Hexafluoroacetone

(CAS reg no: 684-16-2)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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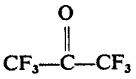
1 Introduction

The present document contains the assessment of the health hazard of hexafluoroacetone by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

The evaluation of the toxicity of hexafluoroacetone has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the data bases Toxline, Medline, and Chemical Abstracts, covering the period of 1981 until July 1999, 1966 until November 1999, and 1937 until September 1999, respectively, using the following key words: hexafluoropropanone, hexafluoroacetone, perfluoropropanone, perfluoroacetone, and 2-propanone, 1,1,1,3,3,3,-hexafluoro-, and the CAS registry numbers 684-16-2 and 10057-27-9, 10543-95-0, 13098-39-0, 32836-39-8, and 34202-69-2 (the latter representing the various hydrated forms). The final literature search has been carried out in November 1999.

In April 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	hexafluoroacetone
synonyms	:	2-propanone, 1,1,1,3,3,3,-hexafluoro-; perfluoroacetone
molecular formula	:	C_3F_6O
structural formula	:	
CAS reg no	:	684-16-2

Data from How92, Lid96.

3 Physical and chemical properties

molecular weight	:	166.02
boiling point	:	-27°C
melting point	:	-125°C
flash point	:	nonflammable
vapour pressure	:	at 21°C: 601 kPa
solubility in water	:	reacts vigorously, to form hydrates
Log $P_{octanol/water}$	:	0.60 (estimated); 1.46 (experimental)
conversion factors (20°C, 101.3 kPa)	:	1 mg/m^3 = 0.15 ppm 1 ppm = 6.9 mg/m^3

Data from Has78, Lid96, http://esc.syrres.com.

Hexafluoroacetone is a colourless, hygroscopic, nonflammable, highly reactive gas with a musty odour. The sesquihydrate (1.5 H_2O) is the most common form (ACG99, Has78).

4 Uses

Hexafluoroacetone is employed in organic syntheses. It is also used as a chemical intermediate for the production of hexafluoroisopropanol, polyacrylates used for textile coating, and polyester coating for textiles, as a solvent for acetal resins and polyamides, and as a polymer adhesive (ACG99).

5 Biotransformation and kinetics

After a subcutaneous injection of 13 mg/kg bw of ^{14}C-hexafluoroacetone into rats, radioactivity was eliminated from the blood in a biphasic manner. ^{14}C-hexafluoroactone was excreted from the body primarily via the urine. Twenty-four hours after injection, radioactivity excreted via the urine and faeces accounted for 36 and 3% of this dose, respectively; after 120 hours, these values increased to 81 and 9%, respectively. In rats dosed with 130 mg/kg, radioactivity excreted via the urine and faeces accounted for only 9 and 0.4% of the dose, respectively, after 24 hours, and for 67 and 3%, respectively, after 120 hours. Negligible amounts of radioactivity were detected in the expired air (<1.5%), and no $^{14}CO_2$ was detected, regardless of the dose. The compound was uniformly

distributed throughout the major organs of the body with the exception of the liver which contained disproportionately higher levels of ^{14}C-hexafluoroacetone. The hepatic binding of ^{14}C-hexafluoroacetone was noncovalent and capacity-limited. Notably, the testes, the target organ of hexafluoroacetone-induced toxicity, did not exhibit any unusual accumulation or retention of ^{14}C-hexafluoroacetone (Gil84).

6 Effects and mechanism of action

Human data

For hexafluoroacetone dihydrate, the maximum concentration causing irritation of the upper respiratory tract was reported to be 32 mg/m^3 (equivalent to 26 mg/m^3 hexafluoroacetone). There were no further data presented (Kuz72).

Animal data

Undiluted hexafluoroacetone sesquihydrate is a severe skin irritant as expected by its acidic (pH = 1) nature. Concentrations below 50% produced mild to no irritation on rabbit skin. The irritation response at higher concentrations included definite erythema that became scaly and developed crusts 1 to 5 days postapplication. To guinea pig skin, one drop of undiluted dihydrate produced marked erythema and blanching, but no irritation was seen with dilutions of 0.1 to 10% (Ken90).

Undiluted hexafluoroacetone sesquihydrate was instantly painful and produced a severe extensive injury in the rabbit eye. When rinsed with water 20 seconds after instillation, the eye appeared to return to normal 29 days after exposure except for a small corneal injury with local vascularisation. The unwashed eye showed extensive corneal opacity, scar tissue, pannus, and chronic conjunctivitis (Ken90). The following acute lethal toxicity data have been found:

parameter	*concentration/dose*	*ref*
hexafluoroacetone (HFA)		
LC_{50} inhalation rat 0.5 hours	6210 mg/m^3	Bor65
LC_{50} inhalation rat 3 hours	1898 mg/m^3	
hexafluoroacetone sesquihydrate		
LD_{50} dermal rat	670 mg/kg (equivalent to 576 mg HFA/kg)	Ken90
hexafluoroacetone dihydrate		
LC_{50} inhalation rat ? hours	3500 mg/m^3 (equivalent to 2875 mg HFA/m^3)	Kuz71
LC_{50} inhalation rat 4 hours	2760 mg/m^3 (equivalent to 2268 mg HFA/m^3)	Ken90
hexafluoroacetone trihydrate		
undiluted:		
LD_{50} dermal rabbit 24 hours	113 mg/kg (equivalent to 85 mg HFA/kg)	Bor65
LD_{50} iv mouse	180 mg/kg (equivalent to 155 mg HFA/kg)	Ken90
as a 10% solution in water:		
LD_{50} oral rat	190 mg/kg (equivalent to 143 mg HFA/kg)	Bor65

In these acute inhalation lethal toxicity studies, the following observations were made.

After inhalation exposure, depression of the central nervous system (CNS) was manifest as hind leg instability and loss of postural and righting reflexes in the rats. The effects persisted for several hours. Most of the fatalities occurred 2 to 6 days after exposure. There was little, if any, lung damage. There were no histological findings in heart, kidney, or liver (Bor65).

After dermal application, there was no measurable amount of material remaining on the skin of the rabbits at the end of the exposure period. The exposed area was erythematous and scaly and developed crusts (eschar formation) 2 to 5 days after exposure. Mild CNS depression preceded death, but no other abnormal signs were evident. On gross necropsy, no abnormalities were present except for discolouration and oedema of the exposed skin (Bor65).

After oral dosing, moderate to severe CNS depression persisting for several days was noted in the rats. No other signs were discernible. On gross necropsy, no abnormalities were evident (Bor65).

Male and female rats (ChR-CD; n=30/sex/group) and male dogs (Beagle; n=6) were exposed to hexafluoroacetone concentrations of 0, 0.7, 6.9, or 83 mg /m^3 (0, 0.1, 1, 12 ppm), 6 hours/day, 5 days/week, for 90 days.The effects observed in the male rats are described in the section on reproduction toxicity. In female rats, there was a dose-related increase in urinary osmolality ($p< 0.05$ at the two highest dose levels), a decrease in body weight gain and in pituitary weight (both: $p< 0.05$ at the highest dose level). In the dogs of the high-concentration group, there was a lower erythrocyte count and haemoglobin and haematocrit values after 1, 2, and 3 months on test, but the values returned to normal after a 45-day recovery period (no statistical calculation). In these dogs, there was a decrease in testis weight ($p < 0.05$) and in thymus weight (borderline significance). There was a dose-related increase in pituitary weight (significant at the two highest dose levels). Since the effect of hexafluoroacetone on pituitary weight in dogs differed from that in rats, the authors concluded that hexafluoroacetone affects this aspect of the endocrine system of the two species differently. At the mid-concentration level, the only effects were an indication of reversible kidney dysfunction in the rats and an increased relative lung weight in the dogs. At the low-concentration level, there were no compound-related gross, biochemical, haematological or histological changes in either species.The average relative lung weight in dogs exposed to this level was greater than that of the controls. However, there was no consistent relationship between the increased average relative lung weight of dogs and the hexafluoroacetone concentration, both immediately after exposure and after a 45-day recovery period (Has71). It can be concluded that the no-observed-adverse-effect level (NOAEL) for subchronic inhalation exposure in rats and dogs is 0.7 mg/m^3 hexafluoroacetone.

Carcinogenicity

No data have been found.

Mutagenicity and genotoxicity

Hexafluoroacetone dihydrate was not mutagenic in the Ames assay, using *S. typhimurium* (no details presented) (Ken90).

Hexafluoroacetone sesquihydrate was not mutagenic in the Ames assay, using *S. typhimurium* strains TA97, TA98, TA100 and TA1535, with and without rat- and hamster-liver metabolic activation (Zei88).

Reproduction toxicity

Female rats

Pregnant rats (n=24/group) were exposed to hexafluoroacetone concentrations of 0, 0.76, 6.9, or 48 mg/m^3 (0.11, 1, 6.9 ppm), 6 hours/day, on gestational days 7 through 16. Maternal toxicity was not evident, but liver weights were elevated in dams at the two highest dose levels ($p<0.05$). On gestational days 17 to 22, maternal weight gain in the high-concentration group was less than in the control group ($p<0.05$). This was attributed to embryolethality and an adverse effect on fetal weight in this group rather than to maternal toxicity. The mean number of live fetuses per litter was significantly decreased and the number and percentages of total and later resorptions were significantly increased in the high-concentration group. Late resorptions were also slightly, but significantly increased in the mid-concentration group. It is not clear whether the increase in late resorptions at the mid concentration is a compound-related effect. The weights of male, female, and combined fetuses were significantly lower than controls in both the mid- and high-concentration groups. In addition, female fetuses in the low-concentration group showed a minimal, but statistically significant decrease in body weight when compared with controls (all: $p<0.05$). Malformations were significantly increased at the high concentration, and included increases in anasarca (subcutaneous oedema) and cleft soft palates. External developmental variations (oedema and subcutaneous haemorrhages) were also significantly increased in the high-concentration group. Skeletal variations consisting of extracervical and lumbar ribs were significantly increased at the mid and the high concentration. Variations due to retarded development, primarily delayed ossifications of the skull, vertebrae, ribs, and sternebrae were increased at the high concentration (all: $p<0.05$). The authors concluded that the maternal NOAEL was 0.76 mg/m^3. A NOAEL for the conceptus could not be established (Has89). Based on a minimally decreased body weight in female fetuses, the committee concludes that 0.76 mg/m^3 (0.11 ppm) (the lowest concentration tested) is a lowest-observed-adverse-effect level (LOAEL) for developmental effects in rats.

Pregnant rats received dermal doses of hexafluoroacetone trihydrate of 0, 1, 5, or 25 mg/kg bw/day, on gestational days 6 through 16 (equivalent to 0.75, 3.8, and 18.9 mg hexafluoroacetone/kg bw). The trihydrate was dissolved in water, applied on the shaved back skin, and rubbed in with a Teflon rod until dry. The number of pregnant dams was 11/15, 14/14, 13/14, and 12/14, respectively. Fetal

toxicity, measured by the number of resorptions and life fetuses per litter, was evident at 25 mg/kg bw/day. At 5 and 25 mg/kg bw/day, the mean fetal weights and crown-rump lengths were significantly lower than those of the controls, and maternal weight gain was adversely affected. Teratogenic effects consisting of gross external, internal soft-tissue, and skeletal abnormalities were observed at 5 and 25 mg/kg bw/day. At 1 mg/kg, there was a statistically significant increased incidence in hydronephrosis (in 9/14 litters - 21/47 fetuses - *vs* 2/10 litters - 3/34 fetuses - in the control group; $p<0.05$). At this dose level, there was no significant increase in the number of litters with abnormalities. Because the low-dose group had a higher incidence of hydronephrosis and anophthalmia (1 fetus) and stunting (2 fetuses), which were absent in the control group (no statistical calculation), the authors found it difficult to consider this low dose a NOAEL (Bri79). The committee considers the low dose, equivalent to 0.75 mg HFA/kg bw, an LOAEL for fetotoxic effects in rats.

Daily doses of hexafluoroacetone of 0, 5, or 10 mg/kg bw (dissolved in water) were applied to the clipped skin of pregnant Sprague Dawley rats, 8 hours/day, on gestational days 6 through 15. Each female was fitted with a collar designed to prevent ingestion of the test material. The number of pregnant dams was 3/5, 4/5, and 24/25, respectively. At 5 mg/kg bw, there were no effects on the number of viable offspring, the number of implantations and resorptions, and the mean fetal body weight. At 10 mg/kg bw, the number of resorptions was increased and the mean fetal body weight decreased, and skeletal effects like missing sternebrae, wavy ribs, rudimentary ribs, and incomplete ossification, were observed (all: $p<0.05$). There were no soft tissue anomalies. Maternal effects were not seen (Bec82).

Male rats

Male rats were exposed to hexafluoroacetone concentrations of 0, 0.7, 6.9, or 83 mg/m^3 (0, 0.1, 1, 12 ppm), 6 hours/day, 5 days/week, for 90 days (n=40/group). Five males from each group were killed after 30 or 90 days of exposure, and 28 or 84 days post-exposure. There were no exposure-related histological lesions in the rats of the low- and mid-concentration groups. After 30 days of exposure to 83 mg/m^3 (12 ppm), rats showed lower body weight gain, testicular atrophy, and oligospermia or aspermia in the epididymal tubules. At 90 days of exposure, the testes showed severe atrophy with almost all seminiferous tubules affected. After a 28-day recovery period, regeneration of atrophic testes was evident but varied markedly among the exposed rats. At 84 days postexposure,

spermatogenesis was still only partially restored (Lee91, also in: Has71). It can be concluded that inhalation exposure to 6.9 mg/m^3 (1ppm) is an NOAEL for testicular effects in rats.

Male rats received dermal doses of hexafluoroacetone sesquihydrate of 0, 13, 39, or 130 mg/kg bw/day, for 14 days (equivalent to 11, 34 and 112 mg HFA/kg bw) (n=8/group). The mid and the high dose induced moderate or severe testicular atropy, respectively. Histological evaluation of the testes revealed that spermatids followed by spermatocytes were the germ cells mostly affected; spermatogonia and Sertoli cells appeared to be less vulnerable. Possibly the altered lipid metabolism, in particular sterol metabolism, is associated with the development of hexafluoroacetone-induced testicular atrophy. No testicular effects were found at the low dose (Gil83). The committee considers the low dose, equivalent to 11 mg hexafluoroacetone/kg bw, an NOAEL for testicular effects in rats.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for hexafluoroacetone in the Netherlands is 0.7 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for hexafluoroacetone in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

Hexafluoroacetone is chemically very reactive; it reacts vigorously with water, forming hydrates (ACG99).

From the limitedly reported data, the committee consideres undiluted hexafluoroacetone sesquihydrate as (at least) severely irritating to the skin and eyes of rabbits.

From acute lethality data and using EC classification criteria (if applicable), the committee considers hexafluoroacetone (3-hour LC_{50} in rats: 1898 mg/m^3) and its dihydrate (4-hour LC_{50} in rats: 2760 mg/m^3) as 'harmful' by inhalation, the sesquihydrate (LC_{50} in rabbits: 670 mg/kg) and the trihydrate (LC_{50} in rabbits: 113 mg/kg) as 'harmful' and 'toxic', respectively, in contact with skin, and the trihydrate (LC_{50} in rats: 190 mg/kg) as 'toxic' if swallowed. The major effect before death after the various routes of exposure was severe CNS depression.

In subchronic inhalation studies, intermittent exposure to 6.9 mg/m^3 caused reversible kidney dysfunction and increased relative lung weight in rats and

dogs, respectively. This concentration did not induce testicular effects in rats (Lee91, Has71). In separate reproduction toxicity studies in which pregnant rats were exposed during organogenesis, minimal but statistically significant decreases in female offspring body weight were seen at exposure by inhalation to 0.76 mg/m^3 (Has89), and a higher incidence of hydronephrosis, one anophthalmic fetus and 2 stunted fetuses at a dermal dose of 0.75 mg /kg bw (Bri79), the lowest concentration/dose tested.

The committee considers these fetotoxic effects as the critical effects and takes the LOAEL of the developmental toxicity inhalation study of 0.76 mg/m^3 as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 18 is established. This factor covers the following aspects: the absence of a NOAEL, and intra- and interspecies variation, as well as the findings of the subchronic inhalation studies in rats and dogs (Has71, Lee91). Thus, applying this factor of 18 and the fixed/preferred value approach, a health-based occupational exposure limit of 0.05 mg/m^3 is recommended for hexafluoroacetone and its hydrates.

The committee recommends a health-based occupational exposure limit for hexafluoroacetone (and its hydrates) of 0.05 mg/m^3, as an 8-hour time-weighted average (TWA).

From the results of a dermal reproduction toxicity study in which hexafluoroacetone doses of 0.75 mg/kg bw/day (the lowest dose tested) induced fetotoxic effects in rats, the committee concludes that the compound can be taken up via the skin. Although there were no data to make quantitative estimations for dermal uptake, the committee is of the opinion that dermal uptake may add considerably* to the body burden, and, therefore, recommends a skin notation.

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* *i.e.*, the amount taken up by the skin following exposure of hands and forearms to the liquid compound for 1 hour is 10% or more of the amount taken up by 8-hour inhalation at the HBROEL

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Annex

Occupational exposure limits for hexafluoroacetone in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry	0.1	0.7	8 h	administrative		SZW01
Germany						
- AGS	-	0.7	8 h		S	TRG00
- DFG MAK-Kom.	-	-				DFG01
Great Britain						
- HSE	-	-				HSE01
Sweden	-	-				Arb00b
Denmark	0.1	0.7	8 h			Arb00a
USA						
- ACGIH	0.1	-	8 h	TLV	S	ACG01
- OSHA	-	-				ACG00
- NIOSH	0.1	0.7	10 h	REL	S	ACG00
European Union						
- SCOEL	-	-				CEC00

[a] S = skin notation, which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation

[b] Reference to the most recent official publication of occupational exposure limits