Nonane

(CAS No: 111-84-2)

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 nonane 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 KJ van den Berg, Ph.D., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of nonane has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in November 1997, literature was retrieved from the on-line databases Medline, Toxline, and Chemical Abstracts covering the period 1966 to November 1997, 1965 to October 1997, and 1965 to November 1997, respectively, and using the following key words: nonane and 111-84-2.

In March 2000, the President of the Health Council released a draft of the document for public review. The committee received comments by the following individuals and organisations: W ten Berge, Ph.D. (DSM, Heerlen, the Netherlands), P de Kettenis (CEFIC, Brussels, Belgium), and L Whitford (Health and Safety Executive, London, England). These comments were taken into account when deciding on the final version of the document.

An additional search in Toxline and Medline in February 2005 did not result in information changing the committee's conclusions.

2 Identity

name	: nonane
synonyms	: n-nonane, nonyl-hydride, Shellsol 140
molecular formula	: C_9H_{20}
structural formula	: CH_3-$(CH_2)_7$-CH_3
CAS number	: 111-84-2

3 Physical and chemical properties

molecular weight	: 128.26
boiling point	: 150.8°C
melting point	: -513°C
flash point	: 31°C (closed cup)
vapour pressure	: at 25°C: 0.59 kPa
solubility in water	: insoluble (at 20°C: 0.007 mg/100 mL)
log $P_{octanol/water}$	: 4.76 (estimated), 5.46 (estimated)
conversion factors	: at 20°C, 101.3 kPa: 1 ppm = 5.34 mg/m^3 1 mg/m^3 = 0.187 ppm

Data from ACG91, NLM04, Ric94, http://www.syrres.com/esc/est_kowdemo.htm.

Nonane is a colourless liquid, having a gasoline-like odour (ACG91). Odour thresholds of 250 (47 ppm) (Amo83) and 3412 mg/m^3 (638 ppm) (Rut86) have been reported.

4 Uses

Nonane is used in organic synthesis, as a solvent, as a distillation chaser, as a fuel additive, and in biodegradable detergent. Nonane is an ingredient of such petroleum fractions as VM&P naphtha, 140 flash, and Stoddard solvents, and gasoline (ACG91, Ric94).

5 Biotransformation and kinetics

In a volunteer exposed to approximately 100 ppm nonane (534 mg/m^3) for 200 minutes in an exposure chamber, blood levels reached 1.4 mg/L at the end of the exposure. Thereafter, nonane was eliminated rapidly from the blood, with blood levels of 0.5-0.6, 0.3-0.4, and 0.2-0.3 mg/L at 20, 40, and 60 minutes post-exposure, respectively (Gil91).

The uptake rate in rats (n=2/group), exposed by inhalation to 100 ppm (534 mg/m^3) nonane for 80 minutes was found to be approximately 9 nmol/kg bw/min/ppm (i.e., 1.2 µg/kg bw/min/ppm) (Dah88).

The organ distribution of nonane observed in various studies following exposure to concentrations ranging from 75-5200 ppm (400-27,770 mg/m^3) indicated the highest uptake in fat, followed by brain, kidneys, liver, and blood (Eid96, Nil88, Zah90, Zah92). After a 12-hour recovery period, the nonane levels were decreased by approximately 95% and more in most tissues, with the

exception of fat (44% decrease) (Zah92). Blood/air and urine/air partition coefficients of 50 and 33.8, respectively, have been reported for nonane (Imb85).

The metabolism of nonane was studied in rats (n=10/group) given oral (gavage) doses of 800 mg/kg bw/day on every other day for 2 days. Metabolites identified in the urine included monoalcohols (2-, 3-, 4-nonanol, 1-heptanol), mono- and diketones (4-nonanone, 2,5-hexanedione), lactones (γ-valerolactone, δ-hexanolactone, δ-heptanolactone), a furan (2-methyl-2-(3-oxoxbutyl) furan), and dicarboxylic acids (malonic acid, glutaric acid) (Ser95). The commission notes that the lactones and furan identified in this study may be an artefact of the sampling and analytical procedures as was suggested in reports on the metabolism of hexane and heptane (see e.g., Bah84, Fed87, Man99, Per86).

6 Effects and mechanism of action

Human data

The committee did not find data on toxic effects in workers occupationally exposed to nonane.

Animal data

The skin irritating properties of nonane were studied using a standard test protocol (EEC Directive 79/831/EEC) with rabbits. Pure nonane was found to be irritating to the skin (Jac87a). In a modified test with rabbits, using a Finn chamber, a limit test with nonane showed that concentrations >50% in the vehicle were irritating (Jac87b).

With respect to the respiratory tract, Kristiansen and Nielsen studied the sensory irritation of nonane in the upper part of the respiratory tract by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}) in male Ssc:CF1 mice. An RD_{50} could not be established since the decrease in respiratory rate did not exceed 40% at the concentration range tested (up to ca. 6200 ppm or 33,110 mg/m^3) (Kri88). Schaper listed an RD_{50} of 332,200 mg/m^3 (62,210 ppm), which was indicated to be an extrapolated value (probably from the data from Kristiansen and Nielsen) (Sch93).

In rats, a 4-hour (inhalation) LC_{50} of 3200 ppm (17,090 mg/m^3) was reported for nonane. Effects observed progressed from early lachrymation, salivation, and coordination loss to clonic and tonic convulsions, tremors, and death (Car78). The 8-hour LC_{50} in rats was reported to be 4400 ppm (23,500 mg/m^3). Effects of nonane observed during the 8-hour exposure were gross ataxia, general and focal

seizures, tremor, spasms, limb paralysis, and death. At the end of the 14-day recovery period following the 8-hour exposure period, severe cerebellar damage was observed: a loss of Purkinje cells as well as a high number of severely damaged neurons in animals surviving the 4400-ppm exposure. No symptoms of neurotoxicity were reported in animals exposed to nonane concentrations of 2400 ppm (12,820 mg/m^3) (Nil88).

The LD_{50} in mice following intravenous administration was reported to be 220 mg/kg bw (Ric94).

Carpenter et al. exposed a group of 10 female rats for 2 consecutive days (5 hours and 2.25 hours/day, respectively) to a nonane concentration of 1800 ppm (9610 mg/m^3). On the first day of exposure, signs of toxicity observed were lachrymation, loss of coordination, tremors, and clonic spasms. All rats (except one) appeared normal prior to the second exposure. On the second day of exposure, the signs included loss of coordination, tremors, and spasms. In addition, they exposed a group of 10 female rats to 1500 ppm (8010 mg/m^3) on 3 consecutive days (6 hours/day) followed, after a rest period of a weekend, by a further exposure period of 4 consecutive days (6 hours/day). All rats appeared normal during the first day of exposure. On the second day, minor loss of coordination, mild tremors, and slight irritation of the eyes and extremities were seen. Loss of coordination was observed on the third exposure day. Following the rest period, signs of toxicity observed during the next 4 consecutive days had a similar pattern as in the first 3 days. Body weight gains were normal during the exposure period and the recovery period of 14 days (Car78).

In a subchronic study, male rats (n=25/group) were exposed to 360 ppm (1920 mg/m^3), 590 ppm (3150 mg/m^3), and 1600 ppm (8545 mg/m^3), 6 hours/day, 5 days/week, for 13 weeks. Interim kills and examinations were performed at 4 and 8 weeks. Two animals of the highest dose group died at the first day of exposure. Necropsy of the dead animals revealed lung congestion and haemorrhage; no other lesions were observed upon histological examination. In the high-concentration group, mild coordination loss and fine tremors were observed during the first 4 days of exposure. Signs of toxicity observed during exposure throughout the experimental period were salivation and lachrymation. Mean final body weights and body weight gain were statistically significantly lower when compared with control animals. The effect on final body weight was small (decrease: 7%) and the exposed animals gained more weight during the last 3 weeks of he experiment than the controls. A statistically significant increase inserum alarine aminotransferase (ALAT) activity was found at week 4, but not at the other time points. No other statistically significant differences were found with regard to haematology and urinalysis parameters. Histological evaluation of

tissues after 4, 8, and 13 weeks did not reveal treatment-related changes. When slides of the kidneys of the animals of this experiment were analysed by an independent pathology laboratory, no histological lesions were found in any of the exposure groups at any of the time points. No signs of toxicity were seen in the mid- and low-concentration groups. The no-observed-adverse-effect level (NOAEL) was established at 590 ppm (3150 mg/m^3) (Car78, Exx81). Since no lung lesions were observed at the end of the 13-week exposure period, the committee considered the 2 deaths in the high-dose exposure groups as incidental and not treatment-related.

Following oral (gavage) administration of doses of nonane of 0, 100, 1000, and 5000 mg/kg bw to groups of 10 female F 344 rats and 10 male C57BL/6 mice, 7 days/week, for 90 days, no mortality or body weight changes were seen in any of the dosed groups. In the high-dose rat and mouse groups, clinical signs including urogenital wetness, perianal alopecia, diarrhoea, and hunched posture were seen. There were significant differences in haematology and serum chemistry values, but they were within normal species limits. In high-dose rats, increases in liver and adrenal weights and decreases in spleen and ovary weights were observed. In mid-dose rats, adrenal weights were increased and ovary weights were decreased. In mice, there were increased liver and decreased kidney weights at the mid and high dose. Microscopic examination showed varying degrees of hyperplasia and hyperkeratosis of squamous epithelium in the non-glandular stomach in all rat and mouse nonane-treated groups, mild inflammation of the proximal small intestinal mucosa in high-dose rats, and mild perianal squamous hyperplasia in high- and mid-dose animals of both species. Dodd et al. considered the proliferative forestomach lesions as a species-specific response not relevant to humans because of lack of an analogous structure in the human stomach and the absence of lesions in the glandular stomach in the test animals in this study. For both (female) rats and (male) mice, Dodd et al. established a NOAEL of 100 mg/kg bw (no more data presented) (Dod00).

Following an intraperitoneal dose of 1.0 mL/kg bw administered to rats, a decreased body weight and an increased relative liver weight were observed. Other effects observed were altered activities of hepatic and serum enzymes, protein and cholesterol levels, and increased phenobarbital-induced sleeping times. In spleen and bone marrow, increased activity of alkaline phosphatase was found that persisted in the spleen up to 42 days after a single dose of nonane. Furthermore, the activity of a number of hepatic microsomal enzymes (benzo[*a*]pyrene hydroxylase, benzphetamine-*N*-demethylase and *p*-nitroanisole-*O*-demethylase) was inhibited, while also a reduction of hepatic cytochrome P450 content was found. In addition, the total and free sulphydryl

content of the liver as well as glutathione-*S*-transferase activity were found to be decreased. A 2- to 3-fold increase in liver peroxidation was observed after nonane exposure (Kha80a, Kha80b, Kha85, Pan82).

Rabovsky et al. examined the effects of nonane on cytochrome P450 enzyme activities *in vitro* in induced rat liver and lung microsomes. Nonane (at 2mM) inhibited the activity of benzo[*a*]pyrene hydroxylase in rat liver but not in lung microsomes and the activity of 7-ethoxycoumarin deethylase in both microsomal preparations. Nonane did not affect the NADPH generation system (Rab86). In further *in vitro* studies using lung microsomes, nonane also inhibited the activity of the cytochrome P450-dependent enzyme benzyloxyphenoxazone dealkylase (Rab89).

Nonane was cytotoxic (LC_{50}=5 mM) to cultures of rat pulmonary alveolar macrophages (PAM). Nonane, at a concentration of 0.5-1.0 mM, also caused release of the lysosomal enzymes cathepsin B and D and loss of cell respiration in rat PAM cells. In rabbit PAM cells, 1 mM nonane increased lipid peroxidation (Sul87).

Mutagenicity and genotoxicity

Nonane at concentrations up to 10 mg/plate did not cause mutations in vitro in a mutagenicity assay with *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA 1537, with or without metabolic activation (Zei92).

The committee did not find data from mutagenicity or genotoxicity studies in mammalian cell systems or experimental animals.

Nonane did not induce morphological transformation of Syrian hamster embryo cells. The transformation frequency by benzo[*a*]pyrene was not enhanced by nonane. Nonane did not reduce intercellular communication in primary Syrian hamster embryo cells (Riv92).

The committee did not find data from studies on the long-term toxicity, including carcinogenity, or reproduction toxicity studies of nonane.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for nonane in the Netherlands is 200 ppm (1050 mg/m^3), 8-hour TWA.

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

8 Assessment of health hazard

The committee did not find data on the health effects in workers occupationally exposed to nonane.

In experimental animals, uptake of nonane (C9) was found to be much higher than butane (C4). Nonane may accumulate in fat. Some metabolism of nonane has been reported, indicating the formation of monoalcohols, and ketones by a cytochrome P450-containing mixed function oxidase system.

Nonane was found to be irritating to the skin. The committee did not find data from studies on potential eye irritation or sensitisation.

The 4-hour LC_{50} in rats was 3200 ppm (17,090 mg/m^3). Exposure of rats to (lethal) levels of 3200-4400 ppm (17,090-23,500 mg/m^3) for 4 hours and to 3200 ppm (17,000 mg/m^3) for 8 hours caused neurotoxicity (loss of coordination, ataxia, seizures, tremors, spasms, paralysis). Severe cerebellar and axonal damage was observed 14 days after a single 8-hour exposure to 4400 ppm (23,500 mg/m^3), but not after exposure to 2400 ppm (12,820 mg/m^3). Signs of irritation and neurotoxicity were seen in rats exposed to 1500 ppm (8010 mg/m^3) for 3 and 4 consecutive days (with a week-end break). In a 13-week study, exposure to 1600 ppm (8545 mg/m^3), 6 hours/day, 5 days/week, caused salivation, lachrymation, a small decrease (7%) in mean final body weight, decreases in body weight gain during the first 10 weeks, and transient effects with regard to coordination, tremors, and ALAT activity, while no such effects were seen at 590 ppm (3150 mg/m^3). Following oral (gavage) administration of doses 100 mg/kg bw/day, 7 days/week, for 90 days, no effects were observed. At 1000 mg/kg bw/day, there were increased adrenal weights and decreased ovary weights in rats and increased liver and decreased kidney weights in mice and, upon microscopic examination, proliferative forestomach lesions (seen in all other nonane-treated groups as well) and mild perinanal squamous hyperplasia in both species.

Nonane was not mutagenic in *S. typhimurium*. It did neither induce morphological transformation nor reduce intercellular communication in Syrian hamster embryo cells.

No studies were available to assess the potential carcinogenic or reproductive or developmental effects of nonane.

The committee takes the NOAEL of 590 ppm (3150 mg/m^3) from the 13-week inhalation rat study (Car78) as a basis for deriving a health-based recommended occupational exposure limit (HBROEL). In establishing the size of the overall assessment factor for the extrapolation to an HBROEL, the

committee takes into account the mild nature of the adverse effects occurring at 1600 ppm (8545 mg/m^3) that, moreover, were either transient or decreased in severity in the course of the study. Against this background, the committee considers an overall assessment factor of 9, covering intra- and interspecies variation and differences between experimental conditions and the exposure pattern of the worker, appropriate. Applying this factor and the preferred value approach, a health-based occupational exposure limit of 500 mg/m^3 (100 ppm) is proposed for nonane.

The committee recommends a health-based occupational exposure limit for nonane of 500 mg/m^3 (100 ppm), as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for nonane 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	200	1050	8 h	administrative		SZW05
Germany						
- AGS	-	-				TRG04
- DFG MAK-Kommission	-	-				DFG05
Great-Britain						
- HSE	-	-				HSE02
Sweden	150	800	8 h		[c]	Swe00
	200	1100	15 min			
Denmark	200	1050	8 h	OEL		Arb02
USA						
- ACGIH	200	-	8 h	TLV	[c]	ACG05
- OSHA	-	-				ACG04
- NIOSH	200	1050	10 h	REL		ACG04
European Union						
- SCOEL	-	-				EC05

[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.

[c] For all nonane isomers.