the upper 3 vinyl bromide dose groups of Benya et al. (1982) did not show a clearcut dose-response, as the range of saturation of metabolism to the active principle had been reached in these exposure groups.

A comparison of the data of the oral bioassay with vinyl chloride of Feron et al. (1981) and of the inhalation bioassay with vinyl bromide of Benya et al. (1982) is possible, when toxicokinetics are considered; both compounds are similarly transformed in a first decisive step to the ultimate carcinogen, the respective epoxide (*Figure 1*). The carcinogenicity of the reactive metabolites produced per unit time from inhaled vinyl bromide is about 1.8 fold that of vinyl chloride metabolites (*Figure 2*). Because in the relevant low-dose range (below 50 ppm airborne exposure) vinyl bromide is about 1.7 times faster metabolised than



vinyl chloride, it can be derived that vinyl bromide is 3 times more carcinogenic than vinyl chloride at occupationally relevant exposure levels. This ratio is in accordance with the higher blood/air partition coefficient and the resulting higher tissue affinity of vinyl bromide, compared to vinyl chloride (see chapter "Toxicokinetics and Metabolism"). This notion is further supported by Storm and Rozman (1997), who introduced the bioassay data of vinyl chloride and vinyl bromide into different extrapolation models (no-threshold and threshold approaches). These authors claimed that humans were less susceptible to both vinyl halides than rats, and that vinyl bromide was more potent than vinyl chloride. The different approaches used, however, produced incongruent risk assessment figures. It appears therefore not possible to draw firm quantitative conclusions from these particular estimates.

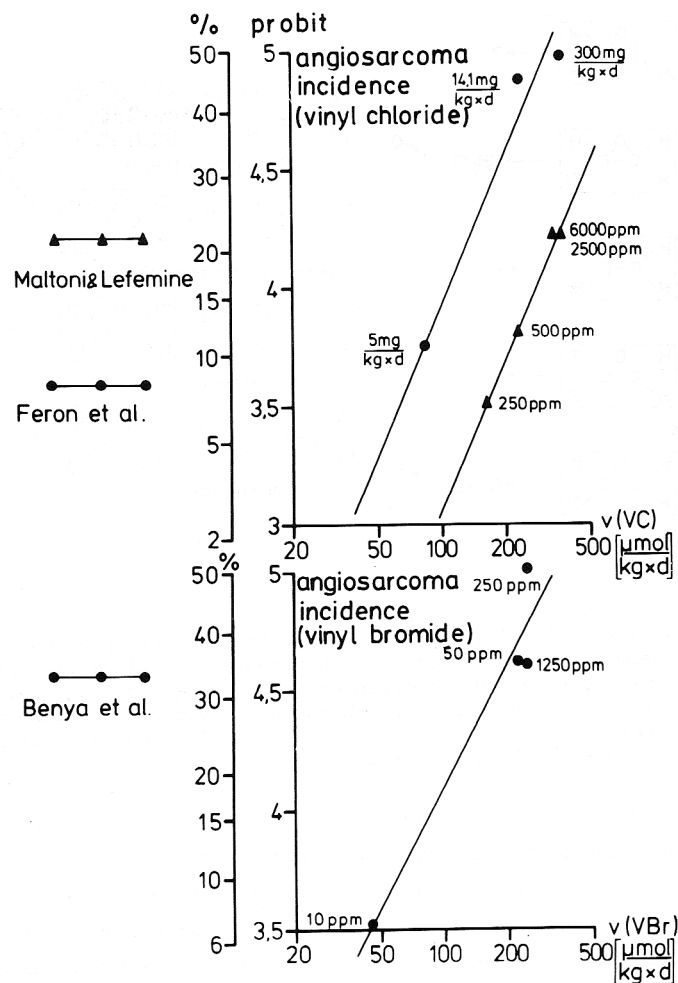


Figure 2: Hepatic angiosarcoma (haemangioepithelioma) incidences in 3 long-term bioassays of vinyl chloride (top panel) and vinyl bromide (bottom panel) in rats. Probit incidences are plotted versus the metabolised daily doses of the test compounds, under the conditions of the respective experiment. Calculated from the data of Maltoni and Lefemine (1975), Feron et al. (1981) and Benya et al. (1982). Reprinted from Bolt (1988).



Recommendation

Vinyl bromide is clearly carcinogenic in experimental animals. It has been categorized by IARC (2008) as “probably carcinogenic to humans (Group 2A)”. According to the available bioassay data the carcinogenic effects are similar to those of vinyl chloride. The close relation between vinyl bromide and vinyl chloride is supported by comparative data on metabolism, nucleic acid adduct formation and formation of pre-neoplastic hepatic foci. This is consistent with the view of IARC (2008) that vinyl bromide should be considered to act similarly to the established human carcinogen, vinyl chloride. A reasonable quantitative comparison of the experimental carcinogenicity of vinyl bromide and vinyl chloride is possible when toxicokinetic aspects are integrated. This leads to the conclusion that in the occupationally relevant low exposure range vinyl bromide appears to be about 3 times more active than vinyl chloride.

Based on the argumentations on the mode of action for vinyl chloride (SCOEL/SUM/109) and considering the close similarity of both vinyl halides no threshold mechanism can be supported for both vinyl halides. In consequence and according to the SCOEL strategy for carcinogens (Bolt and Huici-Montagud 2008), vinyl bromide is grouped into group A of carcinogens (*non-threshold carcinogen; for low-dose assessment of risk the linear non-threshold model appears appropriate*).

As the available body of data that can be used for a quantitative assessment of carcinogenic risk is much larger for vinyl chloride than for vinyl bromide, SCOEL recommends to use the existing quantitative risk assessment for vinyl chloride (SCOEL/SUM/109) also for vinyl bromide, considering a three times higher potency of vinyl bromide compared to vinyl chloride.

The hepatic angiosarcoma risk for vinyl chloride, upon inhalation exposure for working lifetime to 1 ppm inferred from epidemiological data, has been assessed by SCOEL to be 3×10^{-4} (SCOEL/SUM/109). Independent data, derived from animals and using PBPK modelling, point to a similar order of magnitude (between 0.2 and 1.6×10^{-3} , and thereby confirm this approach. Accordingly, for a similar exposure to vinyl bromide the hepatic angiosarcoma risk is considered to be 9×10^{-4} .



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