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Documentation of OEL

Bromoform
$CHBr_3$
[CAS No. 75-25-2]
OEL-M 1 ppm (10.3 mg/m^3)
(proposed in 1997)

1. Bromoform (tribromomethane) is a non-flammable colorless transparent liquid at room temperature, with chloroform-like smell. Molecular weight, 252.8; melting point 9°C, boiling point 149–150°C (for conversion factor and other physico-chemical properties, see Table 1). Industrially, bromoform is used as an agent for geochemical analysis, and heavy fluid ore dressing[1].
2. In the following discussion, the toxicity of bromoform is compared with that of three structurally related chemicals of chloroform (CAS No. 67-66-3), bromodichloromethane (CAS No. 75-27-4) and dibromochloromethane (CAS No. 124-48-1).
3. Bromoform can be absorbed via oral and respiratory routes[2, 3]. The rate of skin penetration of bromoform may be low, by analogy to chloroform[4]. It is known, however, that a toxic dose of methyl bromide can be absorbed through intact human skin[4]. Bromoform, when absorbed, will be exhaled in an unchanged form and also as carbon dioxide[2, 3], similar to the cases of chloroform, bromodichloromethane and dibromochloromethane[2, 3, 5]; the ratios between bromoform and carbon dioxide, and also their ratios over the total dose given varies among the species of experimental animals, e.g., between rats and mice[2, 3] (Table 2).
4. No substantial difference is observed among the LD_{50} values of the four trihalomethanes when evaluated on an equimolar basis[6–11] (Table 2).
5. Liver damage was observed when bromoform was given orally to mice at 50, 250 mg/kg/d for l4 d[12]. The oral administration to mice at 145, 289 mg/kg/d for 14 d also resulted in liver damage at both of the two doses, and kidney damage at the higher dose[13].
6. When given orally 5 d/wk for 13 wk, vacuolation of hepatocytes was observed in rats given at 12 mg/d, and in mice at the doses of 200, 400 mg/d.
7. It is common to the four trihalomethanes that the liver and kidney are the major target organs of the toxicity after repeated dosing[6, 9, 15].
8. In an experiment in which male $B6C3F_1$ mice were given bromoform (diluted in corn oil) at 0, 50, 100 mg/kg/d, female mice at 0, 100, 200 mg/kg/d, and male and female Fischer 344 rats at 0, 100, 200 mg/kg/d for 103 wk, fatty degeneration of the liver was detected in male and female rats and female mice of all bromoform-dosed groups[6]. In the experiment, no dose-dependent increase in occurrence of tumors was observed either in the mice or in the rats except that adenomatous polyps increased dose-dependently the large intestine of the female rats (0/50, 1/50, 6/50; $p<0.004$)[6].
9. In carcinogenicity studies with related chemicals, hepatocellular carcinoma was observed in mice given chloroform[16], cancer in the kidney of rats, and adenoma in the liver, the kidney and the thyroid gland of mice given bromodichloromethane[9], carcinoma and adenoma in the liver and adenoma in the thyroid gland of mice given dibromochloromethane[16] (Table 3).
10. It should be noted that, in these experiments, the dose of chloroform was twice as much as that of other trihalomethanes[6, 9, 10, 16]. Nevertheless, the results as a whole appear to suggest that carcinogenic potency tends to be weaker with further replacement of chlorine atoms with bromine atoms (i.e., from chloroform to bromoform), with one exception that dibromochloromethane administration induced hepatocellular carcinoma in mice (Table 3). The observation agrees well with the decision of IARC to classify chloroform[17] and bromodichloromethane[18] in Group 2B, and dibromochloromethane[19] and bromoform[20] in Group 3.
11. When the evaluation by various agencies/organizations on the carcinogenicity potential of 7 brominated or chlorinated aliphatics which are structurally related to the four trihalomethanes, classification of 1,2-dibromoethane by IARC in Group 2A is the case in which the chemical is given the highest rank in the hazard rating among them, and no agencies/organizations classifies any of the 7 chemicals as a human carcinogen[22–26] (Table 4).
12. Mutagenicity of bromoform is negative in presence of S_9-mix and mostly negative in absence of S_9-mix in Ames test[27, 28]. The mutagenicity is positive, however, in chromosome aberration studies with cultured mammalian cells[6, 29], and also in a sister chromatid exchange study in presence of S_9-mix[30].
13. Chloroform is negative in Ames test[31]. Bromodichloromethane and dibromochloromethane are either positive or negative in Ames test[15, 16, 29, 32, 33] and positive at least in one of chromosome aberration or sister chromatid exchange studies with cultured mammalian cells[30, 33, 34] (Table 3).
14. In a reproduction toxicity study in which bromoform

Table 1. Physicochemical properties of bromoform and other three trihalomethanes

Chemical	Molecular formula	CAS No.	Molecular weight	1 ppm = (mg/m^3)	Appearance	Melting point (°C)	Boiling point (°C)
Chloroform	$CHCl_3$	67-66-3	119.39	4.9	Colorless liquid	−63.5	61.2
Bromodichloromethane	$CHBrCl_2$	75-27-4	163.83	6.7	Colorless liquid	−57.1	90.1
Dibromochloromethane	$CHBr_2Cl$	124-48-1	208.29	8.5	Colorless to pale-yellow liquid	<−20	119–120
Bromoform	$CHBr_3$	75-25-2	252.75	10.3	Colorless liquid	8.3	149.5

Table 2. Metabolism of [^{14}C]bromoform and other three trihalomethanes when given orally

Chemical	Metabolism
$CHCl_3$	In monkeys, rats and mice, the radioactivity was exhaled as unmetabolized and also as CO_2. The ratio of the CO_2/the unmetabolized was the highest in monkeys, followed by rats and the lowest in mice[2, 3]. Exhaled radioactivity was mostly as unmetabolized in monkeys, as umetabolized and also as CO_2 in rats, and mostly as CO_2 in mice.
$CHBrCl_2$	In rats and mice, the radioactivity was exhaled as unmetabolized and also as CO_2. The ratio of the CO_2: the unmetabolized was 14%: 42% of the given dose in rats and 81%: 7% in mice.
$CHBr_2Cl$	Similar to the case of $CHBrCl_2$, except that the ratio of the CO_2: the unmetabolized was 18%: 48% in rats and 72%: 12% in mice.
$CHBr_3$	Similar to the case of $CHBrCl_2$, except that the ratio of the CO_2: the unmetabolized was 4%: 67% in rats and 40%: 6% in mice.

For chemical names, see Table 1.

Table 3. Toxicity profile of bromoform and other three trihalomethanes (Part 1)

Chemical	Oral LD_{50} (mg/kg)	Major findings after 13-wk repeated p.o. dosing	Major findings after 2-yr repeated p.o. dosing
$CHCl_3$	Rats: 445–1,336[7] Mice: 120–490[8]	The major target is liver[14]	Rats (90–100, 180–200 mg/kg/d): Epithelial tumors in males[6] Mice (138,277 mg/kg/d for males, 238, 477 mg/kg/d for females): Hepatocellular carcinoma[16]
$CHBrCl_2$	Rats: 300–600[9] Mice: 651[9]	Rats (19–300 mg/kg/d): Liver and kidney damage[9]	Rats (50, 100 mg/kg/d): Necrosis and other lesions in liver. Carcinoma in kidney, adenoma of renal tubules and large intestine[9] Mice (50, 150 mg/kg/d): Adenoma of thyroid gland, renal tubules, and liver
$CHBr_2Cl$	Rats: 848–1,186[10] Mice: 800–1,200[11]	Rats (15–250 mg/kg/d): Liver and kidney damage[15] Mice (15–250 mg/kg/d): Liver and kidney damage[15]	Rats (40, 80 mg/kg/d): No tumors[15] Mice (40, 80 mg/kg/d): Hepatocellular carcinoma, adenoma of thyroid gland and liver[15]
$CHBr_3$	Rats: 1,147–1,138[10] Mice: 933[6]	Rats (12–200 mg/kg/d): Vacuolation of hepatocytes[6] Mice (25–400 mg/kg/d): Vacuolation of hepatocytes (no change at <200 mg/kg/d[6])	Rats (100, 200 mg/kg/d): Adenoma of large intestine[6] Mice (50, 100 mg/kg/d): No tumors[6]

For chemical names, see Table 1.

Table 3. Toxicity profile of bromoform and other three trihalomethanes (Part 2)

Chemical	S_9-mix	Mutagenicity			Class. by IARC [c]	Reprod. tox. [d]	Occupational Exposure Limit		
		Ames	CA [a]	SCE [b]			JSOH [e]	ACGIH [f]	DFG [g]
$CHCl_3$	Absent	–[31]			2B[17]	None[36]	10 ppm: 2B (49 mg/m^3)	10 ppm: 2B (49 mg/m^3)	10 ppm: 2B (50 mg/m^3)
	Present	+[31]							
$CHBrCl_2$	Absent	+[27], –[32]	+[33]	+[30], –[33]	2B[18]	None[37]	–: 2B [h]	–	–
	Present	+[33], –[32]	–[9]						
$CHBr_2Cl$	Absent	+[27], –[15]	–[34]	+[30]	3[19]	None[37]	–	–	–
	Present	+[27], –[15]	+[34]						
$CHBr_3$	Absent	+[21], –[27]	+[6]	+[30]	3[20]	None or very weak[35]	–	0.5 ppm: A3, S	–: B
	Present	–[27]	+[29]	–[6]					

For chemical names, see Table 1. [a] Chromosome aberration test. [b] Sister chromatid exchange test. [c] Classification by International Agency for Research on Cancer. [d] Reproduction toxicity. [e] Japan Society for Occupational Health[24]. [f] American Conference of Governmental Industrial Hygienists[25]. [g] Deutsche Forshungsgemeinschaft[26]. [h] Provisional.

Table 4. Carcinogenicity hazard classification and occupational exposure limit for related chemicals

Chemical		CAS NO.	IARC [a]	JSOH [b]	ACGIH [c]	DFG [d]
Bromomethane	CH_3Br	74-83-9	–	–	A4, 5 ppm S (A4, 1 ppm S)[e]	B, —
Bromochloromethane	CH_2BrCl	74-97-5	–	–	200 ppm	200 ppm
Bromoethane	C_2H_5Br	74-96-4	3	–	A3, 5 ppm S	A2, —
1,2-Dibromoethane	CH_2BrCH_2Br	106-93-4	2A	–	A3, —S	A2, —
1,2-Dichloroethane	CH_2ClCH_2Cl	107-06-2	–	2B, 10 ppm	A4, 10 ppm	A2, —
1,2-Dibromo-3-chloropropane	$CH_2BrCHBrCH_2Cl$	96-12-8	2B	–	–	A2, —
2-Bromopropane	$CH_3CHBrCH_3$	75-26-3	–	–	–	–

[a] International Agency for Research on Cancer[22, 23]. [b] Japan Society for Occupational Health[24]. [c] American Conference of Governmental Industrial Hygienists[25]. [d] Deutsche Forshungsgemeinschaft[26]. [e] An intended change.

was given to female mice at the doses of 0, 50, 100, 200 mg/kg/d p.o. for one week before mating, 14 wk during mating, and 3 wk after mating. Decreases in body weight and kidney weight, and an increase in liver weight were observed in the females given 100 or 200 mg/kg/d[35]. No apparent reproduction toxicity was observed, however, in any dosed groups except that the survival rate was reduced in newborns from mothers given 200 mg/kg/d[35].

15. No apparent reproduction toxicity was detected in experiments with chloroform, bromodichloromethane or dibromochloromethane[36, 37].
16. Among brominated aliphatic chemicals, reproduction toxicity has been observed in humans exposed to 1,2-dibromomethane[38, 39] or 1,2-dibromo-3-chloropropane[40, 41]. In addition, toxic effects of 2-bromopropane on the testes and the ovaries ware demonstrated both in workers and in rats in recent years[42–45].
17. In summary, it is likely that general toxicity and carcinogenicity of bromoform are similar to and no more potent than that of chloroform. Reproductive toxicity of bromoform is quite suspicious. Thus, one ppm is proposed as a provisional occupational limit for bromoform.
18. No SKIN notation is given to bromoform. This is, however, primarily due to lack of information, and skin contact with liquid bromoform should be minimized.

References

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Ethyl ether
$(C_2H_5)_2O$
[CAS No. 60-29-7]
OEL-M 400 ppm (1,200 mg/m^3)
(proposed in 1997)

1. Ethyl ether (diethyl ether) is a very volatile colorless transparent liquid with so-called ‘ether smell’: Molecular weight, 74.12; melting point − 116°C; boiling point, 34.6°C. The ether is extremely flammable.
2. Ethyl ether is used as an extractant and a solvent[1] in industries.
3. Ethyl ether has a narcotic potential, as well known through its clinical application for inhalation anesthesia. Ethyl ether, when in contact with air, will form peroxide(s) which is irritative to the respiratory tract. Thus, the irritability of the ether varies depending on its purity, especially depending on the extent of the peroxide(s) formation[2]. Furthermore the peroxide(s) are explosive, posing a serious problem in work safety[2].
4. In 1966, This Society (then The Association) proposed 400 ppm (1,200 mg/m^3) as the occupational exposure limit for ethyl ether[2]. The proposal of this concentration took narcotic action of this chemical into consideration, and probably based on the opinions of Amor[3] and Cook[4] that the working condition is unsatisfactory when the exposure to ethyl ether is in excess of 500 ppm.
5. According to the experiences in clinical anesthesia, sense of pain and then consciousness will be lost when exposed at 2,800 to 10,000 ppm, and surgical anesthesia will be maintained at about 40,000 ppm[5]. Such experiences suggest that the safety margin at 400 ppm will be several times larger for the former concentration and about 100 times larger for the latter.
6. No opinion against the proposal has ever been expressed since 1966.
7. Thus, there is no positive reason at present to change the occupational exposure limit for ethyl ether from the proposed value of 400 ppm.

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