Summary statement

12.121 Trihalomethanes (bromoform, bromodichloromethane, dibromochloromethane, chloroform)

Trihalomethanes (THMs) are formed in drinking-water primarily as a result of chlorination of organic matter present naturally in raw water supplies. The rate and degree of THM formation increase as a function of the chlorine and humic acid concentration, temperature, pH and bromide ion concentration. Chloroform is the most common THM and the principal DBP in chlorinated drinking-water. In the presence of bromides, brominated THMs are formed preferentially and chloroform concentrations decrease proportionally. It is assumed that most THMs present in water are ultimately transferred to air as a result of their volatility. For chloroform, for example, individuals may be exposed during showering to elevated concentrations from chlorinated tap water. For the volatile THMs, approximately equal contributions to total exposure come from four areas: ingestion of drinking-water, inhalation of indoor air largely due to volatilization from drinking-water, inhalation and dermal exposure during showering or bathing, and ingestion of food, with all but food exposure arising primarily from drinking-water. Indoor air exposure to the volatile THMs is particularly important in countries with low rates of ventilation in houses and high rates of showering and bathing.

Guideline values	
Chloroform	0.3 mg/litre
Bromoform	0.1 mg/litre
Dibromochloromethane (DBCM)	0.1 mg/litre
Bromodichloromethane (BDCM)	0.06 mg/litre
Occurrence	THMs are not expected to be found in raw water (unless near a pollution source) but are usually present in finished or chlorinated water; concentrations are generally below 100 µg/litre. In most circumstances, chloroform is the dominant compound.
TDIs	
Chloroform	15 µg/kg of body weight, derived from the lower 95% confidence limit for the 5% incidence of hepatic cysts, generated by PBPK modelling, in beagle dogs that ingested chloroform in toothpaste for 7.5 years, using an uncertainty factor of 25 (10 for intraspecies differences in toxicokinetics and toxicodynamics and 2.5 for differences in interspecies toxicodynamics)
Bromoform	17.9 µg/kg of body weight, based on the absence of histopathological lesions in the liver in a well conducted and well documented 90-day study in rats, using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for possible carcinogenicity and short duration of exposure)

DBCM	21.4 µg/kg of body weight, based on the absence of histopathological effects in the liver in a well conducted and well documented 90-day study in rats, using an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the short duration of the study); an additional uncertainty factor for potential carcinogenicity was not applied because of the questions regarding mouse liver tumours from corn oil vehicles and inconclusive evidence of genotoxicity
Basis of guideline derivation for BDCM	Application of the linearized multistage model for the observed increases in incidence of kidney tumours in male mice observed in an NTP bioassay, as these tumours yield the most protective value
Limit of detection	0.1–0.2 µg/litre (method detection limits) by purge-and-trap and liquid–liquid extraction and direct aqueous injection in combination with a chromatographic system; 0.1 µg/litre by GC with ECD; 2.2 µg/litre by GC/MS
Treatment achievability	Concentrations of chloroform, bromoform, BDCM and DBCM in drinking-water are generally below 0.05 mg/litre. Concentrations can be reduced by changes to disinfection practice (e.g., reducing organic THM precursors) or using air stripping.
Guideline derivation • allocation to water • weight • consumption	 20% of TDI for bromoform and DBCM 75% of TDI for chloroform 60-kg adult 2 litres/day
Additional comments on THMs	For authorities wishing to establish a total THM standard to account for additive toxicity, the following fractionation approach could be taken: $\frac{C_{bromoform}}{GV_{bromoform}} + \frac{C_{DBCM}}{GV_{DBCM}} + \frac{C_{BDCM}}{GV_{BDCM}} + \frac{C_{chloroform}}{GV_{chloroform}} \leq 1$ where C = concentration and GV = guideline value. It is emphasized that adequate disinfection should never be compromised in attempting to meet guidelines for THMs. Nevertheless, in view of the potential link between adverse reproductive outcomes and THMs, particularly brominated THMs, it is recommended that THM levels in drinking-water be kept as low as practicable.

Additional comments on chloroform	• In countries with low rates of ventilation in houses and high rates of showering and bathing, the guideline value could be lowered to account for the additional exposures from inhalation of indoor air largely due to volatilization from drinking-water and inhalation and dermal exposure during showering or bathing. • The guideline value is based on the same study as in the third edition; the increase in value is primarily a result of an increase in the allocation of exposure in drinking-water from 50% to 75% to account for the fact that chloroform is used less now than it was in 1993 when the original guideline was developed.
Additional comments on BDCM	• Although a health-based value of 21 µg/litre is derived, the previous guideline of 60 µg/litre has been retained for two reasons: 1) both calculations were based on the same study, the only differences being the model and model assumptions used to derive the guideline value; there is therefore no scientific basis on which to justify a change in the guideline value; and 2) BDCM concentrations below 50 µg/litre may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection. • As with chloroform, countries with low rates of ventilation and high rates of showering and bathing may wish to lower the guideline value to account for dermal and inhalation exposures, although, as noted above, concentrations below 50 µg/litre may be difficult to achieve using currently available technology without compromising the effectiveness of disinfection.

Toxicological review

Chloroform

The weight of evidence for genotoxicity of chloroform is considered negative. IARC has classified chloroform as possibly carcinogenic to humans (Group 2B) based on limited evidence of carcinogenicity in humans but sufficient evidence of carcinogenicity in experimental animals. The weight of evidence for liver tumours in mice is consistent with a threshold mechanism of induction. Although it is plausible that kidney tumours in rats may similarly be associated with a threshold mechanism, there are some limitations of the database in this regard. The most universally observed toxic effect of chloroform is damage to the centrilobular region of the liver. The severity of these effects per unit dose administered depends on the species, vehicle and method by which the chloroform is administered.

Bromoform

In an NTP bioassay, bromoform induced a small increase in relatively rare tumours of the large intestine in rats of both sexes but did not induce tumours in mice. Data from a

variety of assays on the genotoxicity of bromoform are equivocal. IARC has classified bromoform in Group 3 (not classifiable as to its carcinogenicity to humans).

Dibromochloromethane

In an NTP bioassay, DBCM induced hepatic tumours in female and possibly in male mice but not in rats. The genotoxicity of DBCM has been studied in a number of assays, but the available data are considered inconclusive. IARC has classified DBCM in Group 3 (not classifiable as to its carcinogenicity to humans).

Bromodichloromethane

IARC has classified BDCM in Group 2B (possibly carcinogenic to humans). BDCM gave both positive and negative results in a variety of *in vitro* and *in vivo* genotoxicity assays. In an NTP bioassay, BDCM induced renal adenomas and adenocarcinomas in both sexes of rats and male mice, rare tumours of the large intestine (adenomatous polyps and adenocarcinomas) in both sexes of rats and hepatocellular adenomas and adenocarcinomas in female mice. Exposure to BDCM has also been linked to a possible increase in reproductive effects (increased risk for spontaneous abortion or stillbirth).

History of guideline development

The 1958, 1963 and 1971 WHO *International Standards for Drinking-water* did not refer to THMs. In the first edition of the *Guidelines for Drinking-water Quality*, published in 1984, no guideline values for THMs other than chloroform were recommended after a detailed evaluation of the compounds. A health-based guideline value of 0.03 mg/litre was established for chloroform only, as few data existed for the remaining THMs and, for most water supplies, chloroform was the most commonly encountered member of the group. It was noted that the guideline value for chloroform was obtained using a linear multistage extrapolation of data obtained from male rats, a mathematical model that involves considerable uncertainty. It was also mentioned that although the available toxicological data were useful in establishing a guideline value for chloroform only, the concentrations of the other THMs should also be minimized. Limits ranging from 0.025 to 0.25 mg/litre, which represent a balance between the levels that can be achieved given certain circumstances and those that are desirable, have been set in several countries for the sum of bromoform, DBCM, BDCM and chloroform. In the second edition of the Guidelines, published in 1993, no guideline value was set for total THMs, but guideline values were established separately for all four THMs. Authorities wishing to establish a total THM standard to account for additive toxicity could use a fractionation approach in which the sum of the ratios of each of the four THMs to their respective guideline values is less than or equal to 1. The 1993 Guidelines established health-based guideline values of 0.1 mg/litre for both bromoform and DBCM, and guideline values of 0.06 mg/litre for BDCM and 0.2 mg/litre for chloroform, associated with an upper-bound excess lifetime cancer risk of 10^{-5}, were derived. The guideline value of 0.2 mg/litre for chloroform was retained in the addendum to the second edition of the Guidelines, published in 1998, but was developed on the basis of a TDI for threshold effects. These guideline values were brought forward to the third edition.

Assessment date
The risk assessment was conducted in 2004.

Principal references
IPCS (2000) *Disinfectants and disinfectant by-products*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 216).

IPCS (2004) *Chloroform*. Geneva, World Health Organization, International Programme on Chemical Safety (Concise International Chemical Assessment Document 58).

WHO (2005) *Trihalomethanes in drinking-water. Background document for development of WHO Guidelines for drinking-water quality*. Geneva, World Health Organization (WHO/SDE/WSH/05.08/64).