Perhydro-1,3,5-trinitro-1,3,5-triazine

(CAS No: 121-82-4)

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

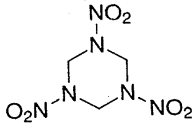
The present document contains the assessment of the health hazard of perhydro-1,3,5-trinitro-1,3,5-triazine (hexogen*) by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The evaluation of the toxicity of hexogen has been based on the reviews by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG99) and the Agency of Toxic Substances and Disease Registry (ATSDR) (ATS95). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in May 2000, literature was searched in the databases Toxline, Medline, and Chemical Abstracts, starting from 1981, 1966, and 1937, respectively, and using the following key words: cyclonite; hexogen; RDX; 1,3,5-triazine, hexahydro-1,3,5-trinitro-; and 121-82-4. The final literature search was carried out in Toxline and Medline in October 2003.

In October 2003, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: TML Scheffers (DSM Chemelot, Geleen, the Netherlands). These comments were taken into account in deciding on the final version of the document.

* Name used in this document.

2 Identity

name	:	perhydro-1,3,5-trinitro-1,3,5-triazine
synonyms	:	hexahydro-1,3,5-trinitro-1,3,5-triazine; hexogen; cyclonite; hexolite; cyclotrimethylenenitramine; cyclotrimethylenetrinitramine; hexahydro-1,3,5-trinitro-S-triazine ; 1,3,5-triaza-1,3,5-trinitrocyclohexane; 1,3,5-trinitro-1,3,5-triazacyclohexane; trimethylenetrinitramine; trinitrotrimethylenetriamine; RDX (Royal Demolition Explosive)
molecular formula	:	$C_3H_6N_6O_6$
structural formula	:	
CAS number	:	121-82-4

Data from ACG99, NLM03.

3 Physical and chemical properties

molecular weight	:	222.26
boiling point	:	decomposes
melting point	:	205.5°C
flash point	:	no data
vapour pressure	:	at 20°C: 0.1×10^{-6} Pa
solubility in water	:	insoluble (at 20°C: 4-6 mg/100 mL)
log $P_{octanol/water}$	:	0.87 (experimental); 0.68 (estimated)
conversion factors	:	not applicable

Data from ACG99, ATS95, NLM03, http://esc.syrres.com.

Hexogen is a white, crystalline powder.

The stability of hexogen is considerably superior to that of pentaerythritol tetranitrate (PETN) and nearly equal to that of TNT (trinitrotoluene). It withstands storage of 85°C for 10 months or at 100°C for 100 hours without measurable deterioration (Dav93).

Due to its sensitivity to electrostatic charge, dry hexogen should be stored and handled in a static-free environment. Once in solution, hexogen does not require special handling (Bur88).

Hexogen does not explode on heating when unconfined, as do some other high explosives; it either fumes off and ignites or deflagrates. Upon explosion, the following gases are produced: CO, CO_2, water, H_2, and N_2 (Fed66).

4 Uses

The compound is used as an explosive, a base charge for detonators, and as an ingredient of bursting-charge and plastic explosives by the military (Dav93, NLM03). It has also been used as a rodenticide (Etn89). In a mixture with pentaerythritol tetranitrate, it is called semtex (Bud96). During the 1960s, hexogen was the third most important explosive from a tonnage viewpoint, after TNT and nitrocellulose (Etn89). Thereafter, production of hexogen fell in the USA to a yearly total of approximately 10% of the amount produced from 1969 to 1971 (ATS95).

5 Biotransformation and kinetics

Human data

In a human study, 100 μg hexogen was applied on the left and right hand of 5 volunteers, without occlusion. The mean amount of hexogen remaining on the hands at 30 minutes and 8 hours after application was 8.0 and 1.2 μg, respectively. No data were given on percentage of hexogen absorbed through the skin (Twi84). In a human case study, a 3-year-old boy, after chewing on clumps of plasticised hexogen, showed a peak plasma hexogen concentration of 10.7 mg/L at 24 hours after ingestion. Levels dropped to 3.6 and 0.7 mg/L at 48 and 96 hours after ingestion, respectively, and were below the limit of detection at 144 hours post-ingestion. The apparent half-life of elimination from the serum was 15 hours. The hexogen concentration in cerebrospinal fluid also peaked after 24 hours post-exposure, amounting to 8.9 mg/L. In the urine (38 mg/L) and the faeces, hexogene levels peaked 48 and 96 hours post-exposure, respectively. Hexogen was still detectable in the faeces at 144 hours post-ingestion. The amount of hexogen ingested was estimated to be 1.23 g (Woo86).

In an unpublished study, mixtures containing 33% of hexogen in DMSO, 75% in cyclohexanone, or 5.4% in acetone were applied to the clipped backs of rabbits for 24 hours or 5 days. Guinea pigs were treated in the same way with a solution containing 33% hexogen in DMSO, and dogs with mixtures containing 33% hexogen in DMSO (289 mg/kg bw), 2.5% in cyclohexanone (65.7 mg/kg bw), or 5.4% in acetone (47.3 mg/kg bw). No skin penetration of hexogen was found in either species. No further information was given (McN74).

In rats given a single oral dose of hexogen of 50 mg/kg bw, hexogen levels were 3-4 and 5-9 µg/mL in plasma and brain, respectively, at 2 to 24 hours after dosing. No hexogen was detectable anymore at 3 days after administration (McP85).

In another study, 3 groups of Sprague-Dawley rats (n=10/group) were dosed by gavage with 50 mg of [^{14}C]-hexogen. The total recovery of radioactivity at 4 days after administration was approximately 90%: 3% in the faeces, 10% in the carcass, 34% in the urine, and 43% as $^{14}CO_2$. About 80% of the urinary radioactivity was excreted in the first 48 hours. Concentrations of radioactivity in tissues were in the order: kidney > liver > brain, heart, or plasma. When rats were given a single oral dose of 100 mg/kg bw, tissue concentrations reached a plateau at 2 hours after dosing, which was maintained for 24 hours. Hexogen concentrations were highest in the kidneys, followed by brain, heart, plasma, and liver. The half-life of disappearance in the plasma, studied in rats given a single intravenous dose of 5 to 6 mg/kg bw, was approximately 10 hours (Sch77).

Groups of Sprague-Dawley rats were either dosed with unlabelled or [^{14}C]-labelled hexogen by gavage at 20 mg/kg bw/day for up to 90 days, or allowed free access to drinking water saturated with unlabelled or [^{14}C]-labelled hexogen (50-70 mg/L) for up to 90 days. Giving unlabelled hexogen, variable hexogen levels were found in tissues measured at 30, 60, or 90 days after the beginning of exposure, but there was no accumulation in any of the tissues. There was no preferential tissue distribution of hexogen. Following administration of labelled compound, the average amounts of radioactivity as percentage of the daily dose excreted at the end of 1, 4, 8, or 13 weeks were 36.3 (range: 27-51%), 30.5 (range: 22-35%), and 4.5% (range: 4.0-5.3%) in 24-hour exhaled breath (as $^{14}CO_2$), in 48-hour urine, and in 48-hour faeces, respectively. The amount of parent compound in the urine accounted for 3 to 5% of total urinary radioactivity and the remainder was associated with unidentified metabolites (Sch78).

Male mice were administered [^{3}H]-hexogen either by gavage or by intravenous injection (doses not given). After administration by either method,

hexogen was rapidly distributed throughout the body. After dosing by gavage, peak concentrations of radioactivity in tissues were in the order: liver > kidney > muscle > lung > spleen > heart > brain > testis > adipose tissue. Radioactivity levels in tissues decreased significantly at 12 to 24 hours, and were close to background levels at day 7 after administration. The percentage of the administered radioactivity that was eliminated via the urine and the faeces during the first day was 65%, with more radioactivity excreted via the urine than via the faeces (no further data given). After intravenous injection, peak concentrations of radioactivity in tissues were in the order: lung > heart > liver > kidney > brain > spleen > testis > adipose tissue > muscle (Guo85).

In a 3-month study, monkeys (n=3/sex/dose level) were given oral (gavage) doses of hexogen of 0, 0.1, 1.0, or 10 mg/kg bw. At 30, 60, or 90 days after the beginning of dosing, all plasma hexogen levels in the low- and mid-dose animals were 0.02 mg/L. Monkeys in the high-dose group had mean plasma hexogen levels of 1.08 mg/L, 0.31 mg/L, and 0.62 mg/L, respectively (Mar74).

6 Effects and mechanism of action

Human data

No signs of irritation were noted 48 hours after occluded application of a wet patch covered with dry hexogen to human forearm skin (Oet49).

Hexogen does not exhibit pharmacological effects similar to the nitrites or nitrates. However, convulsions have been reported in workers manufacturing hexogen. The convulsions occurred either without warning or after 1 or 2 days of insomnia, restlessness, and irritability. There were generalised clonic-tonic convulsions resembling in all clinical respects the seizures seen in epilepsy, but occurring in individuals without a previous history of seizures. They were most frequent in persons doing the drying, sieving, and packing of hexogen, where the dust could be inhaled. The seizures were followed by temporary post-convulsive amnesia, malaise, fatigue, and asthenia. Eventually, there was complete recovery (Dav93). More specifically, 10 Italian munitions workers showed toxic effects characterised by generalised convulsions of a clonic-tonic type, 4 had loss of consciousness without convulsions, 2 had vertigo, and 1 had vomiting and confusion (Bar49). In another report, 5 cases of convulsions and/or unconsciousness were described in workers exposed to hexogen in its finely powdered form. The typical symptoms of hexogen intoxication occurred either at work or several hours later at home, with few prodromal signs of headache,

nausea, and vomiting. Unconsciousness lasted several minutes to 24 hours. Recovery was complete with no sequelae (Kap65). Two cases of hexogen-induced intoxications in a French explosive factory were described, after hand sieving large amounts of dry hexogen for about 5 hours. One worker had clonic-tonic convulsions, while the other became unconscious without convulsions. Recurrent seizures occurred despite anticonvulsant therapy, 6 and 2 hours after admission in hospital. Electroencephalographic findings were normal and both workers recovered completely with no sequelae (Tes96).

Several severe cases of hexogen intoxication have been described in military in Vietnam following exposure to composition C-4, a 'plastic' explosive containing 91% hexogen. Exposure occurred either following accidental ingestion or inhalation to its fumes when used as a field cooking fuel. In 3 men ingested C-4 explosive in amounts of 25 to 180 gram, symptoms of intoxication were lethargy, semi-comatose, generalised seizures, nausea and vomiting, headache, myalgias, and fever. The men recovered within 4 to 37 days after hospitalisation (Sto69). In another paper, signs and symptoms of C-4 intoxication reported in 18 men were confusion, marked hyperirritability, involuntary myoclonic contractions of the extremities, severe prolonged generalised seizures, nausea and vomiting, and prolonged post-ictal mental confusion. Abnormal electroencephalographic findings were seen in 9 patients. Apart from effects on the central nervous system, signs of renal toxicity were reported in 3 and increased white blood cell count in 13 men. The effects involving the central nervous system were completely reversible, often within weeks and occasionally over several months (Ket72).

A cross-sectional study was conducted on employees in 5 different US Army munitions plants to examine the relationship between hexogen exposure and autoimmune disease. The fluorescent antinuclear antibody test was used to detect autoimmune disease. In addition, standard haematological and clinical chemical laboratory tests were used to identify haematological abnormalities or adverse hepatic or renal effects. The hexogen-exposed group comprised 69 workers (26 females, 43 males) exposed to hexogen alone and 24 male workers exposed to both hexogen and cyclotetraethylenetetranitramine (HMX); the control group comprised 338 non-exposed persons (101 females, 237 males). The mean 8-hour time-weighed average airborne hexogen concentration in the breathing zone of the workers was 0.28 mg/m^3 (range: <0.01-1.57 mg/m^3). There were no statistically significant differences between the hexogen-exposed group and the control group in any of the tests examined (Hat77).

Animal data

Irritation and sensitisation

Rabbits developed dermatitis when a mixture containing 33% of hexogen in DMSO was applied to the clipped backs for 24 hours or 5 days. No evidence of sensitisation was reported, but no further details were provided (McN74).

Acute toxicity

Results of acute lethal toxicity tests with hexogen are summarised in Table 1.

Table 1 Summary of acute toxicity studies in experimental animals.

exposure route	species (sex)	LD_{50} (mg/kg bw)	reference
dermal	rabbit (male, female)	>2000	Fur84
oral	rat	approx. 200	Oet49
	rat (male, female)	119	Cho80
	rat (male, female)	100[a]	Sch77
	rat (male, female)	300[b]	Sch77
	mouse (male)	97	Cho80
	mouse (female)	59	Cho80
intravenous	mouse	19	McN74

[a] Fine powder in solution or slurry.
[b] Coarse granular hexogen.

Signs of intoxication in rodents included laboured breathing, hyperirritability, and convulsions (ACG99). Macroscopic examination of rats revealed moderate to marked congestion of the gastrointestinal tract and the lungs in some animals (Oet49).

In acute neurotoxicity screening experiments, the susceptibility to audiogenic seizures was examined in male Long-Evans rats (n=10-16/group) 8 hours after oral administration of hexogen doses of 0, 10, 20, or 60 or 0, 12.5, 25, or 50 mg/kg bw. Animals were monitored for spontaneous seizures during the 8-hour interval between dosing and audiogenic seizure testing. In the 60-mg/kg bw group, 6/16 animals died during spontaneous seizure during the 8-hour interval period and another 6 animals during audiogenic seizure testing. In the 50-mg/kg bw group, 3/12 animals died during the 8-hour interval while there was no additional mortality probably because of the exsanguination procedures that immediately followed testing. The incidence of spontaneous seizures, monitored in the second experiment, was dose relatedly increased reaching

statistical significance at doses of 25 mg/kg bw and higher. The proportion of animals that experienced spontaneous seizures peaked at 2 hours for all treatment groups and amounted to 80% for the high- and mid-dose groups and to 20% for the low-dose group. The next 6 hours, this proportion dropped to stable levels of 20 and 0% for the mid- and low-dose groups, respectively, but remained 70-80% for the high dose. Audiogenic seizures were observed in 1/10, 0/10, 3/10, 4/10, 7/9, and 9/11 rats treated with 10, 12.5, 20, 25, 50, and 60 mg/kg bw, respectively. Evaluation of the time course of audiogenic seizures, determined at 2, 4, 8, 16 hours post-treatment in an additional experiment at a dose of 37.5 mg/kg bw, showed seizures only at 8 or 16 hours in 4/13 and 1/13 animals, respectively, despite significant elevation of plasma hexogen levels at 2 and 4 hours. Plasma hexogen concentrations varied between 6.5 and 7.5 mg/L during the 16-hour test interval (Bur88).

When rats were given hexogen as single oral doses in the range of 12.5 to 50 mg/kg bw, dose-related decreases in startle-response amplitude, motor activity, and rates of schedule-controlled response, and dose-related increases in startle-response latency were observed. No behavioural effects were observed in rats after oral hexogen doses of 1, 3, or 10 mg/kg bw/day for 30 days. McPhail et al. concluded that single high doses of hexogen are likely to be associated with multiple deficits in neurobehavioural integrity (McP85).

Sprague-Dawley rats treated with a single intraperitoneal injection of hexogen of 500 mg/kg bw developed severe clonic-tonic convulsions 24 minutes after administration. The plasma hexogen concentration at the first seizure was intrapolated to be 5.2 mg/L (Sch77).

Liver and kidney effects were observed in rats 24 hours following a single oral hexogen dose of 100 mg/kg bw. Hepatic effects included dilation of the rough endoplasmatic reticulum, mitochodrial swelling, and the presence of concentric membrane arrays, as well as extensive, long-lasting proliferation of the liver smooth endoplasmatic reticulum, indicating induction of microsomal enzymes. Kidney effects were restricted to the distal convoluted tubular cells. Haematuria was indicated due to the presence of erythrocytes in nephron tubulus (Fre76). In dogs, single oral doses of 5, 10, or 20 mg/kg bw did not induce changes in physiological functions of the lungs or the circulation, studied over 3 to 4 hours (Oet49).

Short-term toxicity

When groups of rats (n=15) were given dietary doses of hexogen of 0, 15, 50, or 100 mg/kg bw for 10 weeks, 13 rats of the high-dose group and 9 rats of the mid-

dose group died. Symptoms of toxicity were viciousness, hyperirritability, convulsions, and decreased body weights. In the low-dose group, no abnormalities were observed. The only macroscopic change noted was congestion of the lungs and gastrointestinal tract (Oet49).

In a follow-up study, groups of 20 rats were given dietary doses of hexogen equivalent to 0, 15, 25, or 50 mg /kg bw for 3 months. Mortality was 8/20, 8/20, and 1/20 in the high-, mid-, and low-dose groups, respectively, vs. 0/20 in controls. The animals in the mid- and high-dose groups lost some weight in the course of the experiment, but this weight loss was regained rapidly in the weeks later on in the experiment. Other symptoms of toxicity were convulsions, hyperirritability and viciousness. Autopsy of the animals that died showed congestion of the lungs and the gastro-intestinal tract and bladders distended with heavily blood-tinged urine. No abnormalities were noted in haematological parameters or upon macroscopic and microscopic examination in surviving animals. The NOAEL was 15 mg/kg bw/day (Oet49).

In an unpublished study, groups of 10 male and 10 female Fischer 344 rats received hexogen via the food at doses (calculated by Cholakis et al.) of 0, 10, 14, 20, 28, or 40 mg/kg bw for 13 weeks. At the high dose, body weights and food consumption were decreased, and haematological effects, lower relative heart weights, foci of myocardial degeneration, and hepatic portal inflammation were observed. Only haematological effects were noted at 28 mg/kg bw/day. The NOAEL was 20 mg/kg bw/day (Cho80).

In another study, groups of 10 male and 10 female Fischer 344 rats were given dietary hexogen doses of 0, 10, 30, 100, 300, or 600 mg/kg bw for 13 weeks (the control group consisted of 30 male and 30 female rats). A dose-related increased mortality was observed at 100 mg/kg bw/day and higher. Signs of toxicity were hyperreactivity to approach at 100 mg/kg bw/day and higher and tremors and convulsions at 600 mg/kg bw/day. Male rats showed reduced body weight gain and food consumption at 30 and 100 mg/kg bw/day, respectively, whereas no changes were observed in females up to 100 mg/kg bw/day. Dose-related leukocytosis was seen in both sexes, which was statistically significant at 10 mg/kg bw/day and higher in females only. None of these elevations were accompanied by any change in the proportion of leukocyte cell types. Serum triglyceride levels were significantly decreased at 30 mg/kg bw/day and higher in both sexes. No other haematological or clinical chemical abnormalities were found. Absolute and relative liver weights were statistically significantly increased in female animals given 100 mg/kg bw. No treatment-related macro- or microscopic lesions were observed (Lev81). The committee concludes that the NOAEL in this study was 10 mg/kg bw/day.

In an unpublished study, groups of 10 male and 10 female B6C3F$_1$ mice received hexogen via the food at doses equivalent to 0, 10, 14, 20, 28, or 40 mg/kg bw for 3 months. A later supplemental study included 4 groups (n=10 mice/sex/group), fed 0, 40, 60, or 80 mg/kg bw/day, for 2 weeks, followed by 0, 320, 160, or 80 mg/kg bw/day, respectively, for 11 weeks, resulting in time-weighted doses during the 13-week period of 0, 80, 145, or 277 mg/kg bw/day. Effects seen in one or both sexes included increased mortality, hyperactivity, and increased absolute and relative liver weight at 277 mg/kg bw/day, accompanied by hepatocellular vacuolisation or microgranulomas and tubular nephrosis of the kidneys. At 145 mg/kg bw/day, decreased haemoglobin levels and haematocrit were found (Cho80).

Female dogs (n=7) were given 50 mg/kg bw by gavage, 6 days/week, for 6 weeks. The control group consisted of 5 animals. One dog in the treatment group died during the study, whereas the remaining dogs lost weight during the experiment. Signs of toxicity were irritability, hyperexcitability, irregular walking, and convulsions. No changes were found in haemoglobin or methaemoglobin concentration or in erythrocyte or white blood cell count during the course of the experiment. The only gross changes noted were distention of the mesenteric blood vessels and slight congestion of the mucous membranes of the small intestines. No treatment-related microscopic changes were found (Oet49).

In an unpublished study, groups of 3 male and 3 female Beagle dogs received hexogene via the food at doses equivalent to 0, 0.1, 1.0, or 10 mg /kg bw/day for 90 days. There was no treatment-related mortality. Signs of toxicity were scattered instances of nausea and vomiting during the first 2 weeks. No treatment-related body weight, haematological, clinical chemical, macroscopic, or microscopic changes were found (Har74).

In another unpublished study, groups of 3 male and 3 female cynomolgus monkeys (*Macaca fascicularis*) received oral (gavage) hexogen doses of 0, 0.1, 1.0, or 10 mg/kg bw, 7 days/week, for 90 days. Signs of toxicity in high-dose animals were frequent episodes of emesis and central nervous system disturbances, including salivation and tonic-type convulsions. Plasma hexogen levels in 3 of the monkeys in this group ranged between 2.0 and 3.7 mg/L during convulsive events. One of these monkeys was euthanatised while the others recovered and survived the experiment. No signs of toxicity were observed in the low- and mid-dose animals. Results of haematological or clinical chemical tests and of organ weight determinations did not reveal treatment-related changes in any of the groups. Microscopic examination revealed some increases in numbers of necrotic or degenerative megakaryocytes in the bone marrow and in the

amounts of iron-positive material present in liver cord cell cytoplasm of high-dose animals, compared with the controls. No statistical analysis was performed, due to a low number of animals per dose group, and no microscopic examination was conducted on animals in the low- and mid-dose groups. According to Martin and Hart, the toxicological importance of these findings was uncertain (Mar74). The committee concluded that in this study, 1 mg/kg bw/day was the NOAEL.

In summary, the target organ for short-term toxicity of hexogen was the central nervous system in all species examined. The monkey was the most sensitive species (13-week NOAEL: 1 mg/kg bw/day) and the mouse the least sensitive (13-week NOAEL: 80 mg/kg bw/day). Rats and dogs were approximately equally sensitive (13-week NOAELs: 10 to 28 mg/kg bw/day and between 10 and 50 mg/kg bw/day, respectively).

Long-term toxicity and carcinogenicity

In an unpublished study, rats (Sprague-Dawley; n=100/sex/group) received dietary hexogen doses equivalent to 0, 1.0, 3.1, or 10 mg/kg bw/day for up to 24 months. Interim kills were performed after 13, 26, and 52 weeks of exposure. Haematological tests showed fluctuations in red blood cell and reticulocyte counts, packed cell volumes and haemoglobin concentrations, and clinical chemical tests particularly in electrolytes. In none of the tests, a clear dose-related effect occurred, and the fluctuations were not considered to be of toxicological significance. No treatment-related changes were found in organ weights or in macroscopic or microscopic examinations. Hart concluded that the highest dose level tested, 10 mg/kg bw per day, was the NOAEL of the study (Har76).

In another study, F344 rats (n=75/sex/group) received hexogen (purity: 93%) via the food at doses equivalent to 0, 0.3, 1.5, 8.0, or 40 mg/kg bw/day, 7 days/week, for up to 24 months. The main contaminant was cyclotetraethylenetetranitramine (HMX), and represented approximately 3-10% of the sample. Ten rats/sex/dose were killed after 6 and 12 months. A statistically significant increased mortality was seen for both males and females in the high-dose group, compared with the controls. Prior to death, tremors and/or convulsions were observed. In addition, many of the males and some of the females were occasionally hyperreactive to approach. Other signs of toxicity were discoloured and/or opaque eyes in high-dose females. Body weight gain was statistically significantly decreased at 8 mg/kg bw/day and higher and food consumption at 40 mg/kg bw/day. Haematological results showed reduced

haematocrit, haemoglobin, and red blood cells throughout the study in high-dose males and females. The anaemia was mild, as demonstrated by the absence of compensatory responses, i.e., reticulocytosis or macrocytosis. Platelet counts were increased throughout the study for rats of both sexes administered 40 mg/kg bw/day, and occasionally in males at 8 mg/kg bw/day. Clinical chemical tests showed significantly reduced serum cholesterol and triglyceride levels in both sexes at 40 mg/kg bw/day. In female rats, decreased serum total protein and glucose levels and an increased serum alkaline phosphatase activity were found at 40 mg/kg bw/day. Other clinical chemical parameters remained within normal limits. A statistically significant increased incidence of cataracts was observed in the high-dose females. At termination, relative liver, kidney, brain, and heart weights were statistically significantly increased for male and female rats and relative adrenal weight for females administered 40 mg/kg bw/day. Testes weights were decreased at week 52 at the high dose (not evaluated at termination). Hepatomegaly was seen at the high-dose group and to a much lesser extent for females of the 8-mg/kg bw/day group, although microscopic liver changes were not apparent. Microscopic examination did not reveal treatment-related lesions of the central nervous system. Macroscopic and microscopic examination of the urogenital system revealed urinary bladder lesions with luminal distension and cystitis, dark-brown kidneys with renal pelvis dilatation and medullary papillary necrosis, and testicular atrophy with germinal cell degeneration and enlarged seminal vesicles in high-dose animals. Suppurative inflammation of the prostate and increased levels of a haemosiderin-like pigment deposited in the spleen were observed in rats administered 1.5 mg/kg bw/day or more. Based on these effects, the NOAEL of the study was 0.3 mg/kg bw/day (Lev83). As no data were shown of increased frequencies of neoplastic lesions in treatment groups compared with the control group, the committee concludes that hexogen was not carcinogenic in rats under the conditions of this study.

B6C3F$_1$ mice (n=85/sex/group) received hexogen (purity: 93%) via the food at initial doses equivalent to 0, 1.5, 7.0, 35, or 175 mg/kg bw, 7 days/week, for up to 24 months. The main contaminant was HMX, which represented approximately 3-10% of the sample. Due to excess mortality of high-dose females during the first 10 weeks, this dose was reduced to 100 mg/kg bw/day from week 11 onwards. Interim kills were made at 6 and 12 months after the beginning of dosing, and surviving animals were killed after 24 months of treatment. Following dose level change, mortality rates were similar in all groups. Signs of toxicity were a single occurrence of convulsions at 35 and

175/100 mg/kg bw/day and significant skin lesions in males of the highest dose group, apparently associated with fighting wounds. Body weight gains were significantly reduced for males and females in the highest dose group. Apart from statistically significantly increased cholesterol levels at 6 and 12 months in males and females of the highest dose group, no statistically significant changes in haematological or clinical chemical parameters were found in any of the treated groups, compared with the control group. Ophthalmological examination revealed an increased incidence of cataracts in male mice administered 175/100 mg/kg bw/day. At termination, increases in absolute and relative liver and in relative kidney and heart weights were observed in the highest dose group. Microscopic examination revealed a, not statistically significantly, increased incidence of testicular degeneration in mice given either 35 or 175/100 mg/kg bw/day, when compared with the concurrent and historical controls. The incidence of hepatocellular carcinoma showed a not statistically significant increase in mid- and high-dose female mice compared to the controls. However, the combined incidences of hepatocellular carcinoma and adenoma were statistically significantly higher in females receiving doses of 7 mg/kg bw and above, compared to either concurrent or historical control data. The incidence of combined hepatocellular adenomas and carcinomas in male mice was not statistically significantly different in any of the treatment groups compared to the control group (see Table 2). An increased incidence of lymphoid hyperplasia was found in the spleen of males dosed with 1.5 and 7 mg/kg bw/day, but not at the higher doses. Lish et al. could not establish the toxicological significance of this finding. The incidence of other neoplastic lesions did not differ significantly between treated and control groups. Lish et al. concluded that under the conditions of the study the NOAEL for mice was 1.5 mg/kg bw/day (Lis84).

Table 2 Incidence of neoplastic liver and spleen lesions in male and female $B6C3F_1$ mice treated with hexogen for 24 months (Lis84).

	males				
	0 mg/kg bw (n=44)	1.5 mg/kg bw (n=41)	7 mg/kg bw (n=40)	35 mg/kg bw (n=36)	175/100 mg/kg bw (n=21)
hepatocellular adenoma	8/63 (12.7%)	6/60 (10.0%)	1/62** (1.6%)	7/59 (11.9%)	7/27 (25.9%)
hepatocellular carcinoma and adenoma (combined)	21/63 (33.3%)	26/60 (43.3%)	17/62* (27.4%)	25/59 (42.4%)	13/37 (48.1%)
spleen, lymphoid hyperplasia	6/63 (9.5%)	18/60** (30.0%)	17/62 (27.4%)	9/59 (15.2%)	1/27 (3.7%)
	females				
	0 mg/kg bw (n=48)	1.5 mg/kg bw (n=44)	7 mg/kg bw (n=49)	35 mg/kg bw (n=43)	(175)100 mg/kg bw (n=25)
hepatocelluar adenoma	1/65 (1.5%)	1/62 (1.6%)	6/64[a](9.4%)	6/64[a] (9.4%)	3/31 (9.7%)
hepatocellular carcinoma and adenoma (combined)	1/65 (1.5%)	5/62 (8.1%)	9/64* (14.1%)	12/64*[a] (18.8%)	6/31*[a] (19.4%)

[a] Significantly different from historical control $p<0.05$; hepatocellular adenoma: 98/2469 (4.0%); hepatocellular carcinoma and adenoma (combined): 199/2469 (7.9%).
* $p<0.05$; ** $p<0.01$.

Mutagenicity and genotoxicity

- *In vitro* tests:
  - Gene mutation tests. Hexogen did not induce reverse mutations in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without rat liver metabolic activation, at doses up to 1 mg/plate (Cho80) or 2.5 mg/plate (Who80). Simmon et al. also reported negative results in these strains but no test concentrations were given (Sim77).
    When tested with and without metabolic activation in strains TA98 and TA100 only, hexogen was negative at concentrations up to 11.7 µM (2600 µg/L) in a fluctuation test (Lac99), at concentrations up to 1000 µg/plate in a plate corporation assay (Tan91), and at concentrations up to 250 µg/plate in a microsuspension assay (Geo01).
    Hexogen did not increase the gene mutation frequency in the HGPRT forward mutation assay when tested with and without metabolic activation in cultured V79 Chinese hamster lung cells at concentrations up to 180 µM (4000 µg/L) (Lac99).
  - Other genotoxicity assays. Hexogen did not induce mitotic gene conversions in *S. cerevisiae* D3 with and without rat liver metabolic activation (no details given) (Sim77).
    Hexogen was not observed to cause DNA damage in cultured human

fibroblasts in the unscheduled DNA synthesis (UDS) assay, with and without metabolic activation, in concentrations ranging from 250 to 4000 mg/L (Dil78).

- *In vivo* tests:
  In a dominant lethal assay, male CD rats (n=19-22/group), i.e., the F0 male of a 2-generation reproduction toxicity study (see 'Reproduction toxicity'), given nominal dietary doses of hexogen of 0, 5, 16, or 50 mg/kg bw/day for 15 weeks were each allowed to mate with 2 unexposed females a week, for 2 weeks. No statistically significant effects on the number of corpora lutea, implants, or of live or dead embryos were observed (Cho80).

The committee concluded that hexogen was not mutagenic, either *in vitro* or *in vivo*.

Reproduction toxicity

In an unpublished study, Fischer 344 rats (n=22/sex/group) received hexogen via the diet at doses of 0, 5, or 16 mg/kg bw/day for 13 weeks prior to mating and during mating, gestation, and lactation through 2 generations, and, because of the high toxicity, at 50 mg/kg bw/day through 1 generation. At 50 mg/kg bw, excessive mortality with decreased body weight and food consumption was observed in F0 animals. Reproductive effects in the high-dose group included a decreased number of pregnancies and a poor survival of the F1 offspring. The reproductive performance of rats in both the low- and mid-dose groups was not significantly different from the controls. At 16 mg/kg bw/day, body weights of female F2 pups were significantly decreased compared with controls, and microscopic examination revealed a significant increase in renal cortical cysts (Cho80). The committee concludes that the NOAEL for parental and reproductive effects was 5 mg/kg bw/day.

In an unpublished developmental toxicity study, groups of pregnant Fischer 344 rats received oral (gavage) hexogen doses of 0, 0.2, 2.0, or 20 mg/kg bw on gestational days 6 to19. At the high dose, maternal toxicity included excessive mortality (6/25 rats), convulsions, hyperactivity, and reduced body weights and food consumption. The only reproductive effect observed was a high incidence of early resorptions in the surviving rats of the high-dose group. There were no significant differences in gross, visceral, or skeletal anomalies in fetuses in any of the treated groups, compared with the control group (Cho80). The committee

concludes that the NOAEL for both maternal and developmental toxicity was 2 mg/kg bw/day.

In another unpublished study, groups of pregnant Sprague Dawley rats received daily oral (gavage) doses of hexogen of 0, 2, 6, or 20 mg/kg bw on gestational days 6 to15 and were sacrificed on gestational day 20. At 20 mg/kg bw/day, maternal effects were high mortality (31%) during the test period, convulsions, hyperactivity, and significantly lower body weights, compared with the controls. There was no effect on reproductive parameters, such as fertility index, gestation index, number of litters, number of implantations, number of early or late resorptions, or number of live or dead fetuses. Furthermore, there were no significant differences in the number of gross, visceral, or skeletal anomalies in any of the treated groups, compared with the controls. However, slight, statistically significant ($p<0.05$) decreases in fetal weights (by 4, 2, and 9% in the low- mid-, and high-dose group, respectively) and lengths (by 1, 0.8, and 5 %, respectively) were seen in all exposed groups (Ang86). The committee concludes that, in this study, the NOAEL for both maternal and developmental toxicity (i.e., decreased fetal weight and length) was 6 mg/kg bw/day.

When pregnant New Zealand white rabbits were given hexogen at doses of 0, 0.2, 2.0, or 20 mg/kg bw/day on gestational days 7 to 29, no maternal or reproductive effects were observed in any of the treated groups compared with the controls. The NOAEL for both maternal and reproductive toxicity was 20 mg/kg bw/day, the highest dose tested (Cho80).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for hexogen in the Netherlands is 1.5 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

The toxicology profile in this review is obtained to a large extent from unpublished reports of toxicology studies, conducted on behalf of the U.S. Army Toxic and Hazardous Materials Agency, or the U.S. Army Medical Research and Development Command.

Workers can be occupationally exposed to hexogen when the compound is used in explosive plants. Exposure may occur by inhalation of dust or through

direct skin contact, principally during dumping of dried hexogen powder, screening and blending, and clean-up of spilled material (Kap65).

The committee did not find data on the percentage uptake of the compound through the lungs or through the skin. In a 3-year-old boy, who accidentally ingested hexogen, a peak level of the compound in plasma was reached at 24 hours after ingestion, and the half-life of elimination from the plasma was 15 hours. In the rat, the extent of absorption after oral administration is close to 100%. Within 48 hours after single oral dosing, 43% of the dose was excreted as CO_2 in exhaled breath, 34% in the urine, and 3% in the faeces, and 10% was retained in the carcass. There was no referential tissue distribution. Similar data were obtained after daily administration of hexogen up to 90 days, demonstrating that no accumulation occurred. No hexogen metabolites were identified.

Most reported human health effects associated with occupational and accidental exposure were central nervous system effects. They included confusion, marked hyperirritability, involuntary myoclonic contractions of the extremities, severe prolonged generalised seizures, nausea and vomiting, prolonged post-ictal mental confusion, and abnormal electroencephalographic findings. In workers, recovery was complete with no sequelae. In the more severe cases, reported in military following accidental or deliberate hexogen exposure, recovery of the central nervous system effects took weeks and occasionally over several months. Apart from effects on the central nervous system, renal effects were also found. In a cross-sectional study involving 69 hexogen workers from 5 different US Army munitions plants, no haematological, hepatic, or renal abnormalities were found. Airborne concentrations in the breathing zone of the workers varied from <0.01 to 1.57 mg/m^3. The committee considered this study of limited value, because no neurophysiological tests were conducted and because the number of hexogen exposed workers was small.

In experimental animals, limited data indicated that hexogen was irritating to the skin of rabbits, but not a skin sensitiser. Based on acute lethal toxicity data, the committee considers the compound as non-hazardous via the dermal route, and toxic via the oral route. On the basis of the occurrence of convulsions and behavioural effects, the central nervous system is the critical organ following acute exposure. Also in 13-week oral studies in rats, mice, dogs, and monkeys, the central nervous system and/or the haematological system were the main targets. The monkey appeared to be the most sensitive species (13-week NOAEL: 1 mg/kg bw/day) and the mouse the least sensitive (13-week NOAEL: 80 mg/kg bw/day). Rats and dogs were approximately equally sensitive (13-week NOAELs: 10 mg/kg bw/day and between 10 and 50 mg/kg bw/day,

respectively). Hexogen was not carcinogenic in rats in 2-year oral toxicity and carcinogenicity studies. The NOAEL for non-neoplastic lesions was 0.3 mg/kg bw/day, based on effects on the spleen and the prostate. In a 2-year study in mice, the combined incidences of hepatocellular carcinoma and adenoma were statistically significantly higher for females receiving hexogen doses of 7 mg/kg bw and above, compared to either concurrent or historical control data. Non-neoplastic lesions included not statistically significantly increased incidences of testicular degeneration in mice given 35 or 175/100 mg/kg bw/day, when compared with the concurrent or historical controls. The NOAEL was 1.5 mg/kg bw/day. Hexogen did not induce gene mutations or unscheduled DNA synthesis in *in vitro* tests and no dominant lethal mutations in rats. In view of the absence of genotoxicity or mutagenicity, the committee is of the opinion that the carcinogenicity in mice is induced through a non-genotoxic mechanism, for which a threshold exposure level exists.

In a 2-generation reproduction study in rats, the NOAEL for parental and reproductive toxicity was 5 mg/kg bw/day. From 2 developmental toxicity studies in rats, with doses of 0.2, 2, or 20 and 2, 6, or 20 mg/kg bw/day, the committee concludes 6 mg/kg bw/day to be a NOAEL for maternal and developmental toxicity. In rabbits, the NOAEL for maternal and developmental toxicity was at least 20 mg/kg bw/day (the highest level tested).

Based on the above data, the committee takes the 2-year oral toxicity and carcinogenicity study in rats, with a NOAEL of 0.3 mg/kg bw/day, as a starting point in establishing a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days/week) is adjusted by multiplying with a factor of 7/5 resulting in a no-adverse-effect level (NAEL) of 0.42 mg/kg bw. For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 9, covering inter-and intraspecies variation, are applied, resulting in a NAEL for humans of 0.01 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and applying the preferred value approach, a HBROEL of 0.1 mg/m^3 is recommended for hexogen.

The committee recommends a health-based occupational exposure limit for hexogen of 0.1 mg/m^3, as inhalable dust, as an 8-hour time-weighted average (TWA).

In view of the low dermal toxicity of hexogen, the committee considers a skin notation not necessary.

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). Cyclonite. In: TLVs® and other occupational exposure values - 1999. [CD-ROM]. Cincinnati OH, USA: ACGIH®, Inc, 1999.

ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 37.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2003: 24.

Ang86 Angerhofer RA, Davis G, Balezewski L. Teratological assessment of trinitro-RDX in rats. Aberdeeen Proving Ground MD, USA: US Army Environmental Hygiene Agency, 1986; study no USAEHA-75-51-0573-86 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A166249).

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002; 36 (At-vejledning C.0.1).

ATS95 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for RDX. Atlanta GA, USA: US Department of Health and Human Services, Public Health Service, 1995; http://www.atsdr.cdc.gov/toxprofiles/tp78.html (also available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/PB95-264255).

Bar49 Barsotti M, Crotti G. [Epilectic attacks as manifestations of industrial intoxication caused by trimethylenetrinitroamine (T4)]. In Italian. Med Lav 1949; 40: 107-12; cited in ATS95, Dav93, and Kap65.

Bud96 Budavari S, O'Neill MJ, Smith A, et al, eds. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 12th ed. Whitehouse Station, NJ, USA: Merck & Co, 1996; 461.

Bur88 Burdette LJ, Cook LL, Dyer RS. Convulsant properties of cyclotrimethylenetrinitramine (RDX): spontaneous audiogenic, and amygdaloid kindled seizure activity. Toxicol Appl Pharmacol 1988; 92: 436-44.

Cho80 Cholakis JM, Wong LCK, van Goethem DL, et al. Mammalian toxicological evaluation of RDX. Frederick MD, USA: US Army Medical Research and Developmental Command, Fort Detrick, 1980; unpublished report, cited in ATS95 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A092531).

Dav93 Davis RA. Aliphatic nitro, nitrate, and nitrite compounds. In: Clayton GD, Clayton FE, ed. Toxicology. 4th ed. New York, USA: J Wiley and Sons Inc, 1993: 599-662 (Patty's industrial hygiene and toxicology; Vol II A).

Dil78 Dilley JV et al. Mammalian toxicological evaluations of TNT wastewaters. Volume II: Acute and subacute mammalian toxicity of TNT and the LAP mixture. Frederick MD, USA: US Army Medical Research and Developmental Command, Fort Detrick, 1978; unpublished report, cited in ATS95.

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2003; rep no 39.

EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs). http://europe.eu.int/comm/employment_social/health_safety/areas/oels_en.htm.

Etn89 Etnier EL. Water quality criteria for hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). Regul Toxicol Pharmacol 1989; 9: 147-57.

Fed66 Federoff BT, Sheffield OE, ed. HMX and RDX. In: Encyclopedia of explosives and related items. Dover NJ, USA: Picatinny Arsenal, 1966: C605-30 (Vol 3).

Fre76 French JE, Bradley SL, Schneider NR, et al. Cyclotrimethylenetrinitramine (RDX)-induced ultrastructural changes in rat liver and kidney. Toxicol Appl Pharmacol 1976; 37:122

Fur84 Furedi MM, Levine BS, Lish PM. Determination of the chronic mammalian toxicological effects of RDX. Acute dermal toxicity test of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in rabbits. Chicago IL, USA: IIT Research Institute, 1984 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A174710).

Geo01 George SE, Huggins-Clark G, Brooks LR. Use of a Salmonella microsuspension bioassay to detect the mutagenicity of munitions compounds at low concentrations. Mutat Res 2001; 490; 45-56.

Guo85 Guo L, Xu H, Chen Y, et al. [Distribution and metabolism of ^{3}H-RDX in mice.] In Chinese. Zhonghua Laodong Weisheng Zhiyebing Zazhi 1985; 3: 335-9; cited in Chem Abstr 105:73861c.

Har74 Hart ER. Subacute toxicity of RDX and TNT in dogs. Kensington MD, USA: Litton Bionetics, Inc, 1974 (available from the National Technical Information Service, Springfield VA, USA; order no: AD-A035717).

Har76 Hart ER. Two-year chronic toxicity study in rats. Kensington MD, USA: Litton Bionetics, Inc, 1976 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A040161).

Hat77 Hathaway JA, Buck CR. Absence of health hazards associated with RDX manufacture and use. J Occup Med 1977; 19: 269-72.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational exposure limits 2002. Sudbury (Suffolk), England: HSE Books, 2002: 19.

Kap65 Kaplan AS, Berghout CF, Peczenik A. Human intoxication from RDX. Arch Environ Health 1965; 10: 877-83.

Ket72 Ketel WB, Hughes JR. Toxic encephalopathy with seizures secondary to ingestion of composition C-4: a clinical and electroencephalographic study. Neurology 1972; 22: 871-6.

Lac99 Lachance B, Robidoux PY, Hawari J, et al. Cytotoxic and genotoxic effects of energetic compounds on bacterial and mammalian cells in vitro. Mutat Res 1999; 444: 25-39.

Lev81 Levine BS, Furedi EM, Gordon DE, et al. Thirteen week toxicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in Fischer 344 rats. Toxicol Lett 1981; 8: 241-5.

Lev83 Levine BS, Furedi EM, Rac VS, et al. Determination of the chronic mammalian toxicological effects of RDX. Twenty-four month chronic toxicity/carcinogenicity study of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) in the Fischer 344 rat. Final Report - phase V. Chicago IL, USA: IIT Research Institute, 1983 (Vol1) (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A607746).

Lis84 Lish PM, Levine BS, Furedi EM, et al. Determination of the chronic mammalian toxicological effects of RDX. Twenty-four months chronic toxicity/carcinogenicity study of hexahydro--1,3,5-trinitro-1,3,5-triazine (RDX) in the B6C3F$_1$hybrid mouse. Final report – Phase VI. Chicago IL, USA: IIT Research Institute, 1984 (Vol 1) (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A1817667).

Mar74 Martin DP, Hart ER. Subacute toxicity of RDX and TNT in monkeys. Kensington MD, USA: Litton Bionetics, Inc, 1976 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A044650).

McN74 McNamara BP, Averill HP, Owens EJ, et al. The toxicology of cyclotrimethylenetrinitramine (RDX) and cyclotetramethylenetetranitramine (HMX) solutions in dimethylsulfoxide (DMSO), cyclohexanone, and acetone. Aberdeen Proving Ground MD: US Army, Edgewood Arsenal; Edgwood Arsenal Technical Report EB-TR-73040; unpublished report, cited in ATS95 and Toxline (abstract).

McP85 MacPhail RC, Walker QD, Cook LC. Neurotoxicity of cyclotrimethylenetrinitramine (RDX). Frederick MD, USA: US Army Medical Research and Developmental Command, Fort Detrick, 1985 (available from the National Technical Information Service, Springfield VA, USA; order no: NTIS/AD-A168266/5).

NLM03 US National Library of Medicine (NLM), ed. Cyclonite. In: Hazardous substances data bank (HSDB) (last revision date cyclonite file: 8 September 2002; last review date: 23 January 1997); http://toxnet/nlm.nih.gov.

Oet49 Von Oettingen WF, Donahue DD, Yagoda H, et al. Toxicity and potential dangers of cyclotrimethylenetrinitramine (RDX). J Ind Hyg Toxicol 1949; 31: 21-31.

Sch77 Schneider NR, Bradley SL, Andersen ME. Toxicology of cyclotrimethylenetrinitramine: distribution and metabolism in the rat and the miniature swine. Toxicol Appl Pharmacol 1977; 39: 531-41.

Sch78 Schneider NR, Bradley SL, Andersen ME. The distribution and metabolism of cyclotrimethylenetrinitramine (RDX) in the rat after subchronic administration. Toxicol Appl Pharmacol 1978; 46: 163-71.

Sim77 Simmon VF, Eckford SL, Griffin AF, et al. Munitions wastewater treatments: does chlorination or ozonation of individual components produce microbial mutagens? Toxicol Appl Pharmacol 1977; 41: 197.

Sto69 Stone WJ, Paletta TL, Heitman EM, et al. Toxic effects following ingestion of C-4 plastic explosive. Arch Intern Med 1969; 124: 726-30.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 30.

Tan92 Tan EL, Ho CH, Griest WH, et al. Mutagenicity of trinitrotoluene and its metabolites formed during composting. J Toxicol Environ Health 1992; 36: 165-75.

Tes96 Testud F, Glanclaude JM, Imperator J, et al. Intoxications aiguës professionnelles par l'hexogène, un explosif nitré original. Arch Mal Prof Med Trav Secur Soc 1996; 57: 342-6.

Twi84 Twibell JD, Turner SL, Smalldon KW, et al. The persistence of military explosives on hands. J Forensic Sci 1984; 29: 284-90.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz. Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Who80 Whong W-Z,Speciner ND, and Edwards GS. Mutagenic activity of tetryl, a nitroaromatic explosive, in three microbial test systems. Toxicol Letters 1980; 5: 11-7.

Woo86 Woody RC, Kearns GL, Brewster MA, et al. The neurotoxicity of cyclotrimethylenetrinitramine (RDX) in a child: a clinical and pharmacokinetic evaluation. J Toxicol Clin Toxicol 1986; 24: 305-19.

Annex

Occupational exposure limits for hexogen in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	1.5	8 h	administrative	S	SZW03
Germany						
- AGS	-	1.5	8 h			TRG00
- DFG MAK-Kommission	-	-				DFG03
Great Britain						
- HSE	-	1.5	8 h		S	HSE02
		3	15 min			
Sweden	-	-				Swe00
Denmark	-	1.5			S	Arb02
USA						
- ACGIH	-	0.5	8 h	TLV	S, A4[c]	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	1.5	10 h	REL	S	ACG03a
		3	15 min	STEL		
European Union						
- SCOEL	-	-				EC03

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

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

[c] Classified in carcinogenicity categorie A4: i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agents into one of the other categories.