HALOTHANE

CAS number: 151-67-7

Synonyms: 2-Bromo-2-chloro-1,1,1-trifluoroethane, Bromochloro-trifluoroethane, Fluoroethane, 1,1,1-Trifluoro-2-chloro-2-bromoethane

Chemical formula: $C_2HBrClF_3$

Structural formula: —

Workplace exposure standard (interim)

TWA: **0.5 ppm (4.1 mg/m^3)**

STEL: —

Peak limitation: —

Notations: —

IDLH: —

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 0.5 ppm (4.1 mg/m^3) is recommended to protect for reproductive effects and effects on the liver and central nervous system (CNS) in exposed workers.

It is recommended an investigation of additional data sources be undertaken at the next scheduled review.

Discussion and conclusions

Halothane has been used as a clinical anaesthetic for over 40 years.

Critical effects of exposure include adverse reproductive effects, liver toxicity and neurotoxicity. Limited dose-response data exists in humans. In volunteers, exposure at 1,000 ppm for 30 minutes did not influence performance.

A national survey of operating room personnel in the United States of America reported increased incidence of spontaneous abortions among female employees and an increased risk of congenital abnormalities in their offspring. Increased incidence of spontaneous abortions in the wives of male anaesthetists and increased frequency of congenital abnormality in their children were also reported along with an increased incidence of hepatic disease. The average concentration in operating rooms ranged between 1 and 4.6 ppm (ACGIH, 2018).

Rats exposed at 10 ppm for 10 weeks developed ultrastructural changes in the liver and kidney. Pups of eight rats exposed daily during gestation at 10 ppm showed cellular damage in liver and diminished learning ability (ACGIH, 2018). Reproduction and developmental studies in rats and mice identified a LOAEC of 10 ppm for liver effects in neonates (HCOTN, 2002). Inconsistencies were noted in the recommended occupational exposure limits by primary sources.

The current TWA of 0.5 ppm (4.1 mg/m^3) is recommended to be retained in the interim. Noting there are inconsistent TWA recommendations by primary sources and decisions about the critical effects, it is recommended that an investigation of additional data sources is undertaken at the next scheduled review.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

There are insufficient data to recommend a skin notation.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.5 ppm (4.1 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 50 ppm (404 mg/m^3)***

TLV-TWA is recommended to minimise the potential for liver toxicity; adverse reproductive effects; neurotoxicity.

Summary of data:

TLV-TWA based on comparison with the toxicity and the TLVs for trichloroethylene (50 ppm) and chloroform (10 ppm); hepatotoxicity and adverse effect on reproduction of chloroform is more severe than for trichloroethylene or halothane.

Human data:

- Anaesthesia induced by 5,000–30,000 ppm; maintained by 5,000–15,000 ppm
- Exhibits biological activity in the CNS, cardiovascular system and liver
- In volunteers 0.5 h at 1,000 ppm did not influence performance; 4,000 ppm caused amnesia for word pairs and impairment of manual dexterity
- Epidemiological studies not suitable to identify dose-response
- A national survey study in the US reports the following additional health hazards to operating room personnel:
    - increased incidence of spontaneous abortions among female employees and an increased risk of congenital abnormalities in their offspring;
    - increased incidence of spontaneous abortions in wives and increased frequency of congenital abnormality in children of male anaesthetists
    - increased incidence of hepatic disease
    - average concentrations measured in unscavenged rooms: 4.6 ppm halothane 216 ppm nitrous oxide
    - average concentrations measured in scavenged rooms: 1 ppm halothane 77 ppm nitrous oxide
- Similar study performed in the UK; increased reproductive risk to female anaesthetists; no effect on congenital abnormalities in the offspring of male anaesthetists and the effect on their female partner's pregnancy
- Concentrations in operating rooms of 2–4 ppm and 5–50 ppm; 163 anaesthetists; reports of irregularities in menstrual periods and an increased number of subjective complaints (such as headache and fatigue).

Animal data:

- LC_{50}: 100 ppm (rats); 150 ppm (guinea pigs); 5-wk continuous exposure
- Rats and rabbits: 500 ppm 7 h/d, 5 d/wk for 7 wk; developed centrilobular fatty infiltration of the liver; no significant changes in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT)
- Rats: 10 ppm 7 h/d, 5 d/wk for 8 wk; some ultrastructural changes in the neural rough endoplasmic reticulum and in liver and kidney
- Rats: 500 ppm 7 h/d, 5 d/wk for 4 wk; extensive ultrastructural changes in the neural rough endoplasmic reticulum and in liver and kidney

Source	Year set	Standard
• No carcinogenic effect in rats exposed for 7 h/d, 5 d/wk for 2 yr to a mixture of halothane (10 ppm) and nitrous oxide (500 ppm) • Pups of 8 rats exposed daily during gestation at 10 ppm showed cellular damage in liver and diminished learning ability • Other studies failed to observe adverse effects on reproduction in rats exposed at much higher concentrations. Insufficient data to recommend a skin or sensitiser notation or STEL.		
DFG	***1979***	***MAK: 5 ppm (41 mg/m³)***
Summary of additional data: • Accumulation of metabolite trifluoroacetic acid should limit the concentration to a maximum of 2.5 µg/mL (whole blood); corresponds to an average 5 ppm over the course of one working week (no further information).		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2002***	***TWA: 0.05 ppm (0.41 mg/m³)***
Summary of additional data: • Short-term exposure at 123–410 mg/m³ (15–50 ppm) caused liver injury in mice and rats; no further information • Reproduction and developmental studies of rats and mice observed fatty changes in neonatal livers, ultrastructural changes in kidneys and brain and neurobehavioural changes at ≥82 mg/m³ (10 ppm); considered a LOAEL • TWA derived using LOAEL and applying uncertainty factors of 20 for lack of NOAEL and 10 for intra- and inter- species variations.		

Secondary source reports relied upon

Source		Year	Additional information
US NIOSH	✓	1976	• 4-h exposure 50 ppm nitrous-oxide plus 0.5, 1.0 or 10 ppm significantly impaired performance on the visual acuity and digit span tests and a divided attention task • Exposure at 25 ppm nitrous-oxide plus 0.5 ppm halothane did not cause any significant performance decrement.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	—
HCIS	NA
NICNAS	NA
EU Annex	NA
ECHA	NA
ACGIH	Carcinogenicity – A4
DFG	—
SCOEL	NA
HCOTN	—
IARC	NA
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation
Insufficient data to assign a skin notation

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	197.38
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 8.06 mg/m^3; 1 mg/m^3 = 0.124 ppm
This chemical is used as a pesticide:	☐
This chemical is a biological product:	☐
This chemical is a by-product of a process:	☐

Molecular weight:	197.38
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 8.06 mg/m^3; 1 mg/m^3 = 0.124 ppm
This chemical is used as a pesticide:	☐
A biological exposure index has been recommended by these agencies:	☐ ACGIH ✓ DFG ☐ SCOEL

Workplace exposure standard history

Year	Standard
Click here to enter year	

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2001) Halothan – MAK value documentation.

Health Council of the Netherlands (HCOTN) (2002) Halothane. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2002/14OSH.

National Institute for Occupational Safety and Health (NIOSH) (1976) Effects of Trace Concentrations of Anesthetic Gases on Behavioral Performance of Operating Room Personnel.