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NIOH and NIOSH Basis for an Occupational Health Standard

2-Ethyl-2-hydroxymethyl-1,3-propanediol

by

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PREFACE

A memorandum of understanding has been signed by two government agencies in the United States and Sweden—the Division of Standards Development and Technology Transfer, National Institute for Occupational Safety and Health (DSDTT/NIOSH), U.S. Department of Health and Human Services; and the Criteria Group of Occupational Standards Setting, Swedish National Institute of Occupational Health (NIOH). The purpose of the memorandum is to exchange information and expertise in the area of occupational safety and health. One product of this agreement is the development of documents to provide the scientific basis for establishing occupational exposure limits. These limits will be developed separately by the two countries according to their different national policies.

This document on the health effects of occupational exposure to 2-ethyl-2-hydroxymethyl-1,3-propanediol (trimethylolpropane) is the sixth product of that agreement. The document was written by Dr. Robert Wålinder, Department of Occupational Medicine, University Hospital, Uppsala, Sweden, and was reviewed by the Criteria Group and by DSDTT/NIOSH.

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CONTENTS

ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
BIBRA	British Industrial Biological Research Association
b.wt.	body weight
CNS	central nervous system
CAS RN	Chemical Abstracts Service Registry Number, of the American Chemical Society
EPA	Environmental Protection Agency (USA)
GLP	good laboratory practice
HPV	high production volume (OECD program)
LC_{50}	lethal concentration for 50% of the animals
LD_{50}	lethal dose for 50% of the animals
LOEL	lowest observed effect level
NIOH	National Institute of Occupational Health (Sweden)
NIOSH	National Institute for Occupational Safety and Health (USA)
NOEL	no observed effect level
OECD	Organization for Economic Cooperation and Development
RTECS	Registry of Toxic Effects of Chemical Substances
SAP	serum alkaline phosphatase
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIDS	screening information data set (of OECD)
TLV	threshold limit value
TMP	trimethylolpropane
TWA	time-weighted average
w/v	weight/volume (g of substance in 100 ml solution)
w/w	weight/weight (g of substance in 100 g solution)

1 INTRODUCTION

2-Ethyl-2-hydroxymethyl-1,3-propanediol is a polyalcohol with three functional hydroxymethyl groups. The substance has several different chemical names and the most common synonym found in the literature is trimethylolpropane. This name is used in the present document.

At room temperature trimethylolpropane is a solid substance consisting of white crystal flakes with mild aromatic odor. The substance is listed by the Organization for Economic Cooperation and Development (OECD) Program of High Volume Products and its main use is as a solvent and intermediate in the production of resin and synthetic lubricating oil (14, 10).

Trimethylolpropane can affect humans by inhalation, via an oral route, or by contact exposure to skin and mucous membranes, either as solid powder, in liquid solution, or in vaporized form.

A literature search has been performed in medical and toxicological databases (Medline, Toxline, Riskline, Cancerlit, Chemical Abstracts, Healthline, NIOSHTIC, CISILO), resulting in 10 of the references listed in the present document.

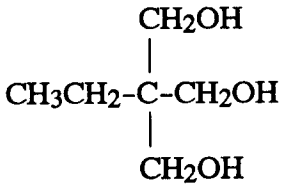
The British Industrial Biological Research Association (BIBRA) conducted a Toxicity Profile on 1,1,1-trimethylolpropane in 1986 (3) and an OECD document was presented in 1993 (14). Most of the original data on the toxicity of trimethylolpropane in these documents are from unpublished reports. The citations in these reviews are sometimes short, and therefore complementary data from the original unpublished sources are included in the present document to give a more detailed description of test conditions.

Of the 18 references listed in the present survey on trimethylolpropane, five contain information about toxic effects of this substance in mammals. Only one describes toxicological data on humans.

2 PHYSICAL AND CHEMICAL PROPERTIES

Information about physical and chemical properties was obtained from references 5, 10, 13, and 14. There is some confusion in the literature about the chemical structure of trimethylolpropane. The CAS Registry Number 77-99-6 has falsely been used for another substance, namely o,o,o-trimethyl-S-ethyl-phosphorothionate, in three of the references of the literature search.

Chemical name:	2-Ethyl-2-hydroxymethyl-1,3-propanediol
CAS Registry Number:	77-99-6
Synonyms:	2,2 dihydroxymethylbutan-1-ol, Ethriol, ethyltrimethylolmethane, hexaglycerine hexaglycerol, TMP, 1,1,1-tri(hydroxymethyl) propane, 1,1,1-trimethylolpropane
Molecular formula:	$C_6H_{14}O_3$

Structural formula:	
Molecular weight:	134.18
Physical state at room temperature:	White crystal flakes
Melting point/Freezing point:	58-61°C
Boiling point:	292°C at 101.3 kPa
Vapor pressure:	0.02 Pa at 25°C 1 Pa at 50°C 67 Pa at 160°C 6.7 kPa at 210°C
Flash point (liquid):	172°C
Ignition temperature:	375°C
Bulk density:	0.590 g/cm^3
Solubility in water:	Soluble. More than 100 g/l at room temperature.
Solubility in organic solvents:	Freely soluble in glycerol, ethanol, and other lower alcohols. Forty grams of TMP soluble in 100 ml of acetone; 8 g in 100 ml of ethyl acetate and 0.02 g in 100 g of benzene. It is slightly soluble in carbon tetrachloride and chloroform. It is insoluble in aliphatic, aromatic, and chlorinated hydrocarbons.
Partition coefficient: (n-octanol/water):	log Pow=-0.47 (GC-analysis [14]) log Pow=-2.4 (calculated [14]) log Pow=-2.29 (calculated [12])
pH in water:	5.2 at a concentration of 250 g/l.

Trimethylolpropane is a white, crystalline substance that is mildly aromatic. In crystalline form, trimethylolpropane shows no decomposition at room temperature, but the substance has a strong hygroscopic property. Trimethylolpropane is totally soluble in water and has a half-life in solution of more than one year at pH 4.7 and 9.0, at 25°C (14).

The industrial product contains no additives. Major impurities are trimethylolpropane-monomethylether and trimethylol-methylformal. According to one source the purity of trimethylolpropane as an industrial product is more than 99% (wt) (14).

In solid form trimethylolpropane is inflammable but a mixture of dust and air is explosive at concentrations of 2 % to 11.8 % by volume. At high temperature the substance vaporizes and forms a vapor/air mixture that is heavier than air and explosive in contact with hot surfaces, sparks, or flames.

3 USES AND OCCURRENCE

3.1 Production and Uses

Esters of neopentyl polyols, e.g. trimethylolpropane, have been manufactured since 1940 by the IG Farbenindustrie (11). Trimethylolpropane contains only primary hydroxyl groups, no hydrogen in beta position and no tertiary hydrogen atoms, but a considerable degree of branching, and is therefore (together with other neopentyl polyols) used in the production of synthetic lubricant oils. Since 1960 these ester oils have gained special importance as high-temperature resistant lubricants for jet turbine engines. Because of the thermal properties these polyol esters are used today also as hydraulic fluids, rolling oil additives, heat exchange fluids, explosives, lubricating greases, and additives for silicones and silicate esters.

A variety of chemicals may be added to these ester oils. Phosphorous additives are included as antiwear substances and metal deactivators. When used as synthetic aircraft engine lubricant it has been shown that thermal decomposition of trimethylolpropane-based oil forms a pyrolysate called trimethylolpropanephosphite (8, 18), also named 4-ethyl-1-phospa-2,6,7-trioxobicyclo(2,2,2)octane (4). This substance belongs to a class of highly neurotoxic compounds, commonly referred to as bicyclophosphorous esters (18).

Trimethylolpropane is also used in the production of polyurethanes and polyester resins. The first report on the formation of trimethylolpropane-phosphite came in 1975. It was a combustion product after pyrolysis of a trimethylolpropane-based polyurethane foam, that had been treated with a phosphorous fire retardant (15). After these reports, the production of trimethylolpropane-based urethanes has declined (10).

Trimethylolpropane is used in the production of both alkyd coatings and acrylates. Trimethylolpropane-based acrylates and metacrylates are used in photocurable coatings, paints, varnishes and dental sealants. Multifunctional acrylates have a considerable chemical reactivity and are used in many applications with opportunities for contact exposure. They represent appreciable eye and skin contact hazards, and a number of multifunctional acrylates, such as trimethylolpropane triacrylate and trimethylolpropane trimetacrylate, have been identified as sensitizers (2, 7).

Trimethylolpropane can be formed by the reaction of n-butyraldehyde and formaldehyde together with sodium hydroxide in a condensation reaction. The intermediate 2,2-dimethylol-butyraldehyde formed by the aldol reaction is reduced with another molecule of formaldehyde

in a Cannizzaro reaction to give trimethylolpropane. Continuous closed systems are used and the final product is also extracted and purified during the processes (10, 14).

No published data on world production rates of trimethylolpropane have been found. An estimation of the world production, and the Swedish production, was given by U. Rich (personal communication) at the Swedish Products Register at the National Chemical Inspectorate. His estimation of the world production level was approximately 100,000 metric tons per year, and there is one producer in Sweden, Perstorp AB, with a production of 20,000 metric tons per year.

According to the Japanese OECD report (14) the production level in Japan in 1991 was about 10,000 tons (not specified if it is metric tons) per year. In 1991 about 2,000 tons of trimethylolpropane were imported to Japan. The major part was used for paint resin (7,500 tons), urethane resin (1,500 tons), setting resin by UV-ray (1,400 tons), synthetic lubricant oil (800 tons), and others (1,200 tons). Hoechst-Celanese Chemical Company is the only United States producer of trimethylolpropane with a plant at Bishop, Texas (10).

3.2 Occupational Exposure and Analytical Methods for Air Monitoring

No data were available on the present occupational exposure levels or techniques for sampling and analysis of trimethylolpropane in ambient air.

3.3 Present Occupational Standards

A Soviet study on the toxicology of trimethylolpropane (16) recommended a maximum permissible concentration of 50 mg/m^3 in factory air. This recommendation was based on studies on rats, where a subchronic inhalation experiment (3.5 months) shows an "arbitrary threshold concentration" of 0.13 mg/l (130 mg/m^3). What this expression stands for is unclear. The maximum permissible concentration of 50 mg/m^3 in factory air was accepted by the Commission of the Ministry of Health of the USSR (9).

Neither an ACGIH TLV nor a German MAK value has been established. At present there are no standards or recommendations for occupational exposure to trimethylolpropane in Sweden. The present occupational standard for the respirable fraction of dust and organic dust in Sweden is 5 mg/m^3 (17). According to ACGIH a TLV, 8-hour TWA of 10 mg/m^3 for particulates not otherwise classified has been established. The same value was adopted for nuisance particulates. A TLV, 8-hour TWA of 5 mg/m^3 for respirable dust has also been established (1).

4 TOXICOKINETICS

There are no data on human uptake, distribution, biotransformation, or elimination of trimethylolpropane. In experimental animals no quantitative data were found on toxicokinetics.

4.1 Uptake

In animals trimethylolpropane is absorbed via dermal, oral, and respiratory routes of exposure. Systemic effects after dermal absorption have been observed. In an unpublished report, cited in BIBRA (3), trimethylolpropane was applied to closely clipped intact abdominal rabbit skin. After 24 hours there was residual substance at all dosage levels (2.15, 4.64, and 10.0 g/kg of b.wt.), except at the lowest (1.00 g/kg of b.wt.). Although no analysis was made on the amount of residual substance on the skin, the nonresidual part was assumed to have been absorbed by the skin. No systemic effects apart from kidney changes were observed.

No systemic effects were seen in mice after immersion of their tails in 50% solution (w/w or w/v not specified) of trimethylolpropane for 4 hours according to a Soviet study (16). In the same paper a test is described where 0.5 ml of 50% solution (the dose/kg • day was not specified) of trimethylolpropane was applied daily to the skin of rabbits for 3 months. No gross change in the general condition of the animals was observed. Histopathological data were not given.

An unpublished report from the German manufacturer, AG Bayer, cited by two reviews (3, 14), indicated there were no signs of intoxication due to dermal resorption after a single dose of trimethylolpropane (0.5 g/kg b.wt.) was applied to the shaved nonabraded skin of rats. These dermal tests are further described in section 5.1.

In none of these dermal studies has the quantity of absorbed substance been estimated. Resorption through the skin has only been assumed or observed indirectly via clinical signs or morphological changes of internal organs.

4.2 Distribution, Biotransformation, and Elimination

No data are available.

5 GENERAL TOXICITY

No data on the general toxicity in humans have been found. In the literature available on trimethylolpropane, only toxic mechanisms causing a narcotic effect have been discussed (12).

5.1 Acute Toxicity

In laboratory animals the acute toxicity of trimethylolpropane is extremely low after oral administration, inhalation, and dermal exposure. The LC/LD_{50}-values found in the literature on trimethylolpropane are listed in Table 1.

Test conditions of the different studies are described in Section 6, except for the following:

The first is an unpublished study cited in reference 14. Five male and five female Wistar rats received a single oral dose of 5 g/kg b.wt. of trimethylolpropane. The animals were observed for 14 days and no changes of body weights or clinical signs of toxicity were observed.

Table 1. LD_{50}/LC_{50} values in acute toxicity tests

Route of administration	Species	LD_{50}/LC_{50}*	Reference
Oral	Rat	>2.5 g/kg	Unpublished study cited in references 3 and 14
Oral	Rat	>5 g/kg	Unpublished study cited in reference 14
Oral	Rat	14.1 g/kg	Reference 16
Oral	Rat	14.7 g/kg	Unpublished study cited in reference 3
Oral	Mouse	13.7 g/kg	Reference 16
Dermal	Rat	>0.5 g/kg	Unpublished study cited in references 3 and 14
Dermal	Rabbit	>10 g/kg	Unpublished study cited in reference 3
Inhalation	Rat, mouse, rabbit, guinea pig	>290 mg/m^3 • 4h	Unpublished study cited in references 3 and 14
Inhalation	Rat	>700-2,000 mg/m^3 • 4h	Reference 16

*The LC_{50} values are for inhalation studies and the LD_{50} values are for the other routes of administration.

The second study is unpublished and cited in reference 3 and 14. Twenty rats, 20 mice, 3 rabbits, and 5 guinea pigs were acutely exposed to an average ambient concentration of 0.29 mg trimethylolpropane/liter of air (290 mg/m^3) for 4 hours. No clinical signs of intoxication were observed during exposure or the 14-day observation period.

Clinical signs of acute intoxication are mainly of narcotic (i.e., depressed respiration rate and reduced reflexes of pain and placement) (reference 16 and unpublished study cited in reference 3) or respiratory type (i.e. respiratory distress) (16).

Postmortem histological examination of animals that died after they were given lethal single oral doses (up to 21.5 g/kg b.wt.) of trimethylolpropane showed hyperaemic lungs, irritation of the stomach, small intestine, and peritoneum (reference 16 and an unpublished study cited in reference 3). It could not be judged if death was caused by CNS-depression or damage to other internal organs.

5.2 Chronic Toxicity

No chronic toxicity studies were found.

6 ORGAN EFFECTS

6.1 Skin and Mucous Membranes

The only data found on human tests on trimethylolpropane originate from the Encyclopedia of Chemical Technology (10), but the original source of information could not be obtained because of an error in the reference list of this encyclopedia. According to this source, patch tests were performed on 200 humans. These tests showed that trimethylolpropane is neither a primary skin irritant nor a skin sensitizer. No further data on test conditions were given in this short citation.

The effects of cutaneous application of trimethylolpropane to rabbits were evaluated by two Soviet studies (16). In one test 0.5 ml of 50% solution (w/w or w/v not specified) of trimethylolpropane was applied daily to the skin of rabbits for 3 months. Contact time was not mentioned. In another test the tails of mice were immersed in 50% aqueous solution (w/w or w/v not specified) of trimethylolpropane for 4 hours. No visible changes of the skin at the site of application could be observed in these two tests. No information was given about test conditions such as the observation period, the number of animals tested, their gender, and strain, whether the skin was shaved or abraded, or whether animals were used as controls.

A 24-hour covered dermal exposure test is described in an unpublished report cited in BIBRA (3). Moistened trimethylolpropane was applied to the closely clipped intact abdominal skin of 16 albino rabbits. Dosage levels were 1.0, 2.15, 4.64, and 10.0 g/kg b.wt., and the test material was removed after 24 hours. During the 7-day observation period all animals exhibited normal behavior and appearance. There was an increase in body weight in all animals and a very mild degree of skin irritation occurred at each dosage level. The irritation was characterized at the end of the exposure period by a mild erythema, which subsided within an additional day, after which the exposed skin area appeared grossly normal. Since no animals were used as controls and a mild degree of dermal irritation was observed at all dosage levels, no definite conclusion about the irritative effect can be made.

A 25% aqueous solution of trimethylolpropane was applied daily to the shaved unabraded skin of rats at a single dose of 0.5 g/kg of body weight as presented in an unpublished study cited in reference 3 and 14. Neither the number of animals used nor the contact time was mentioned. During 7 days of observation of the animals, no signs of intoxication or irritation of the skin occurred.

In another study, cited by reference 3, cotton wool impregnated with trimethylolpropane was put inside the external ear of two rabbits and one drop of trimethylolpropane was put into the conjunctival sac of another rabbit. The rabbits were observed for 7 days without any signs of irritation to the skin or conjunctiva, or corneal damage. No data on the concentration or the contact time for the ear were mentioned.

The BIBRA document (3) also presents brief information about eye irritancy, but the original studies are not published. According to one study, 50 mg trimethylolpropane was not irritating to the rabbit eye when observed for up to 7 days. The number of animals tested or other test conditions were not described in this short citation. There were indications of mild transient irritation (particularly in two animals) when 0.1 cm^3 powder was introduced into the eye of nine rabbits. Four days after application there were no signs of irritation.

No inflammation of the skin or the mucous membrane of the eye was observed according to an unpublished study cited by an OECD document (14). A dose of 0.5 g of trimethylolpropane was put into the ear of two rabbits for 24 hours and 50 mg of trimethylolpropane was put into the conjunctival sac of the eye of two rabbits.

6.2 Nervous System

Trimethylolpropane belongs chemically to a group of alcohols that are organic chemicals associated with narcotic-type toxicity. Human data are missing, but CNS depressive symptoms have been observed in experimental animals after exposure to trimethylolpropane. No data have been found on the toxicity to the peripheral nervous system.

A Soviet paper presents subchronic inhalation toxicity data for trimethylolpropane (16). This study is cited in a BIBRA document (3), which gives a description of this study as "obscure and poorly reported."

Twenty albino rats (gender or strain not specified) were divided into two groups (size not given). The animals were exposed to either a concentration of 100-700 mg/m^3 (mean 130 mg/m^3) or a concentration of 700-1,800 mg/m^3 (mean 1,100 mg/m^3). Exposure time was 4 hours per day in chambers during a period of 3.5 months (it was not specified if it was for 7 or 5 days per week). The air supplied to the chambers passed through a tube, with the preparation placed in a boiling water bath, so as to resemble the technological process, where temperatures of up to 100 °C are used. A dysfunction of the nervous system was described, measured by the threshold of neuromuscular excitability after electric stimuli. A raised threshold could be noticed after 8 weeks of exposure to trimethylolpropane at a concentration of 1.1 mg/l air (1,100 mg/m^3). A concentration of 0.13 mg/l (130 mg/m^3) caused "recorded shifts" beginning with the 12th week. According to a BIBRA document (3), the results of this experiment remain obscure and can therefore not be evaluated. The effect of raised neuromuscular excitability was noticed earlier in the control animals than in the animals exposed to trimethylolpropane, according to the figures presented in the report.

A short-term experiment was also performed using the concentrations mentioned above (700-2,000 mg/m^3), where an unspecified number of animals were exposed for 4 hours. No antemortem signs of toxicity were noticed but terminal histopathology revealed a "swelling of the cells" in some organs including the brain.

The report also describes signs of poisoning of the nervous system of rats after oral administration of trimethylolpropane. The symptoms were sluggishness, decreased respiration rate, and clonic-tonic spasms. Test conditions are poorly described. The number of animals tested was

not given, and it was not mentioned if controls were used. Even data about actual doses at which these effects occurred are missing.

Inhibition of the central nervous system was observed in an unpublished study cited in BIBRA (3). Twenty-five male albino rats (strain not defined), divided into five groups, received trimethylolpropane orally at doses of 1.0, 2.15, 4.64, 10.0, and 21.5 g/kg b.wt. No animals were used as controls. Within 1 to 2 hours after a single dose of 2.15 g/kg or more, the animals appeared depressed and exhibited lacrimation, slow and labored respiration, ataxia, and splaying of the legs. The animals at the 21.5 g/kg level all died and the premortal signs of intoxication were depressed or absent reflexes of pain, righting, and placement. Symptoms remained for 24 hours; but at 43 hours following dosage, the surviving animals exhibited normal appearance and behavior.

6.3 Toxic Effects in Other Internal Organs

No human data have been found. Acute and repeated administration of trimethylolpropane to experimental animals has revealed toxic effects in internal organs, mainly the liver and the kidneys. The hepatotoxicity was manifested as general enlargement of the liver as well as enlarged hepatocytes and pericholangitis. Renal changes included increased kidney weight, deposits of proteinaceous material in the Bowmans space, and tubular nephrosis.

A Soviet paper (16) presents toxic effects on internal organs following inhalation of trimethylolpropane. Twenty albino rats were divided into two groups, exposed to either a concentration of 100-700 mg/m^3 (mean 130 mg/m^3) or a concentration of 700-1,800 mg/m^3 (mean 1,100 mg/m^3). Exposure time was 4 hours per day in chambers during a period of 3.5 months. Test conditions are further described in section 6.2. The exposed rats displayed no grossly observable toxic signs, statistically significant difference of body weight, or any abnormal composition of peripheral blood (RBC, WBC, Hb, and differential count) in comparison with control animals. Histopathology of tissues from the final sacrifice revealed interstitial pneumonia, focal emphysema, and degeneration of the liver, heart, and kidneys. In addition, increased relative adrenal weights were present. The number of animals used and the strain were not described. No data were given on the use of controls or on the dose at which the effects occurred.

Another inhalation study performed on rats (6) did not show any toxic effects on internal organs at terminal autopsy. The animals (two male and two female Alderley-Park rats) inhaled trimethylolpropane at a concentration of 20 microgram/l (20 mg/m^3), 6 hours daily for 15 days. Urine tests (pH, sugar, protein, and specific gravity) and blood tests (electrolytes, urea, Hb, WBC, RBC, and differential count) were normal.

Changes in several internal organs were observed following oral administration of trimethylolpropane to rats, according to an unpublished report cited in BIBRA (3) and OECD (14). Five groups, each consisting of ten male and ten female Wistar rats were fed trimethylolpropane for 90 days at various dietary levels. The animals had intake levels of 0, 0.03, 0.1, 0.3, and 1.0% from their food, which corresponds to approximately 20, 67, 200, and 667 mg/kg • day.

Biochemical analysis of blood revealed a significant decrease of hepatic enzymes (SGPT and SAP) at a dosage level of 200 mg/kg • day and above for male rats. Corresponding changes were also seen in female rats at a dosage level of 667 mg/kg • day. SGOT levels remained unchanged. After the administration of hepatotoxic substances there is usually an increase of liver enzymes in blood (e.g., SGPT and SGOT). Therefore no safe conclusions can be based on these results.

At a dose of 667 mg/kg • day there was a significant increase in the relative weight of the liver, kidneys, spleen, thyroid (female), adrenals (male), ovary, and brain (female) when compared with a nonexposed control group. There was no significant difference in terminal body weights between the various groups, including controls.

Morphological changes of liver and spleen were observed. Lymphocyte infiltration and normoblasts were observed in the sinusoids of the liver at the highest dosage level (667 mg/kg). In female rats there were enlarged Kuppfer cells containing pigment granules at the highest dose level. Treatment-related changes in the spleen were also reported (hyperplasia of phagocytically active reticuloendothelial cells).

The subchronic oral toxicity of trimethylolpropane was investigated in sls strain Sprague-Dawley rats as presented in an unpublished report cited in OECD (14). The animals received doses of 0 to 800 mg/kg • day in distilled water. Before mating, the administration period was 42 days for male rats and 14 days for female rats. Dosing of females continued after mating until day 3 of lactation. It is not specified in this short citation if it was for a consecutive number of days or 5 days per week. No deaths occurred among the 60 animals and no clinical signs attributable to the treatment were observed. Body weights of both male and female animals receiving 800 mg/day were lower than those of the control group. Liver weight (absolute and relative) was significantly elevated in rats of both sexes receiving 800 mg/kg • day. Histopathological examination revealed renal changes (slight tubular basophilic change of tubular epithelial cells) in male rats of all groups and in some of the females, but no dose-related morphological lesions of the liver or the kidneys were noticed.

Another unpublished study cited in OECD (14) showed significantly increased liver and kidney weights (absolute and relative) of rats (40 male and 40 female Wistar rats) after an oral dose of 2,000 mg/kg • day for 28 days. The animals were divided into four groups, each consisting of ten animals, with intake levels from their food of 0, 0.33, 1.00, and 3.00 % (which corresponds to 0, 220, 667, and 2,000 mg/kg • day).

Treatment-related morphological changes (enlarged hepatocytes and pericholangitis) of the liver were seen at a dose of 667 mg/kg • day or more. Renal changes (minimal tubular nephrosis and deposits of a proteinaceous material in Bowmans space) were observed at a dose of 2,000 mg/kg • day.

Kidney changes (a hyperemic zone at the periphery of the medulla) were observed according to an unpublished report, cited in BIBRA (3). Twenty-five male albino rats (age and strain not specified) were given trimethylolpropane at doses of 1.0, 2.15, 4.64, 10.0, and 21.5 g/kg b.wt. as a single oral dose. No animals were used as controls. The kidney changes were observed at autopsy in all animals receiving 4.64 g/kg or more.

All animals given the highest dose died within 24 hours after administration, and autopsy showed hyperemic or hemorrhagic lungs, irritation of the pyloric portion of the stomach, small intestine, and peritoneum, as well as congested kidneys and adrenals. The acute oral LD_{50} of trimethylolpropane was estimated to be 14.7 g/kg b.wt. (male albino rats).

7 ALLERGENIC PROPERTIES

Patch tests performed on 200 human subjects indicated that trimethylolpropane was not a skin sensitizer, according to a short citation in a chemical encyclopedia (10). The original report on this study could not be found and evaluated.

No other studies or case reports on the allergenic properties of trimethylolpropane were available.

8 GENOTOXICITY

Available data on the genotoxic effects of trimethylolpropane have not revealed any evidence of genotoxicity. All published information about genotoxicity in this section (exclusively in vitro tests for gene mutations) originates from one single secondary source of information, the OECD document (14).

Four different strains of Salmonella typhimurium (TA100, TA1535, TA98, TA1537) were tested, with and without an exogenous metabolic activation system (the S-9 mix from rat liver). Doses up to 5 mg of trimethylolpropane (99.51% purity) per plate did not cause any bacteriotoxic effects or any evidence of mutagenic activity, in comparison with the negative controls.

A second study on the genotoxicity of trimethylolpropane was also negative (14). The short citation provided no information about the test method or genotoxic end-point. Test species were Salmonella typhimurium (strain TA98, TA100, TA1535, TA1537 and TA1538) and Escherichia coli (strain wp2 and uvrA).

The OECD document (14) also cites a third unpublished study which was negative. The short citation provides no information about test method. Test species were Salmonella typhimurium (strain TA98, TA100, TA1535, TA1537) and Escherichia coli (strain wp2 and uvrA). Mutagenicity was tested both with and without metabolic activation.

In a fourth unpublished study, cited in OECD (14), a nonbacterial in vitro test was performed on cultured Chinese hamster CHL cells. This short citation provides no information about test method or genotoxic end-point. The lowest concentration producing cell toxicity, both with and without metabolic activation, was 1.5 mg/ml. No genotoxic effect was observed.

9 CARCINOGENICITY

No information is available.

10 REPRODUCTIVE TOXICITY AND TERATOGENICITY

One citation of an unpublished report on the reproductive toxicity and teratogenicity of trimethylolpropane was available (14). Sprague-Dawley rats (strain slc) were given trimethylolpropane, in distilled water, by gavage. The administration period was 42 days prior to mating for male rats and from 14 days before mating to day 3 of lactation for female rats. A total number of 60 animals received doses from 0 to 800 mg/kg • day.

No significant toxic effects of test substance were observed on copulation, fertility, and oestrus cycles of rats. There was no increase in the incidence of abnormal pups and no effect on dams during the lactation period. Stillborn pups and pups killed at day 4 of the lactation period showed no gross abnormalities due to the treatment with trimethylolpropane.

11 DOSE-EFFECT AND DOSE-RESPONSE RELATIONSHIPS

The acute toxic effects found in the literature on trimethylolpropane are summarized in Table 2 and the toxic effects of repeated exposure are summarized in Table 3.

12 RESEARCH NEEDS

There is a striking shortage of published material on trimethylolpropane. Most information originates from unpublished reports. Consequently, there is a need for peer-reviewed, published, experimental toxicological studies. Additional inhalation studies are especially needed to quantitatively estimate safe airborne exposures.

There is also an information gap concerning toxicological effects in humans. Only one source of information about toxicological effects in humans was found. No epidemiological studies on health status of workers chronically exposed to trimethylolpropane were available. Information about dermal, narcotic, hepatotoxic, and renal effects would be of great value.

Quantitative data on the toxicokinetics of the substance are absent. Studies on toxicokinetics, both on humans and animals, would be valuable to assess uptake, distribution, metabolism, and excretion.

13 DISCUSSION AND EVALUATION

Limited documentation exists of the toxic effects of trimethylolpropane in experimental animals. Many data originate from unpublished reports cited in reviews. Only two papers contained original information from toxicological studies on trimethylolpropane. One of these two reports gives a brief presentation of trimethylolpropane among 109 industrial chemicals, and the other is a Soviet paper (translated into English) that omits many data on test conditions and results. In an evaluation by BIBRA, this paper was described as obscure and poorly reported.

Table 2. Effects of acute exposure (<= 24 h)

Route of administration	Species	Observed effect (*)	Reference
Oral SD†	Rat	Narcosis at 2.15 g/kg	Reference 3
Oral SD	Rat	LD_{50}>2.5 g	References 3 and 14
Oral SD	Rat	Kidney changes at 4.64 g/kg b.wt.	Reference 3
Oral SD	Rat	LD_{50}>5 g/k b.wt.	Reference 14
Oral SD	Rat	LD_{50} 14.1g/kg b.wt.	Reference 16
Oral SD	Rat	LD_{50} 14.7 g/kg b.wt.	Reference 3
Oral SD	Mouse	LD_{50} 13.7 g/kg b.wt.	Reference 16
Dermal SD	Rat	LD_{50}>0.5 g/kg b.wt.	References 3 and 14
Dermal 24 h	Rabbit	Skin irritation at 1.0 g/kg b.wt.(‡)	Reference 3
Dermal 24 h	Rabbit	Kidney changes at 2.15 g/kg b.wt.	Reference 3
Dermal 24 h	Rabbit	LD_{50}>10 g/kg b.wt.	Reference 3
Inhalation 4 h	Rat	LC_{50}>290 mg/m^3	References 3 and 14
Inhalation 4 h	Rat	Congestion and altered vessel permeability at 700-2,000 mg/m^3	Reference 16

*Lowest identified dose inducing effect.
†SD = Single dose.
‡This was the lowest dose used in the study. Skin irritation occurred at all doses, and no animals were used as controls.

Table 3. Toxic effects after repeated exposure

Route of administration	Dose required for effect or measured entity	Species	Observed effect	Reference
Oral (28 days)	LOEL 667 mg/kg • day NOEL 220 mg/kg • day	Rat	Pericholangitis, enlarged hepatocytes	Reference 14
Oral (28 days)	LOEL 2000 mg/kg • day NOEL 667 mg/kg • day	Rat	Renal changes, increased weight of liver and kidney.	Reference 14
Oral (6 weeks)	LOEL 800 mg/kg • day NOEL 200 mg/kg • day	Rat	Increased rel weight of liver.	Reference 14
Oral (90 days)	LOEL 200 mg/kg • day (M) LOEL 667 mg/kg • day (F) NOEL 67 mg/kg • day (M) NOEL 200 mg/kg • day (F)	Rat	Change of hepatic enzymes.	References 3, 14
Oral (90 days)	LOEL 667 mg/kg • day NOEL 200 mg/kg • day	Rat	Increase of phagocytically active cells in spleen. Increased rel weights of liver, kidney, spleen, thyroid (F), adrenals (M), ovary and brain (F).	References 3, 14
Oral (5 months)	>3,000 mg/kg • day	Rat	Mortality	Reference 16
Inhalation (15 days)	>20 mg/m^3	Rat	No organ changes at autopsy.	Reference 6
Inhalation (3 months)	>700-1,800 mg/m^3	Rat	Mortality	Reference 16
Inhalation (3.5 months)	100-700 mg/m^3	Rat	Increased neuromuscular excitability.	Reference 16
Inhalation (3.5 months)	100-1,800 mg/m^3	Rat	Pneumonia and emphysema. Degeneration of liver, heart, and kidneys.	Reference 16
Inhalation (3.5 months)	700-1,800 mg/m^3	Rat	Increased rel weight of adrenals.	Reference 16

No acute inhalation toxicity studies on experimental animals have shown any antemortem signs of poisoning. However, according to one study with concentrations ranging from 700 to 2,000 mg/m^3, terminal histopathology revealed moderate congestion, a slight disturbance in the permeability of the vessel walls, and swelling of the cells of parenchymatous organs, including the brain. It is uncertain if these changes were significant since relevant data about test conditions were missing. To what extent trimethylolpropane actually is absorbed via the lungs was not investigated since no quantitative toxicokinetic measurements were performed.

In one study, rats were exposed to an aerosol of trimethylolpropane at 100 to 1,800 mg/m^3 for 3.5 months. Subsequent autopsies showed significantly increased relative weight of the adrenals. Histological changes of other internal organs were also noticed but it is uncertain if they were significant, because relevant data concerning test conditions were missing. Consequently, there are no good-quality inhalation data on which to base any safe occupational exposure limit.

The acute oral toxicity of trimethylolpropane in experimental animals is extremely low. The lowest oral LD_{50} value found was 13.7 g/kg b.wt. in mice. In rats the lowest oral LD_{50} value was 14.1 g/kg b.wt. Signs of acute poisoning were noted in the nervous system and some internal organs. The CNS effects were mainly of the narcotic type (e.g., drowsiness, decreased respiration rate, and ataxia). These effects were never seen at oral doses lower than 2.25 g/kg in rats. A physiological narcotic-type reaction could be theoretically anticipated, since this is a well-known effect of other alcohols.

Autopsy of animals that died after they were given high oral doses of trimethylolpropane showed irritation of the gastrointestinal tract, and congested lungs and kidneys. The lowest single oral dose given to animals where morphological changes of internal organs were demonstrated was 4.6 g/kg b.wt. (significant changes in kidney structure of rats).

An oral dose of 667 mg/kg • day to rats for 3 months caused significant enlargement of the liver, kidneys, and spleen. Rats fed trimethylolpropane for 28 days had pericholangitis and enlarged hepatocytes at a dose of 667 mg/kg • day or more and tubular nephrosis at a dose of 2 g/kg • day (significant effects).

Although trimethylolpropane belongs chemically to the group of alcohols of which many are considered toxicologically nonreactive, theoretically some suspicion could be raised about irritative effects of trimethylolpropane. Trihydric alcohols are used for their reactive properties and are used as reagents in the production of plastics such as polyurethanes and multifunctional acrylates. Furthermore, a dissolution effect could reduce the protective fatty layer of the skin. Experimental data on the other hand indicate a mild acute dermal irritative effect in animals. Actually only one study (on rabbits) showed any irritative effect at all and the results of this study can be questioned since irritation of the skin occurred at all dosage levels and no animals were used as controls. Patch tests performed on humans did not reveal any irritative or allergenic effects of trimethylolpropane.

The observed effects following acute exposure to very high doses of trimethylolpropane are damage to internal organs (kidney changes and irritation of the gastrointestinal tract) and signs

of CNS depression. Long-term effects are changes of internal organs such as enlargement of the lungs, liver, kidneys, and spleen as well as some histological changes in these organs, but no conclusion about a critical effect can be made because of insufficient data.

14 SUMMARY

R Wålinder: NIOH and NIOSH Basis for an Occupational Health Standard: 2-Ethyl-2-hydroxymethyl-1,3-propanediol. Arbete och Hälsa 1994:10

This document is a survey of the literature on 2-ethyl-2-hydroxymethyl-1,3-propanediol, also called 1,1,1-trimethylolpropane, as well as an evaluation of data that is relevant for establishing occupational exposure limits.

In experimental animals, 1,1,1-trimethylolpropane seems to be of low toxicity. The toxic effects in experimental animals, following both acute and repeated exposures, are depression of the central nervous system together with hepatic and renal changes. No conclusion about the critical effect or dose can be made because of insufficient data.

Limited studies have revealed mild irritative dermal effects in animals but no convincing evidence of irritation in exposed humans. Epidemiological studies or case reports on workers occupationally exposed to 1,1,1-trimethylolpropane have not been found. Limited in vitro tests did not show any signs of genotoxicity. No studies on carcinogenicity were available. 18 references.

Key-words: 2-ethyl-2-hydroxymethyl-1,3-propanediol; 1,1,1-trimethylolpropane; occupational exposure limits; CNS-effects; hepatotoxicity; renal toxicity.

15 SAMMANFATTNING

R Wålinder: NIOH and NIOSH Basis for an Occupational Health Standard: 2-Ethyl-2-hydroxymethyl-1,3-propanediol. Arbete och Hälsa 1994:10.

I detta dokument redovisas en sammanställning av tillgänglig litteratur om 2-etyl-2-hydroxymetyl-1,3-propandiol, även kallad 1,1,1-trimetylolpropan, och en utvärdering av de datauppgifter som bedöms vara relevanta för fastställande av ett hygieniskt gränsvärde för yrkesmässig exponering.

Toxiciteten hos 1,1,1-trimetylolpropan förefaller att vara låg hos försöksdjur. De toxiska effekterna hos försöksdjur, efter både akut och upprepad tillförsel, är påverkan på centrala nervsystemet tillsammans med lever och njurförändringar. En slutsats om kritisk effekt eller dos går inte att dra pga otillräckligt dataunderlag.

Data från ett begränsat antal studier har visat en lätt hudirritativ effekt hos djur men inga övertygande bevis om hudirritativa effekter hos människor. Epidemiologiska studier eller fallrapporter om arbetare som exponeras för 1,1,1-trimetylolpropan i yrket har ej hittats. Enligt

ett begränsat antal in vitro tester kunde genotoxiska effekter ej påvisas. Inga studier om kancerframkallande egenskaper var tillgängliga. 18 referenser.

Nyckelord: 2-etyl-2-hydroxymetyl-1,3-propandiol; 1,1,1-trimetylolpropan; hygieniska gränsvärden; centralnervösa effekter; levertoxicitet; njurtoxicitet.

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