Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for dimethyl sulphate

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European Commission

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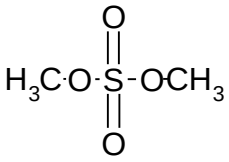
8 hour TWA	: not applicable
STEL (15 min)	: not applicable
Notation	: "skin"

Substance:

Dimethyl sulphate



Synonyms : DMS, methyl sulphate, sulphuric acid dimethyl ester, dimethyl monosulphate

EINECS No : 201-058-1

EEC No: 016-023-00-4

EU-Classification : Carcinogenicity Cat. 2; R45, May cause cancer
Mutagenicity Cat. 3, R68, Possible risk of irreversible effects
T+, R26, Very toxic by inhaltion
T, R25, Toxic if swallowed
C, R34, Causes burns, R43 May cause sensitisation by skin contact

CAS No : 77-78-1

MWt : 126.13 g/mol

Conversion factor (20°C, 101 kPa): 5.242 mg/m^3 = 1 ppm

This document is based on the EU-RAR from 2002, the MAK documentation from 1971 and 1985 (DFG, 1971, 1985) and the EHC report 48 from 1985 and the references listed therein. This was supplemented by a literature survey by SCOEL.

Physico-chemical properties

Dimethyl sulphate is a colour- and odourless oily liquid with a melting point of about -32°C and a boiling point of 188 °C. It is not flammable and not explosive, the flash point is 83°C and the vapour pressure is low with 65 Pa at 20°C.

1. Occurrence/Use

The production of dimethyl sulphate at tonnages of >1 000 t per year is located at three sites in the European Union. The total EU production volume for 1994 was estimated to be between 20 000 and 30 000 t per year. An amount of 5 000-10 000 t per year is exported (outside the EU) and a small quantity of <1 000 t per year is imported. About 20 000 t per year is used industrially within the EU. The production and transferral of DMS takes place in a closed continuous system. Liquid SO_3 is added to gaseous dimethyl ether in a reaction vessel, containing about 97% DMS, sulphuric acid and monomethyl sulphate, which are continuously withdrawn and purified by vacuum distillation over sodium sulphate. The reaction system has an underpressure to avoid leakages of DMS. DMS is mainly used as a chemical intermediate. Its major applications are as a methylating agent of many organic chemicals (e.g. amines, carbon acids, thiols and phenols) both in industry and in laboratories. DMS is used, for example, in the manufacturing of dyes, perfumes, pharmaceuticals, for the separation of mineral oils and for the analysis of automobile fluids (HSE 1996, Kirk & Othmer 1985, NIOSH 1979). The substance also has sulphating properties, with applications in the manufacturing of various products (e.g. dyes and fabric softeners etc).

2. Health significance

2.1 Toxicokinetics

2.2.1 Human data

No toxicokinetic data for humans are available.

Skin absorption

Dermal exposure is considered to occur accidentally. In general, inhalation and dermal contact are the most obvious routes of exposure for humans. Very recent biomonitoring data support the practical importance of skin absorption (Schettgen *et al.* 2004). Ocular exposure is possible due to hand-eye contact. It is reported, that DMS is slowly hydrolysed to methanol and sulphuric acid in the tissues after dermal exposure; however no quantitative data are provided (Kühn/Birett 1994). DMS may be absorbed via the dermal route (EHC report 48, 1985). No further details are given. According to EHC, there are several reports in the literature of toxic effects resulting from skin contamination through spills, although in such cases inhalation of fumes might be a contributory factor (Weber 1902, Balazs 1934 and Littler and McConell 1955).

2.2.2. Animal data

DMS can be absorbed via respiratory and oral routes. Data on dermal absorption are limited and insufficient to draw conclusions. For oral absorption this is concluded from toxicodynamic data. Rapid respiratory absorption is observed in rats exposed to dose levels up to 50.3 mg/m^3 (Mathison *et al.* 1995, 1997). At higher dose levels uptake was decreased, probably due to a decreased minute volume.

Only limited information is available on the metabolism of DMS. DMS may be hydrolysed to methanol, sulphuric acid and methyl sulphate, and, to a lesser extent, to formaldehyde and formate (see Mathison *et al.* 1995, Bogdanffy *et al.* 1997).

Methylating properties

DMS is a strong methylating agent which reacts with tissue nucleophilic groups, e.g. in nucleic acids. As shown in *in vitro* and *in vivo* experiments, the methylating capacities of DMS concentrate mainly on the N^7-guanine and, to a lesser degree, the N^3-adenine sites in the nucleic acids (Swann and Magee 1968, Löfroth *et al.* 1974, Newbold *et al.* 1980, Fox and Brennand, 1980, Shiner *et al.* 1988, Mathison *et al.* 1995). After 20 minutes' exposure (0, 5.3, 15.7, 42, 115 mg/m^3 [0, 1, 3, 8, 22 ppm] in an inhalation experiment with CD-rats (6 animals per group), methylation was found in the respiratory and olfactory mucosa and to a much lesser degree in the lung (Mathison *et al.* 1995).

Quantitative DNA adduct data have been provided by Mathison *et al.* (1995). The half-life of the main DNA adduct, N^7-methylguanine, in the nasal mucosa of the rat was 40-44 h. The N-methyl-purines formed by DMS, and especially the apurinic sites generated following depurination, were viewed as significant contributors to the promotion of heritable changes in DNA. There is parallelism to the DNA adducts of ethylene oxide, where 7-hydroxyethyl-guanine is by far the major primary lesion of DNA. From the data of Mathison *et al.* (1995) and Bogdanffy *et al.* (1997) it may be anticipated that exposures of rats to 1 ppm DMS, 8h/day, would lead to a DNA adduct level in the nasal mucosa in the order of 500-1 000 µmol N^7-methylguanine per mol guanine in DNA. The physiological background level of 7-hydroxyethyl-guanine in the DNA of various rat organs was about 0.3 pmol/µmol [µmol/mol] guanine (Thier and Bolt 2000). A similar low level of N^7-methyl-guanine in DNA would be the result of a daily (8h) exposure of only 0.5 ppb DMS.

2.2 Acute toxicity

2.2.1. Human data

Several case reports on inhalatory and dermal exposure to DMS were found. In all case reports the latency period between exposure and adverse effects ranged from several hours up to one or two days.

After inhalatory exposure to DMS, symptoms of intoxication were irritation of the upper-respiratory tract and fever, irritation of the conjunctivae, glottis oedema and oedema of the lung and brain, and corrosion of the respiratory tract (revealed after autopsy) (Rossmann and Grill 1952). Short-lasting inhalatory exposure to DMS was found to induce irritation of the nose and the eyes, sometimes followed by respiratory problems. All these effects were temporary (Thiess and Goldmann 1968).

2.2.2. Animal data

DMS has to be classified as toxic after oral treatment, with LD_{50} values between 106 mg/kg bw and 440 mg/kg bw in rats (BASF 1968, Kennedy and Graepel 1991, Chemie Bitterfeld-Wolfen 1995, Hoechst 1989, 1996). Reported clinical signs were dyspnoea, convulsions and apathy. In inhalation studies the compound is found to be very toxic. LC_{50} values for rats were determined as 335 mg/m^3, 1 hour (Hein 1969) and 45 mg/m^3, 4 hours (Hoechst 1989, 1996, Batsura *et al.* 1980). Clinical signs were dyspnoea, cyanosis of the mucosa, hyperaemia of the lung, haemorrhage and nasal discharge.

2.3. Irritation and corrosivity

2.3.1. Human data

Several cases of dermal exposure to DMS were reported (Thiess and Goldmann 1968), leading to erythema and oedema of the exposed areas, both lasting for about two weeks.

2.3.2. Animal data

When applied to rabbit skin, DMS caused severe necrosis and oedema and very strong erythema (BASF 1968). Dimethyl sulphate is considered to be corrosive. Very strong oedema, intense redness and corneal opacity were reported after application to the eyes of rabbits (BASF 1968, Guillot *et al.* 1982).

DMS should be considered as an eye irritant with a risk of serious damage to the eyes. It is considered irritating to the respiratory tract in rats at concentrations of 3.7 and 6.3 mg/m^3, based on a repeated-dose study, reported as an abstract by Frame *et al.* (1993).

2.4. Sensitisation

A positive result was obtained with DMS in a murine local lymph node assay (Ashby *et al.* 1995). Although the positive response with DMS may be due to the corrosive properties, in the EU RAR it is concluded that dimethyl sulphate is a potential sensitiser.

2.5. Repeated-dose toxicity

No oral or dermal repeated-dose studies with DMS were reported.

Inhalation

In a two-week inhalation study in rats (Frame *et al.* 1993), DMS was found to induce nasal epithelial cell proliferation at all concentrations tested (0.5, 3.7 and 6.3 mg/m^3, 6hr/day, 5 d/wk), as shown by a 2.0-3.7-fold increase in 2-bromo-5'deoxyuridine (BrdU) incorporation in the olfactory epithelium. In the respiratory epithelium BrdU incorporation was statistically increased in the 6.3 mg/m^3 dose group only. At an exposure concentration ≥ 3.7 mg/m^3 lesions of the nasal and respiratory epithelium were found, including erosion, ulceration and atrophy, which increased in severity with exposure concentration and decreased in severity from anterior to posterior regions. Hypertrophy, hyperplasia and squamous metaplasia were observed in the respiratory epithelium.

Inflammation of the nasal cavity was also seen in rats that were exposed to DMS (15 and 50 mg/m^3 [3 and 10 ppm], 1 hr/d, 5 d/wk for 130 days) in a study by Druckrey *et al.* (1970).

It is reported that repeated inhalative exposure of rats and guinea-pigs for 4 months to 2.64±0.43 mg/m^3 induced changes in nervous system function, liver (fatty degeneration of single hepatocytes), kidney (degeneration of single renal tubuli), respiratory organs (bronchitis) and peripheral blood parameters. All changes except for bronchitis were reversible after a recovery period. A 4-month-exposure to 0.29±0.02 mg/m^3 induced only marginal changes without toxicological relevance (increased body weight, decreased hippuric acid elimination). No morphological changes could be found. In both concentration groups no effects on reproductive organs, spermatogenesis and sperm morphology were detected (Molodkina *et al.* 1986). No data on the number of animals per group, exposure duration per day and parameters studied, and no quantitative data

on the results, are given for this study. According to the EU RAR, due to limited documentation and insufficient study design respectively, no scientifically based NOAEL is derivable for repeated-dose toxicity.

2.6. Mutagenicity

2.6.1. In vitro

Dimethyl sulphate is a potent direct-acting genotoxicant. Results described below have been obtained without metabolic activation (see also IARC 1999).

Bacterial tests

Dimethyl sulphate was found to induce reverse mutations in *Salmonella typhimurium* strains TA 98, 100, 1535, 1537, 1538 (EU-RAR) and also forward mutations in *S. typhimurium* TM35, TM677 and TA1535/pSK1002 and *E.coli* PQ37 (EU-RAR). One host-mediated assay with *S. typhimurium* TA 1950 in NMRI mice was positive (Braun *et al.* 1977). Several fungal assays showed the genotoxic activity of dimethyl sulphate (EU-RAR).

Mammalian tests

DMS induced an increase in cells with chromosomal aberrations in V79-cells (Connell *et al.* 1982). An induction of HPRT gene mutations was found in CHO- and V79-cells (Couch *et al.* 1978). Moreover, DMS induced an increase in SCEs (Connell and Medcalf 1982, Wolff *et al.* 1977) and UDS (Cleaver 1977, Probst *et al.* 1981) in mammalian cells in vitro and showed DNA single-strand and double-strand breaks in an alkaline elution assay with primary rat hepatocytes (Bradley *et al.* 1987). DMS is a directly acting mutagen which methylates DNA especially at the N^7-guanine and the N^3-adenine sites (Newbold *et al.* 1980, Fox and Brennand 1980, Shiner *et al.* 1988).

2.6.2. In vivo - Human data

Increased chromosome and chromatid aberrations in lymphocytes have been reported in workers exposed to DMS at concentrations ranging from 0.2 to 20 mg/m3 (Sanotsky *et al.* 1982, Katsova and Pavlenko 1984).

2.6.3. In vivo- Animal data

Assays in *Drosophila melanogaster* were positive primarily after injection, i.e. in tests for somatic gene-mutations and recombination, for sex-linked recessive lethals and for sex chromosome loss (Alderson 1964, Vogel and Natarajan 1979a,b, Vogel and Nivard 1993).

One dominant lethal assay (23 mg/kg bw i.p) was negative, as appeared from the pregnancy rate, number of total implants and early and late deaths. However, only one dose-group of 5 animals was tested (Epstein and Shafner 1968). The study design was limited. No increase in dominant lethal mutations in germ cells of rats were observed after repeated inhalative exposure for 4 months to DMS (≥ 0.29 mg/m^3, Molodkina *et al.* 1986). The study reporting was very limited.

In the mouse spot test (performed according to OECD 484) DMS (25 or 50 mg/kg bw i.p.) was administered to pregnant mice. The number of somatic coat colour patches was not increased compared to controls (Braun *et al.* 1984).

A brief paper reported DMS positive in a cytogenetic assay in rat bone marrow cells, but the results are not suitable for evaluation due to the poor reporting (Sharma *et al.* 1980).

In a further study with very limited reporting of study design and results, a dose-dependent increase in chromosomal aberrations in bone-marrow cells was observed after exposure to dimethyl sulphate probably for 4 months in mice (≥ 0.24 mg/m^3) and rats (≥ 0.29 mg/m^3) (Molodkina *et al.* 1986).

The number of DNA breaks increased significantly after alkaline elution of brain DNA of rats treated with 0.25 mmol/kg i.v. DMS (Robbiano and Brambilla 1987). The methylating capacity of DMS is demonstrated in several tissues *in vivo* in Wistar rats (Swann and Magee 1968).

2.7. Carcinogenicity

2.7.1. Human data

Druckrey *et al.* (1966) reported the case of a 47-year-old male who died from bronchial cancer after 11 years of occupational exposure to DMS. He suffered from acute poisoning incidents several times (DFG 1971). Three out of ten co-workers also died from bronchial cancer. Lung cancer was reported in a chemist exposed by inhalation to DMS for over 7 years; however, in this case, there was concomitant exposure to other alkylating agents (notably dichlorodimethyl ether) that were present at higher concentrations (Bettendorf 1977). A case of choroidal melanoma has been reported in a man exposed to DMS for 6 years (Albert and Puliafito 1977). Pell (1972) studied a group of 145 workers who had been exposed to DMS for various periods between 1932 and1972. No significant excess in the total number of deaths in the exposed population was reported and, in particular, no significant increase in deaths from lung cancer was noted (according to EHC 1985).

Inhalation

In one inhalational carcinogenicity study with BD-rats (sex unspecified) for 130 days (55 mg/m^3 [10 ppm] and 17 mg/m^3 [3 ppm], 1 hr/d, 5 d/wk) 5/15 rats developed malignant tumours (nasal cavity, cerebellum, thorax) at 55 mg/m^3. At 17 mg/m^3 3/12 showed carcinomas (nasal cavity). Benign tumours were found in the cerebellum and the olfactory nerve. Several deaths due to inflammation of the nasal cavity or pneumonia were reported (Druckrey 1970). This early study was of limited design, according to modern standards.

After inhalative administration of DMS to male and female mice (CBAxC57BC/GI) for 6 months, a statistically significant increase in tumours (mainly lung adenoma) was observed at concentrations of ≥ 1.62 mg/m^3 [3 ppm] (2 hrs/d, 5 d/wk) (Molodkina *et al.* 1986). Study design and reporting was very limited.

Key data are reported in a doctoral thesis (Schlögel 1972; abstract: Schlögel and Bannasch 1970). Male and female rats (Wistar), mice (NMRI) and hamsters (Syrian Golden) were exposed to 2.6 mg/m^3 [0.5 ppm] DMS (6 hr/d, 2d/wk), to 10.5 mg/m^3 [2 ppm] (6hr/d, 1d/2wk) or to a sublethal concentration (4 times per year for 1 hour, 178 mg/m^3 (rats), 252 mg/m^3 (mice), 105 mg/m^3 (hamsters)) for about 15 months (Schlögel 1972; see Table 1). The animals were observed for at least 30 months after the start of exposure. Histopathological examination was restricted to lungs and trachea. When gross examination revealed a tumour in other tissues/organs, this tissue/organ was included for histopathological examination.

In general, survival in groups exposed to DMS was lower than in controls. The survival time in male and female rats of the 2.6 mg/m^3 [0.5 ppm] group was distinctly lower than the survival time in rats of the control or the 10.5 mg/m^3 [2 ppm] group, which is probably due to the initial high exposure regimen applied to this exposure group. The same phenomenon was seen in mice, although less pronounced. Body weight gain in DMS-exposed hamsters, rats and mice was distinctly lower than in control animals. After exposure, the behaviour of exposed animals was affected: animals were apathetic, eyes were half-open or closed and breathing problems were apparent. These effects clearly showed a concentration dependency in severity, total duration and time of onset. An increase in the incidence of inflammation of the lungs was reported in DMS-exposed animals in all species.

DMS exposure resulted in an increased incidence of malignant tumours in the respiratory tract (nose and lungs) of rats and mice (see Table 1). Rats were most sensitive to the tumour-inducing activity of DMS, while hamsters were the least sensitive (only one tumour at 10.5 mg/m^3 [2 ppm] DMS). In all three animal species females appeared more sensitive than males. In female rats of the 10.5 mg/m^3 group, the incidence of lung adenomas was slightly higher than in control females. There were no indications that DMS exposure induced an increase in subcutaneous fibromas. The study was not designed to fulfil the requirements of OECD 451 being established later. However, the results indicate the high carcinogenic potential of DMS.

Other routes

In a mouse skin papilloma test 0.1 mg DMS in 0.1 ml acetone was applied 3 times per week for a period of 385 or 475 days to ICR/Ha Swiss mice (n=20). No increased incidence of papillomas or carcinomas was observed, even when DMS was combined with the tumour promotor phorbol myristate acetate (van Duuren *et al.* 1974).

The carcinogenicity of DMS was demonstrated also in several other older studies, with intravenous or subcutaneous application to rats. Single or multiple subcutaneous injections of DMS in rats resulted in the induction of local sarcomas at the injection site with ensuing metastasis to the lung (Druckrey 1966, 1970).

IARC (1999) concluded that DMS produces mainly local tumours in rats following inhalation or subcutaneous injection and that there is sufficient evidence to classify DMS as "probably carcinogenic to humans" (2A).

2.8. Reproductive toxicity

Fertility

There are no data on either fertility or effects on male and female reproductive organs after repeated exposure to DMS.

In one repeated-dose inhalation study with very limited reporting of study design and results, rats and guinea-pigs were exposed for 4 months to 0.29±0.02 and 2.64±0.43 mg/m^3 dimethyl sulphate. No effects on reproductive organs, spermatogenesis and sperm morphology were detected (Molodkina *et al.* 1986).

Developmental toxicity

In a teratogenicity study, pregnant rats (25 per dose group) were exposed nose only to 0.5, 3.7 or 7.9 mg/m^3 DMS, 6 hours per day during days 6-15 of gestation (Alvarez *et al.* 1997). In pregnant rats exposed to 3.7 and 7.9 mg/m^3 a decrease in food consumption and weight gain was reported. The NOAEL for maternal toxicity was 0.5 mg/m^3. No significant differences in malformations and variations were reported between the foetuses in the control and the experimental groups. At the highest concentration tested, a very slight decrease of foetal weights is reported. It was concluded that a NOAEL of 7.9 mg/m^3 for developmental effects can be derived.

Biological monitoring

In a chemical plant in Germany, exposures to DMS of workers were assessed using biological monitoring by quantitation of N-methylvaline in haemoglobin. In total, 62 workers (38 smokers, 24 non-smokers) with potential exposure to DMS were monitored. Ten laboratory workers, without exposure to methylating agents, were controls. Blood samples of eight workers from one specific working area were analysed for N-methylvaline in a follow-up investigation, four months later. The 95th percentile for N-methylvaline was 80.7 μg/l blood in the exposed workers compared to 12.4 μg/l blood in controls. In a hot-spot area, 10 workers exceeded the current German exposure equivalent value for DMS (40 μg/l blood) up to fourfold. In contrast, dimethyl sulphate had not been detectable in workplace air in this area. In a follow-up investigation of eight of these ten workers, N-methylvaline levels were significantly lower, but were still increased in relation to non-exposed controls. The present study clearly confirmed increased N-methylvaline levels in haemoglobin to occur after occupational exposure to DMS. As ambient monitoring values in the plant could not explain this internal exposure, it was concluded that skin contact was the major route of uptake for DMS under industrial exposure conditions (Schettgen *et al.* 2004).

Risk assessment and recommendations

Dimethyl sulphate (DMS) is a locally active carcinogen, as experimentally proven after both inhalation and subcutaneous administration. It is directly genotoxic and methylates DNA at various positions, preferably at N^7 of guanine. Alkylation at the O^6 position of guanine, in contrast to other DNA methylating agents, is minimal. The available cancer bioassays, dating back to the '60s and early '70s, do not meet modern standards (small group sizes; poor survival due, in part, to overt toxicity; inadequate reporting of control data). However, these bioassays unequivocally prove the strong carcinogenicity of DMS and illustrate a number of factors that need to be reconciled when discussing the potential risk to humans.

Upon inhalation, the target of DMS is the respiratory tract. There is an apparent species specificity of the carcinogenic response. Although rats show a marked increase in nasal tumours (6/27) after 15 months of exposure to 6 ppm (1 h/day) of DMS, only 1/22 hamsters developed a tumour (of the lung) under these conditions. There are clear differences in target organs between species; mice appear less responsive to DMS-induced nasal tumours, but more responsive to the induction of lung tumours (Schlögel 1972). The target organ specificity is strongly influenced by local dosimetry (Mathison et *al.* 1995). In rats, it was demonstrated that concentrations at/above 22 ppm DMS induced a reflex depression in minute volume; this was not observed at 8 ppm. Within the range up to 8 ppm, a linearity of N^7-methylguanine adduct formation in DNA with the absorbed dose of DMS was observed in the respiratory mucosa and (quantitatively much less) in the lung,

but not in the olfactory mucosa where a hockey-stick type of dose-adduct response was seen.

Because of the nature of the present bioassay data and the uncertainties mentioned above, a solid extrapolation of experimentally observed tumour risks to lower dose ranges does not appear feasible. However, it must be underlined that malignant tumours of the respiratory system were induced in rats and mice by inhalation of 0.5 ppm DMS (6 h inhalations, 2 times/week), at a tumour rate of about 5%. Technically based exposure values should consider this considerable carcinogenic potency, also in view of existing allowable exposure levels in different countries (v.s.).

As a consequence, occupational exposures to DMS should strictly be minimised, taking every possible technical precaution.

Under industrial exposure conditions, the most relevant pathway of DMS uptake appears to be via the skin. Hence, biological monitoring appears to be a powerful tool for exposure control, and the magnitude of N-methylation of the N-terminal amino acid, valine, in haemoglobin has been addressed as a relevant parameter for this purpose. Background levels of this adduct, in the absence of occupational exposure, are about 10 □g N-methylvaline adduct per liter blood, equivalent to 525 pmol N-methylvaline per g globin (Thier *et al.* 2001, Schettgen *et al.* 2004). Doubling of this background level (to 20 □g N-methylvaline adduct per litre blood, equivalent to 525 pmol N-methylvaline per g globin) is clearly indicative of industrial exposure to DMS. Because of the relative persistence of haemoglobin alkylations, there are no restrictions with regard to a specific sampling time for adduct measurements.

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Table 1:
Carcinogenicity study with dimethyl sulphate; summary of tumour incidence in animals exposed to DMS for 15 months and held for up to 30 months [a]

	Controls	0.5 ppm 6 h per day, 2 days per week	2.0 ppm 6 h per day, 1 day per 2 weeks	Sublethal 1 h per day, 3 months
ppm-h/week:		6ppm-h	6ppm-h	~4, ~3, ~2 ppm-h[b]
Nasal carcinoma				
Mice	0/19	0/32	0/25	0/17
Rats	0/36	2/37	6/27	1/29
Hamsters	0/15	0/28	0/22	0/51
Lung carcinoma				
Mice	0/19	1/32	3/25	0/17
Rats	0/36	1/37	0/27	1/29
Hamsters	0/15	0/28	1/22	0/51
Total malignant respiratory tract tumours	0/70	4/97	10/74	2/97

[a] Data from Schlögel (1972); compilation by Bogdanffy *et al.* (1997), modified
[b] Exposure concentrations were: mice, 48 ppm; rats, 34 ppm; hamsters, 20 ppm