FOREWORD INTRODUCTION

THIODIGLYCOL

CAS N°: 111-48-8

SIDS Initial Assessment Report

For

SIAM 19

19-22 October 2004 Berlin, Germany

1. Chemical Name:	Thiodiglycol
2. CAS Number:	111-48-8
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Postfach 12 06 29 D- 53048 Bonn
4. Shared Partnership with:	BASF AG, Germany ATOFINA SA, France
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	BASF AG, Germany Contact person: Dr. Rolf Sarafin, BASF AG GUP/CL - Z570 D-67056 Ludwigshafen
• Process used	see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 10 May 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 24 March 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms OECD/ICCA
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9. Date of Submission:	Deadline for circulation: 23 July 2004

10. Date of last Update:

11. Comments:

OECD/ICCA - THE BUA* PEER REVIEW PROCESS

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:

- a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
- Review of data and assessment of the quality of data
- Review of data evaluation
- Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
- Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
- Review of validity of structure-activity relationships
- Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
- In case of data gaps, review of testing plan or rationale for not testing

SIDS INITIAL ASSESSMENT PROFILE

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

CAS No.	111-48-8
Chemical Name	Thiodiglycol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

No data are available on the absorption of thiodiglycol from the gastrointestinal tract, or after dermal or inhalation exposure. In rats ca. 90 % of i.p. injected thiodiglycol is metabolized and excreted via urine within 24 hours after application. The major metabolite detected in urine is thiodiglycol sulphoxide. Only small amounts (0.5-1%) of the administered dose were excreted unchanged within 8 days.

The acute oral LD_{50} value in rats was >9900 mg/kg bw, with depression of the central nervous system as the main clinical sign at doses near to or exceeding the LD_{50} value. The inhalation of the saturated vapour for 8 h resulted in no mortality. Thiodiglycol is not irritating to the skin and slightly irritating to the eyes and mucous membranes. No sensitizing potential was detected in two guinea pig maximization tests following current guidelines.

In a study performed according to OECD guideline 407 (1981), repeated exposure of rats by gavage to 1000 mg/kg bw/day for 28 days resulted in no effects of toxicological relevance. In a 90-day gavage study (comparable to the current OECD guideline 408; 0, 50, 500, 5000 mg/kg bw/day), effects on body and kidney weight (without a histopathological effect) as well as altered parameters of the urine analysis were observed in males and females at 5000 mg/kg bw/day. A dose level of 500 mg/kg bw/day is considered as NOAEL.

With or without addition of a metabolic activation system, thiodiglycol did not induce mutations in bacteria (OECD guideline 471) and in the mouse lymphoma assay (OECD guideline 476). At high dose levels resulting in cytotoxic effects thiodiglycol induced chromosomal aberrations *in vitro*, both in the presence and the absence of a metabolic activation system (study design comparable with OECD guideline 473). No clastogenic activity was detected in the mouse bone marrow micronucleus assay at oral doses up to and including 2000 mg/kg bw (OECD guideline 474). It is therefore concluded that the clastogenic effects seen *in vitro* are not expressed *in vivo*.

There are no fertility studies available. In a 90 day gavage study (see above) no effect was observed on the gonads of male and female rats dosed up to and including 5000 mg/kg bw/day. In two gavage studies (OECD guideline 414) on the prenatal developmental toxicity in Wistar rats, the NOAEL for maternal and developmental toxicity was 400 mg/kg bw/day. Borderline effects concerning a certain type of skeletal variations (dumbbell ossification of thoracic vertebral bodies) were observed at oral doses of 1000 mg/kg bw/day which resulted also in marginal maternal toxicity.

No data are available on carcinogenicity.

Environment

Thiodiglycol is an organic liquid of unpleasant odour with a melting point of -10 °C and a relative density of 1.1824 at 20 °C. It is miscible with water at 20 °C (pH 5 - 9 at 100 g/l) and the vapour pressure at this temperature is < 0.101 hPa. A Henry's law constant of $1.87 \cdot 10^{-4}$ Pa · m³/mol at 25 °C can be calculated. The partition coefficient log K_{OW} is – 0.75 as measured at 25 °C.

According to the distribution model *Mackay*, Level I, the target compartment for thiodiglycol is the hydrosphere with 99.95 %. The substance has a low potential for bio- or geoaccumulation. As shown in a guideline study according to OECD 301 A thiodiglycol can be regarded as readily biodegradable (90 - 100 % after 21 days). Hydrolysis or photodegradation in water do not occur. For indirect photodegradation in air due reaction with OH radicals a half-life of 13.8 hours is calculated.

The aquatic effects data base meets the requirements of the SIDS package. Aquatic effects data are as follows:

fish (*Leuciscus idus):* LC_{50} (96 h) > 10 000 mg/l;
crustacea: (*Daphnia magna)* EC_{50} (48 h) > 500 mg/l;
algae (*Desmodesmus subspicatus*): ErC_{50} (72 h) > 500 mg/l.

These values indicate that thiodiglycol is of low toxicity to aquatic organisms. For microorganisms (activated sludge) an EC_{20} (30 min) of > 1000 mg/l was determined. Applying an assessment factor of 1000 to the lowest available acute effect value according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of ≥ 0.5 mg/l is derived.

Exposure

Thiodiglycol is produced by ATOFINA SA (France) and BASF AG (Germany), further producers in the EU are not known. The production volume in the EU in the year 2003 was 1000 to 5000 tonnes. Imported volumes are not known. Both companies export minor amounts to Asia and the Pacific as well as to the USA. Further producers of thiodiglycol are known in China (4), Japan (1), Mexico (1), and USA (1) but no data on production volumes are available. Thiodiglycol is used as a chemical intermediate, as a solvent in colouring processes in the textile industry, as a solvent in preparations for colouring paper and as a softener in special caoutchoucs. Thiodiglycol is a component of different products listed in European product registers; the substance is used in the manufacture of pulp, paper products, paints, pigments, dyestuffs, varnishes, coatings and inks. Some of them are available to consumers. The chemical may be also used as antioxidant in cosmetics.

Releases of thiodiglycol into the environment may occur from production and processing, from its use as solvent in industrial applications and from use of products containing this substance. However, no detailed exposure information is available. A source of exposure might also be given by the hydrolysis of the chemical warfare agent sulfur mustard (see below) to thiodiglycol.

Thiodiglycol can be converted by chemical synthesis to mustard gas. Therefore the production and export of thiodiglycol is stringently controlled under the International Chemical Weapons Convention.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

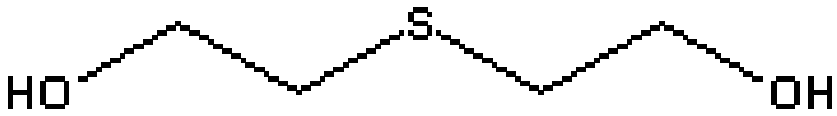
The chemical is currently of low priority for further work due to its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 111-48-8
Chemical Name: thiodiglycol
Molecular Formula: $C_4 H_{10} O_2 S$
Structural Formula:



Molecular Weight: 122.19 g/mol
Synonyms: 2,2'-thiobisethanol
2,2'-thiodiethanol
3-thiopentane-1,5-diol
beta,beta'-dihydroxydiethyl sulfide
beta,beta'-dihydroxyethyl sulfide
beta-hydroxyethyl sulfide
beta-thiodiglycol
Bis(2-hydroxyethyl)sulfide
Bis(beta-hydroxyethyl)sulfide
Glyecine A
Kromfax solvent
sulfide, bis(2-hydroxyethyl)
thiodiethylene glycol

Substance type: organic

Physical status: liquid at room temperature

1.2 Purity/Impurities/Additives

Purity: ≥ 99 %

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	liquid at room temperature	
Melting point	-10 °C	Falbe and Regitz, 1999
Boiling point	282 °C at 1013 hPa	Sax and Lewis, 1989; Falbe and Regitz, 1999
Relative density	1.1824 at 20 °C	Budavari et al., 1989; Falbe and Regitz, 1999
Vapour pressure	< 0.101 hPa at 20 °C	Hommel, 1998
Water solubility	miscible	Budavari et al., 1989; Falbe and Regitz, 1999
Partition coefficient n-octanol/water (log value)	-0.75 at 25 °C (measured)	BASF AG, 1988b
Henry's law constant	1.87 * E-4 Pa * m³/mol at 25 °C	BASF AG, 2004a
pH	5 – 9 (at 100 g/l, 20 °C)	BASF AG, 2002b§

§: Only data from producer without proof (reliability 4) available for this endpoint

Thiodiglycol is a colourless to yellowish liquid with an unpleasant odour (BASF AG, 1999a).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Thiodiglycol is produced by ATOFINA SA (France) and BASF AG (Germany), further producers in the EU are not known. The production volume in the EU in the year 2003 was 1000 to 5000 tonnes. Imported volumes are not known. Both companies export minor amounts to Asia and the Pacific as well as to the USA (BASF AG, 2004d). Further producers of thiodiglycol are known in China (4), Japan (1), Mexico (1), and USA (1) but no data on production volumes are available (DWCP, 2003). Thiodiglycol is used as a chemical intermediate, as a solvent in colouring processes in the textile industry, as a solvent in preparations for colouring paper and as a softener in special caoutchoucs.

In the Swedish Products Register (KEMI, 2003) data are given on the use and quantity of thiodiglycol. Thiodiglycol is contained in 19 products, the total quantity is 0.4 t/a. Three of these products are available for consumers (no data on quantity given). The most frequent use is registered in dyestuffs and pigments (no further details available). In the Danish Product Register (Arbejdstilsynet, 2002), the number of products containing thiodiglycol is 65 with a total quantity of 17 t/a. The substance is used in the manufacture of pulp, paper and paper products, paints, varnishes and coatings as well as in the manufacture of furniture. Similar data were found in the Swiss Product Register (Bundesamt für Gesundheit, 2002); additionally thiodiglycol was also registered as teaching material (no quantification data).

Thiodiglycol is not classified as hazardous under transport regulations.

Thiodiglycol can be used as a precursor for sulphur mustard. Therefore the production and export of thiodiglycol is stringently controlled under the International Chemical Weapons Convention (CWC, 2000).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases of thiodiglycol into the environment may occur from production and processing, from its use as solvent in industrial applications, for example as a solvent in colouring processes, and from use of products containing this substance. Generally, it may be released to the aquatic environment and only traces will reach the atmosphere due to the distribution pattern (see below). However, no detailed exposure information is available. Concerning the release into environment from production it should be mentioned that no thiodiglycol loaded waste water is generated during the production process used by BASF AG (BASF AG, 2004f).

A source of exposure might also be given by the hydrolysis of the chemical warfare agent sulfur mustard to thiodiglycol in the environment (Ermakova et al., 2002).

2.2.2 Photodegradation

Thiodiglycol is indirectly photodegraded by reaction with hydroxyl radicals in the atmosphere. The calculated half-life of thiodiglycol in air due to indirect photodegradation is 13.8 hours, considering a daily mean OH radical concentration of 500 000 radicals/cm³ (calculation; BASF AG, 2004a).

2.2.3 Stability in Water

No detectable photolysis of thiodiglycol was reported after aqueous samples were exposed to sunlight for 14 days (Lee and Allen, 1998). Experimental data show that thiodiglycol does not hydrolyse under environmental conditions (Lee and Allen, 1998).

2.2.4 Transport between Environmental Compartments

The distribution modelling using Mackay, Level I, which is calculated with the values of mol mass, vapour pressure, water solubility, melting point and partition coefficient, indicates water to be the almost exclusive (99.95 %) target compartment at a temperature of 25 °C (BASF AG, 2004e).

The Henry's law constant of $1.87 \cdot 10^{-4}$ Pa·m³/mol (BASF AG, 2004a) indicates that thiodiglycol has a low potential for volatilisation from aqueous solution.

The estimated soil sorption coefficient Koc = 1 (BASF AG, 2002a) suggest a very low potential for sorption to soil. This is in line with the high mobility of thiodiglycol reported in experimental studies on the sorption of thiodiglycol onto different soils (Lee and Allen, 1998).

2.2.5 Biodegradation

In a guideline study according to OECD TG 301A (new version) thiodigylcol was readily biodegraded using domestic activated sludge as inoculum. After 21 days 90 - 100 % biodegradation was measured (BASF AG, 1999c). In a modified MITI test (according to OECD TG 301C) < 30 % degradation was measured after 28 days (MITI, 1992).

Under anaerobic condition thiodiglycol was slowly biodegraded; the degradation reached 42 % after 185 days with a lag period of 52 days (Sklyar et al., 1999).

Conclusions: Under aerobic conditions thiodiglycol is readily biodegradable according to OECD criteria.

2.2.6 Bioaccumulation

No experimental data on bioaccumulation are available. The measured log K_{ow} of -0.75 (see Table 1) indicates a low potential for bioaccumulation.

2.3 Human Exposure

2.3.1 Occupational Exposure

At the production site it is technically ensured that exposure of workers to thiodiglycol is minimized. Significant exposure does not occur during production, filling and sample collection, since these processes are largely enclosed. Occupational exposure is therefore limited to situations of maintenance and repair, and accidental spills. In those situations, the occupational exposure to thiodiglycol is most likely to occur through inhalation and dermal contact.

During processing and particularly through the use of thiodiglycol containing products exposure may occur via inhalation of aerosols or via contact with skin and mucous membranes.

Workplace exposure measurements were not available.

2.3.2 Consumer Exposure

Products containing thiodiglycol are listed in different product registers (see above) but in most instances no clear information is given whether these products are also used by consumers beside the main industrial use. Only in the product register from Sweden (KEMI, 2003) 3 products out of 19 are listed for consumer use.

Consumers may be exposed mainly through the use of varnishes, paints, or inks containing up to 10 % of thiodiglycol (Swiss Product Register, Bundesamt für Gesundheit, 2002). Thiodiglycol may also be used as antioxidant in cosmetics (INCI, 2004).

The most likely routes of human exposure through the use of thiodiglycol containing products are inhalation of aerosols or contact with skin and mucous membranes.

With regard to the available data on environmental fate of thiodiglycol no significant exposure of the general public is expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

No data are available on the absorption of thiodiglycol from the gastrointestinal tract after oral application or by the dermal or inhalation routes. However, the chemical structure (similar molecular shape and log K_{OW} as diethylene glycol) as well as systemic effects after oral exposure indicate gastrointestinal absorption of thiodiglycol, although the absorption rate is unknown.

For the determination of the excretion profile, rats received i.p. ^{35}S-radiolabed thiodiglycol at doses of 24 µg/kg bw to 40 mg/kg bw. Ca. 60 % of the administered dose was excreted via urine within 6 hours, ca. 90 % within 24 hours and virtually all of the dose within 8 days (93 - 99 %), independently of the amount injected. No significant excretion was detected in the faeces (Black et al., 1993).

For isolation and identification of metabolites, rats were i.p. injected with 40 mg/kg bw doubly-labelled ^{13}C4,^{35}S-thiodiglycol. Samples of pooled urine were analyzed 6 and 24 hours after injection and then daily for 8 days. Thiodiglycol sulphoxide was the major metabolite (oxidation at the sulphur atom) accounting for ca. 90 % of the excreted radioactivity. S-(2-hydroxyethylthio) acetic acid was present in significant quantities up to 10 %; thiodigylcol sulphone and S-(2-hydroxyethylsulphinyl)acetic acid were identified as minor metabolites. Only 0.5 - 1.0 % of the administered dose was excreted unmetabolized (Black et al., 1993). No data are given on $^{13}CO_2$ expiration.

Thiodiglycol is an important primary metabolite of sulphur mustard formed by simple hydrolysis (Black and Read, 1995).

Conclusion

No quantitative data are available on the absorption from the gastrointestinal tract, or on the absorption after dermal or inhalation exposure. In rats ca. 90 % of i.p. injected thiodiglycol is metabolized and excreted via urine within 24 hours after application. The major metabolite detected in urine is thiodiglycol sulphoxide. Only small amounts (0.5 - 1 %) of the administered dose were excreted unchanged within 8 days.

3.1.2 Acute Toxicity

Studies in Animals

Thiodiglycol is of low acute toxicity in mammals. The available and reliable acute toxicity studies are presented in Table 2.

An acute approximate lethal dose determination was performed in male and female rats by Angerhofer et al. (1997). Eight animals of each sex were given neat thiodiglycol (purity ≥ 95 %), one dose per rat, by gavage at dose levels of 579, 869, 1304, 1956, 2933, 4400, 6600, or 9900 mg/kg bw. No toxic effects or deaths were produced in female rats. The male rat given 9900 mg/kg bw was slightly lethargic starting 1 hour post-treatment, but recovered within 4 hours. No other effects were noted.

In a poorly documented study, dyspnoea and dizziness were observed as clinical signs of toxicity in rats after gavage of 11 800 mg/kg bw (= the reported approximative LD_{50} value). Gross pathology after the 7-day post-exposure period showed pancreas bleeding (BASF AG, 1966).

No valid acute toxicity data were available for the dermal route.

In the Rat Inhalation Hazard Test, no mortality was reported after 8 h exposure to a saturated atmosphere at room temperature. Immediately after the start of exposure, the animals showed attempts to escape. Irritation of the mucous membranes was observed 1 h after start of exposure. Three out of 12 rats showed chronic bronchitis at necropsy, but these findings were judged to be not treatment related (BASF AG, 1966 & 2004b).

Table 2: Acute toxicity of thiodiglycol in experimental animals

Route	Species[a]	LD_{50}	Reliability/Remarks	Reference
Oral	Rat (male, female; Sprague-Dawley; 8 dose levels, 2 animals/dose)	Acute approximate lethal dose: > 9900 mg/kg bw	1/ slight lethargy of the male rat at 9900 mg/kg bw; no toxic effects in the female rats.	Angerhofer et al., 1997
Oral	Rat (no data)	ca. 11 800 mg/kg bw	4/ post exposure observation period 7 d	BASF AG, 1966
Inhalation (8 hours)	Rat (no data; no data; n = 12)	No mortality	2/ Inhalation risk test; saturated atmosphere at 20 °C	BASF AG, 1966 & 2004b

[a] Data on sex, strain and number (n) per dose in brackets

Conclusion: The acute oral LD50 value in rats was > 9900 mg/kg bw, with depression of the central nervous system as the main clinical sign at doses near to or exceeding the LD50 value. The inhalation of the saturated vapour for 8 h resulted in no mortality.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Acute dermal irritation was tested on rabbits according to OECD guideline 404. A very slight erythema was noted in 1 out of 3 animals 1 hour after treatment until day 4. The effect was completely reversible within 5 days. No cutaneous reactions were observed in the other 2 animals (Elf Aquitaine, 1995a). The chemical can therefore be considered as not irritating to the skin.

Conclusion: Thiodiglycol is not irritating to the skin.

Eye Irritation

Studies in Animals

In a GLP study according to OECD guideline 405 only slight irritation of the eye was observed (Elf Aquitaine, 1995b; ECETOC, 1998). 0.1 ml undiluted thiodiglycol (purity 99.8 %) applied to the eyes of 3 rabbits resulted in no effects on cornea and iris, but slightly affected the conjunctivae of 2 rabbits as shown in Table 3.

Table 3: Grading of effects on conjunctiva (data refer to rabbit no. 1, 2 and 3)

Effect	Draize scores at different times after instillation of test material			
	1 hour	1 day	2 days	3 days
Redness	0 / 0 / 1	0 / 1 / 2	0 / 1 / 1	0 / 0 / 0
Chemosis	0 / 2 / 0	0 / 1 / 1	0 / 1 / 0	0 / 0 / 0

In an early study (BASF AG, 2004c; documentation of the laboratory raw data of an experiment performed in 1966), 50 µl of the undiluted test substance (no data about purity) was applied to the conjunctival sac of one eye of each of 2 rabbits (not rinsed). Effects were described 24, 48, and 72 hours as well as 6 and 8 days after treatment. The 1st rabbit showed slight conjunctival redness (Draize score 1 at 24 - 72 hours) and moderate (Draize score 2 at 24 hours) to slight (Draize score 1 at 48 hours) conjunctival chemosis, slight corneal opacity (Draize score 1 at 24 hours up to day 6)

but no iritis. All effects were reversible at day 8 (study end). In the 2nd rabbit no effects were detected except a slight redness (Draize score 1) 24 and 48 hours after instillation.

Conclusion: Thiodiglycol is slightly irritating to the rabbit eye.

Respiratory Tract Irritation

Studies in Animals

In the Rat Inhalation Hazard Test (see section 3.1.2) irritation of the mucous membranes was observed after 1 h exposure to a saturated atmosphere at room temperature (BASF AG, 1966 & 2004b).

Conclusion: There is evidence that thiodiglycol is slightly irritating to the mucous membranes at a saturated atmosphere.

3.1.4 Sensitisation

Studies in Animals

In a guinea pig maximization test (BASF AG, 1991) according to the current guidelines (Directive 84/449/EEC, B.6; OECD TG 406) a test group of 10 animals received 5 % thiodiglycol in aqueous 0.9 % saline solution for intradermal induction, followed by percutaneous induction with 0.3 g undiluted thiodiglycol (purity 98.4 %) under occlusive dressing for 48 hours. For challenge 0.15 g thiodiglycol (75 % solution in water; no irritating effect at this concentration) was applied to the intact skin for 24 hours (occlusive). The challenge resulted in no skin reaction, neither in thiodiglycol treated animals nor in negative controls. All 20 animals treated with the positive control substance 1-chloro-2,4-dinitrobenzene showed sensitization effects.

In a further guinea pig maximization test (Elf Aquitaine, 1998) according to OECD guideline 406 no cutaneous reactions were observed after the challenge application.

No data are available on humans.

Conclusion: In the guinea pig maximization test no sensitising effects were detected.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Thiodiglycol (purity 98.4 %) was administered by gavage in a 28 day study on male and female Wistar rats at a dose level of 1000 mg/kg bw/day according to the OECD guideline 407 (1981). No toxicologically significant effects were observed concerning clinical symptoms, body weight, food consumption, haematology, clinical chemistry and pathology. In males, a significant decrease in red blood cell counts, haemoglobin level and hematocrit was observed. These alterations in exposed rats were considered to be incidental since the effects were within the range of normal variation (laboratory historical control), and because the values in control males were unusually high. In males, also significant decreases in blood bilirubin and albumin concentrations were detected. These changes were also within the range of normal variation. Furthermore, clinical and histopathological examinations revealed no findings correlated with these alterations. Overall, the detected effects were considered to be of no toxicological significance resulting in a **NOAEL of 1000 mg/kg bw/day** (BASF AG, 1993).

In a 90-day study (Angerhofer et al., 1997; methods comparable to the current OECD guideline 408), male and female Sprague-Dawley rats were treated by gavage with 0, 50, 500, or 5000 mg/kg

bw/day thiodiglycol (purity ≥ 95 %), 5 days per week. Ophthalmic examinations, haematology, clinical chemistry and histopathology (all organs examined which are listed in the OECD guideline 408) revealed no significant treatment related effects. In the high dose group, the body weights of males and females were significantly reduced although the food consumption was not influenced except on day 1 (females) and day 3 (males) of the exposure period. The absolute and the relative kidney weights in males and females of the high dose group were significantly increased. Urine analysis including microscopic examination revealed in the high dose group the following significant effects: increase in urine volume (in males and females), decrease in urine pH (males and females), slight increase in specific gravity of the urine (males), reduction in triple phosphate (males; crystals per field determined), and granular casts in the urine (females). The relative organ weights of liver (males), brain (males), testes (males), and adrenals (females) were significantly elevated in the high dose group. No significant effects were detected on the absolute weight of these organs. Furthermore, no changes were observed in any organ at the histopathological examinations. The only effect seen at 500 mg/kg bw/day was a significant decrease in urine pH in female rats, which is considered as adaptive rather than an adverse effect. The **NOAEL** for subchronic oral exposure to thiodiglycol, as determined from this study, is **500 mg/kg bw/day**. The **LOAEL is 5000 mg/kg bw/day**.

Conclusion: In a 28 day oral study conducted according to OECD guideline 407(1981), repeated exposure of rats by gavage to 1000 mg/kg bw/day thiodiglycol resulted in no effects of toxicological significance. Therefore this dose is considered as NOAEL. In a 90 day gavage study on rats (experimental design is comparable to the current OECD guideline 408), effects on body and kidney weight (without a histological substrate) as well as altered parameters of the urine analysis were observed in males and females of the high dose group at 5000 mg/kg bw/day. 500 mg/kg bw/day is considered as NOAEL.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

Data are available on 2 bacterial mutagenicity assays (BASF AG, 1989a; Stankowski, 2001). These studies were conducted according to the OECD guideline 471 of 1983 and 1997, respectively. Thiodiglycol did not induce reverse gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* WP2uvrA at concentrations up to 5 mg/plate in the presence or absence of metabolic activation. There was no evidence of cytotoxicity except a slight decrease in revertants in the strain TA100 in the presence of metabolic activation at concentrations ≥ 2.5 mg/plate (BASF AG, 1989a).

No significant mutagenic effects were detected in the mouse lymphoma assay (according to OECD guideline 476) at concentrations between 0.05 and 5 mg/ml thiodiglycol, both in the presence and in the absence of a metabolic activation system. No cytotoxicity was observed without metabolic activation and only slight effects without dose dependency in the presence of the metabolic activation system (Clark and Donner, 1998).

In a cytogenetic assay on CHO cells (study design comparable to OECD guideline 473; Tice et al., 1997) thiodiglycol was tested at high dose levels between 1 and 5 mg/ml. An increased number of aberrations like chromosome and chromatid breaks as well as chromatid type rearrangements were detected. The effects were significant at 5 mg/ml without metabolic activation and at ≥ 4 mg/ml with metabolic activation. No effects were recorded on the cell density but the mitotic index was significantly decreased at concentration ≥ 1 mg/ml. In contrast to the cytogenetic study on CHO

cells no clastogenicity was detected in the mouse lymphoma assay (see above) at dose levels up to 5 mg/ml.

In vivo Studies

Thiodiglycol did not induce micronuclei in bone marrow of mice treated with doses of 500, 1000, or 2000 mg/kg bw according to OECD TG 474(1997) by single oral exposure via gavage. No clinical toxicity or cytotoxic effects on the bone marrow were found even at 2000 mg/kg bw, the highest test dose recommended by the current guideline. The positive controls were functional (Erexson, 2001).

Conclusion

Thiodiglycol did not induce mutations in bacteria or mouse lymphoma cells with or without addition of a metabolic activation system. At high dose levels which resulted in cytotoxic effects, thiodiglycol induced chromosome aberrations *in vitro*, both in the presence and the absence of a metabolic activation system. No clastogenic activity was detected in the mouse bone marrow micronucleus assay at oral doses up to and including 2000 mg/kg bw. It is therefore concluded that the clastogenic effects seen *in vitro* are not expressed *in vivo*.

3.1.7 Carcinogenicity

No data are available.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No effects on female gonads were observed in the 90 day gavage study on rats at doses up to 5000 mg/kg bw/day. At the high dose level the ratio of testes weight to body weight was significantly increased in males. However, the body weight of male rats was significantly reduced in this dose group. The absolute testes weight was not altered in any treatment group. Furthermore, no changes in the gonads of males and females were observed at histopathological examinations (accessory genital organs not examined; Angerhofer et al., 1997; see also section 3.1.5).

Conclusion: In a 90 day gavage study no effects were observed on the gonads of male and female rats at doses up to 5000 mg/kg bw/day.

Developmental Toxicity

In a prenatal developmental toxicity study conducted in accordance with OECD guideline 414, 1981 (BASF AG, 1995a), pregnant Wistar rats (n = 24 per group) received, in a limit test, a dose of 0 or 1000 mg/kg bw/day (purity ≥ 98.4 %) by gavage on days 6 to 15 post coitum (p.c.). The animals were sacrificed on day 20 p.c. No maternal toxicity was detected at this dose level concerning body weight gain, food consumption, clinical symptoms and pathological alterations at necropsy. No substance-related differences between the treatment and control group were noted regarding uterus weight, mean number of corpora lutea, live fetuses and dead implantations, early and late resorptions, dead fetuses or in the values calculated for conception rate, pre and post-implantation losses. Examination of fetuses did not reveal any obvious substance-related effects on sex ratio, weights of fetuses, external findings and soft tissue malformations or variations. A significant increase in dumbbell ossifications of thoracic vertebral bodies was noted (12 % versus 5.2 % in control). This skeletal variation was also outside the laboratory historical control range

(0.0 - 8.8 %). Other significant increases in skeletal variations, such as rudimentary cervical ribs were also observed (7.1 % versus 1.2 % in control) as well as a general increase in total variations (concerning affected fetuses/litter: 52.9 % versus 38.6 % in control).

NOAEL maternal = 1000 mg/kg bw/day (only dose tested)
LOAEL development = 1000 mg/kg bw/day (only dose tested)

Due to the observed effects in the limit test a second study was performed (BASF AG, 1995b). In this study (OECD guideline 414, 1981), 21 - 25 pregnant Wistar rats per group received 0, 100, 400, or 1000 mg/kg bw/day by gavage on days 6 - 15 p.c. Experimental design and investigated parameters were the same as described for the limit test. Concerning maternal toxicity none of the determined parameters revealed statistically significant or toxicologically relevant results with exception of the body weight of pregnant rats in the high dose group on gestation day 8 (32 % lower than control value, significant). According to the authors of the study this was a transient and marginal effect but possibly treatment related. Fetal investigation again showed an increase (nonsignificant) in the incidence of dumbbell ossifications of thoracic vertebral bodies in the high dose group (6.3 % versus 3.6 % in control). This type of variation is considered to be of toxicological significance since 1) it was also observed at the same dose level in the limit test and 2) the incidence was in both studies higher than the historical control values (slightly increased in this study: litter incidence 40 % versus 19.5 % in control). The following effects were statistically significant, but not of toxicological relevance (explanation in brackets):

Effect on sex distribution, more females in the mid dose group (no dose dependency)

Decreased placental weights of male fetuses in the mid dose group (within historical control values, no dose dependency)

In the mid dose group increased incidence of fetuses with soft tissue malformations per litter (within historical control data; considered by the authors to be spontaneous in nature and not treatment related)

Number of affected fetuses/litter with accessory 14^{th} rib (skeletal variation) in the high dose group (litter and fetal incidences within historical control range; this effect was not observed in the limit test)

Overall, the study resulted in:
NOAEL maternal = 400 mg/kg bw/day
NOAEL development = 400 mg/kg bw/day.

In a developmental toxicity study using another rat strain (Sprague-Dawley), pregnant rats (n = 25 per group) received a dose of 0, 430, 1290 or 3870 mg/kg bw/day (thiodiglycol, purity ≥ 99.9 %) by gavage on gestation days 5 to 19 inclusive. The animals were sacrificed on gestation day 20. Soft tissue and skeletal alterations were studied. Only in the high dose group body weight gain and food consumption of dams were reduced during certain periods of gestation. The fetal weight was significantly decreased in this dose group, and the incidence of variations was nonsignificantly increased. There was no increased incidence of anomalies when thiodiglycol-treated fetuses were compared to controls. It was concluded that thiodiglycol is not teratogenic, but is a developmental toxicant at high dose levels that produce maternal toxicity (Houpt et al., 2003). The study is only available in the form of an abstract, and its reliability cannot therefore be judged.

NOAEL maternal = 1290 mg/kg bw/day
NOAEL development = 1290 mg/kg bw/day.

Conclusion: In two gavage studies (OECD guideline 414) on the prenatal developmental toxicity in Wistar rats, the NOAEL for maternal and developmental toxicity was 400 mg/kg bw/day.

Borderline effects concerning a certain type of skeletal variations (dumbbell ossification of thoracic vertebral bodies) were observed at oral doses of 1000 mg/kg bw/day which resulted also in marginal maternal toxicity.

3.2 Initial Assessment for Human Health

No data are available on the absorption of thiodiglycol from the gastrointestinal tract, or after dermal or inhalation exposure. In rats ca. 90 % of i.p. injected thiodiglycol is metabolized and excreted via urine within 24 hours after application. The major metabolite detected in urine is thiodiglycol sulphoxide. Only small amounts (0.5 - 1 %) of the administered dose were excreted unchanged within 8 days.

The acute oral LD_{50} value in rats was > 9900 mg/kg bw, with depression of the central nervous system as the main clinical sign at doses near to or exceeding the LD_{50} value. The inhalation of the saturated vapour for 8 h resulted in no mortality.

Thiodiglycol is not irritating to the skin and slightly irritating to the eyes and mucous membranes. No sensitizing potential was detected in two guinea pig maximization tests following current guidelines.

In a study performed according to OECD guideline 407 (1981), repeated exposure of rats by gavage to 1000 mg/kg bw/day for 28 days resulted in no effects of toxicological relevance. In a 90-day gavage study (comparable to the current OECD guideline 408; 0, 50, 500, 5000 mg/kg bw/day), effects on body and kidney weight (without a histological substrate) as well as altered parameters of the urine analysis were observed in males and females at 5000 mg/kg bw/day. A dose level of 500 mg/kg bw/day is considered as NOAEL.

With or without addition of a metabolic activation system, thiodiglycol did not induce mutations in bacteria (OECD guideline 471) and in the mouse lymphoma assay (OECD guideline 476). At high dose levels thiodiglycol induced chromosomal aberrations *in vitro*, both in the presence and the absence of a metabolic activation system (study design comparable with OECD guideline 473). No clastogenic activity was detected in the mouse bone marrow micronucleus assay at oral doses up to and including 2000 mg/kg bw (OECD guideline 474). It is therefore concluded that the clastogenic effects seen *in vitro* are not expressed *in vivo*.
There are no fertility studies available. In a 90 day gavage study (see above) no effect was observed on the gonads of male and female rats dosed up to and including 5000 mg/kg bw/day.

In two gavage studies (OECD guideline 414) on the prenatal developmental toxicity in Wistar rats, the NOAEL for maternal and developmental toxicity was 400 mg/kg bw/day. Borderline effects concerning a certain type of skeletal variations (dumbbell ossification of thoracic vertebral bodies) were observed at oral doses of 1000 mg/kg bw/day which resulted also in marginal maternal toxicity.

No data are available on carcinogenicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Thiodiglycol was tested in aquatic species from all trophic levels in acute toxicity tests carried out according to protocols of standard test guidelines:

a) Fish:

Leuciscus idus: LC_{50} (96 h) > 10 000 mg/l
(static test, no mortality at concentrations up to 10 000 mg/l; BASF AG, 1987)

b) Invertebrates:

Daphnia magna: EC_{50} (48 h) > 500 mg/l
(no immobilisation at 500 mg/l; BASF AG, 1988a)

c) Algae:

Desmodesmus subspicatus: ErC_{50} (72 h) > 500 mg/l
ErC_{10} (72 h) > 500 mg/l
ErC_{90} (72 h) > 500 mg/l
(effects on growth rate; BASF AG, 1989b)

d) Microorganisms:

Activated sludge: EC_{20} (30 min) > 1000 mg/l
(inhibition of oxygen consumption rate; BASF AG, 1999b)

Pseudomonas putida: EC_{50} (17 h) > 10 000 mg/l
(inhibition of cell multiplication; BASF AG, 1988c)

Anaerobic microorganisms: EC_{50} (24 h) = 4200 mg/l
(inhibition of methane production; Sklyar et al., 1999)

All effect values are related to nominal concentrations. However, these nominal values can be considered reliable, because the test substance is freely soluble, not volatile from water and does not hydrolyze.

Based on short-term tests from three trophic levels, thiodiglycol is of low toxicity to the aquatic environment.

Thiodiglycol has not been assessed in chronic studies.

The lowest reported 50 % effective concentration is greater than the highest concentration of 500 mg/l tested in each a daphnia and an algal test. This value is used to derive a predicted no effect concentration ($PNEC_{aqua}$) of ≥ 0.5 mg/l according to the EU Technical Guidance Document (ECB, 2003). An assessment factor of 1000 is considered for this $PNEC_{aqua}$ calculation.

4.2 Terrestrial Effects

No data are available on terrestrial organisms.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

Thiodiglycol is an organic liquid of unpleasant odour with a melting point of -10 °C and a relative density of 1.1824 at 20 °C. It is miscible with water at 20 °C (pH 5-9 at 100 g/l) and the vapour pressure at this temperature is < 0.101 hPa. A Henry's law constant of $1.87 \cdot 10^{-4}$ Pa · m³/mol at 25 °C can be calculated. The partition coefficient log KOW is –0.75 as measured at 25 °C.

According to the distribution model *Mackay*, Level I, the target compartment for thiodiglycol is the hydrosphere with 99.95 %. The substance has a low potential for bio- or geoaccumulation. As shown in a guideline study according to OECD 301-A thiodiglycol can be regarded as readily biodegradable (90 - 100 % after 21 days).

Hydrolysis or photodegradation in water do not occur. For indirect photodegradation in air due reaction with OH radicals a half-life of 13.8 hours is calculated.

The aquatic effects data base meets the requirements of the SIDS package. Aquatic effects data are as follows:

fish (*Leuciscus idus*): LC_{50} (96 h) > 10 000 mg/l;

crustacea: (*Daphnia magna*) EC_{50} (48 h) > 500 mg/l;

algae (*Desmodesmus subspicatus*): ErC_{50} (72 h) > 500 mg/l.

These values indicate that thiodiglycol is of low toxicity to aquatic organisms. For microorganisms (activated sludge) an EC_{20} (30 min) of > 1000 mg/l was determined Applying an assessment factor of 1000 to the lowest available acute effect value according to the EU Technical Guidance Document, a PNECaqua of ≥ 0.5 mg/l is derived.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work due to its low hazard profile.

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I U C L I D

D a t a S e t

Existing Chemical ID:	111-48-8
CAS No.	111-48-8
EINECS Name	thiodiglycol
EC No.	203-874-3
TSCA Name	Ethanol, 2,2'-thiobis-
Molecular Formula	C4H10O2S

Producer Related Part	
Company:	BASF AG
Creation date:	17-JUL-1996
Substance Related Part	
Company:	BASF AG
Creation date:	17-JUL-1996
Memo:	master

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1.0.1 Applicant and Company Information

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

1.1.1 General Substance Information

1.1.2 Spectra

1.2 Synonyms and Tradenames

2,2'-thiobisethanol

04-FEB-2002 (69)

2,2'-thiodiethanol

04-FEB-2002 (69)

3-thiopentane-1,5-diol

06-JUN-2002 (18)

beta,beta'-dihydroxydiethyl sulfide

06-JUN-2002 (69)

beta,beta'-dihydroxyethyl sulfide

06-JUN-2002 (69)

beta-hydroxyethyl sulfide

04-FEB-2002 (69)

beta-thiodiglycol

04-FEB-2002 (69)

Bis(2-hydroxyethyl)sulfide

04-FEB-2002 (69)

Bis(beta-hydroxyethyl)sulfide

04-FEB-2002 (69)

Glyecine A

04-FEB-2002 (69)

Kromfax solvent

04-FEB-2002 (69)

sulfide, bis(2-hydroxyethyl)

04-FEB-2002 (69)

thiodiethylene glycol

06-JUN-2002 (69)

1.3 Impurities

1.4 Additives

1.5 Total Quantity

1.6.1 Labelling

1.6.2 Classification

1.6.3 Packaging

1.7 Use Pattern

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = -10 degree C

Reliability: (2) valid with restrictions
reliable Handbook
Flag: Critical study for SIDS endpoint
24-MAY-2004 (49)

Value: = -16 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (35)

Value: = -16 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (51)

Value: = -11.2 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (72)

Value: = -18 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)

Value: = -16 degree C

Reliability: (4) not assignable
Collection of data
24-MAY-2004 (77)

Value: = -10 degree C

Reliability: (4) not assignable
Collection of data
24-MAY-2004 (68)

Value: = -10 degree C

Test substance: other TS: thiodiglycol, impurities removed by destillation at 153°C (8 mmHg)

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.

14-JUN-2004 (38)

2.2 Boiling Point

Value: = 282 degree C at 1013 hPa

Reliability: (2) valid with restrictions
reliable Handbook
Flag: Critical study for SIDS endpoint
03-JAN-2005 (72)

Value: = 282 degree C at 1013 hPa

Reliability: (2) valid with restrictions
reliable Handbook
Flag: Critical study for SIDS endpoint
03-JAN-2005 (49)

Value: = 164 - 166 degree C at 27 hPa

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (73)

Value: = 168 degree C at 18.7 hPa

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (35)

Value: = 284 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (51)

Value: = 165.1 degree C at 27 hPa

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (84)

Value: = 137 degree C at 6.65 hPa

Test substance: other TS: thiodiglycol, no further data

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
14-JUN-2004 (67)

Value: = 147.5 degree C at 7.98 hPa

Test substance: other TS: thiodiglycol, impurities removed by destillation at

153°C (8 mmHg)

Result: The purified substance distills at 147.5°C (6 mmHg corresponding to 7.98 hPa), 165°C at 20 mmHg (26.6 hPa), 181.5°C at 40 mmHg (53.2 hPa).
No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
14-JUN-2004 (38)

Value: = 220 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
02-MAY-2000 (47)

Value: = 282 degree C

Reliability: (4) not assignable
Collection of data
24-MAY-2004 (68)

Value: = 283 degree C

Reliability: (4) not assignable
Collection of data
22-JUN-2004 (77)

Value: = 194 degree C at 66.5 hPa

Test substance: other TS: thiodiglycol, no further data

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
15-JUN-2004 (59)

2.3 Density

Type: relative density
Value: = 1.1824 at 20 degree C

Reliability: (2) valid with restrictions
reliable Handbook
Flag: Critical study for SIDS endpoint
03-JAN-2005 (35) (49)

Type: relative density
Value: = 1.18 at 20 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (51)

Type: relative density
Value: = 1.1847 at 20 degree C

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (72)

Type: density
Value: 1.18 g/cm³ at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)

Type: density
Value: = 1.182 g/cm³ at 20 degree C

Reliability: (4) not assignable
Collection of data
24-MAY-2004 (77)

Type: relative density
Value: = 1.185 at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
02-MAY-2000 (47)

Type: relative density
Value: = 1.1847 at 20 degree C

Test substance: other TS: thiodiglycol, no further data

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
15-JUN-2004 (59)

Type: relative density
Value: = 1.1793 at 25 degree C

Test substance: other TS: thiodiglycol, impurities removed by destillation at 153°C (8 mmHg)

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
14-JUN-2004 (38)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: < .101 hPa at 20 degree C

Reliability: (2) valid with restrictions
reliable Handbook
Flag: Critical study for SIDS endpoint
27-MAY-2004 (51)

Value: = .41 hPa at 98.7 degree C

Method: other (measured): dynamic (internal BASF standard)
Year: 1972
GLP: no
Test substance: other TS: thiodiglycol; no data on purity of the compound

Result:

temperature (°C)	vapour pressure (torr)	vapour pressure (hPa)
98.7	0.31	0.41
108.6	0.61	0.81
118.3	1.21	1.61
129.8	2.35	3.13
147.1	6.25	8.33
159.6	11.0	14.7
166.3	15.5	20.7
169.3	18.0	24.0
185.1	34.9	46.5
192.5	45.5	60.7
198.9	59.2	78.9
214.3	101.4	135.2
216.9	112.2	149.6
230.5	176.5	235.3

Reliability: (2) valid with restrictions
acceptable study, meets basic scientific principles
24-MAY-2004 (28)

Value: = .0043 hPa at 25 degree C

Remark: Reported to decompose starting at 483°K.
Test condition: Data from literature (4 different studies) plus data from Othmer and Yu (Correlating vapor pressures and vapor volumes. Ind. Eng. Chem. 60, 22 [1968]) used in regression. Coefficients are hypothetical. Min. temperature 262.95°K and max. temperature 731°K.
Reliability: (4) not assignable
Secondary literature
27-MAY-2004 (39) (40)

Value: = .0011 hPa at 20 degree C

Reliability: (4) not assignable
Collection of data
24-MAY-2004 (77)

Value: < 1 hPa at 20 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)
Value: < .0133 hPa at 20 degree C

Test substance: other TS: thiodiglycol, no further data

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
15-JUN-2004 (59)

Value: = 1.33 hPa at 42 degree C

Test substance: other TS: thiodiglycol, no further data

Remark: Interpolation of data from Bauer and Burschkies (1935; see this chapter).
Result:

Temperature in °C	Vapour pressure in mmHg	(in hPa)
42.0	1	(1.33)
96.0	5	(6.65)
128.0	10	(13.3)
165.0	20	(26.6)
210.0 (decomposes)	40	(53.2)
240.5 (decomposes)	60	(79.8)
285 (decomposes)	100	(133)

Reliability: (4) not assignable
Secondary literature
No further details available
14-JUN-2004 (79)

Value: = 7 hPa at 150 degree C

Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)

Value: = .000027 hPa

Remark: original value 0.00002 mmHg
Reliability: (4) not assignable
Secondary literature, no data about temperature.
25-MAY-2004 (61)

Test substance: other TS: Thiodiglycol, purified by destillation

Result: Vapour pressure measured at different temperatures

Temperature in °C	vapour pressure
10	0.7
15	0.7
20	0.8
25	0.8
30	0.9
35	1.0
40	1.1
45	1.3
50	1.5
55	1.7
60	1.9
65	2.1

70	2.3
75	2.6
80	3.0

No further data available; pressure presumably measured in mmHg.
Reliability: (4) not assignable
Documentation insufficient for assessment.
25-MAY-2004 (29)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -.75 at 25 degree C

Method: other (measured): test procedure according to an internal BASF standard, comparable to OECD 107
Year: 1988
GLP: no
Test substance: other TS: thiodiglycol, purity 99.70 % (GC)

Remark: multiple determination (3 * 3 determinations)

log Pow (1) = -0.75
log Pow (2) = -0.75
log Pow (3) = -0.75
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, acceptable for assessment
Flag: Critical study for SIDS endpoint
24-MAY-2004 (3)

Partition Coeff.: octanol-water
log Pow: = -.63

Method: other (measured): both phases analysed
GLP: no data

Reliability: (2) valid with restrictions
Reliable publication
24-MAY-2004 (50)

Partition Coeff.: octanol-water
log Pow: = -.452

Method: other (calculated)
GLP: no

Method: Calculation according to Rekker; computer programm pro-logP (CompuDrug Ltd.)
Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method
08-AUG-2003 (7)

2.6.1 Solubility in different media

Solubility in: Water
Descr.: miscible

```
Reliability:      (2)  valid with restrictions
                  reliable Handbook
Flag:             Critical study for SIDS endpoint
29-JAN-2004                                                    (35) (49)

Solubility in:    Water
Value:            at 20 degree C
pH       value:   = 5 - 9
         Conc.:   100 g/l at 20 degree C
Descr.:           miscible

Method:           other: pH value determined according to DIN 19268

Reliability:      (4)  not assignable
                  Manufacturer/producer data without proof
28-JUN-2004                                                    (19)

Solubility in:    Water
Value:            = 1000 g/l at 20 degree C


Reliability:      (4)  not assignable
                  Secondary literature
28-JUN-2004                                                    (86)

Solubility in:    Water
Descr.:           miscible


Reliability:      (2)  valid with restrictions
                  reliable Handbook
11-AUG-2003                                                    (72)

Solubility in:    Water
Descr.:           miscible


Reliability:      (2)  valid with restrictions
                  reliable Handbook
11-AUG-2003                                                    (51)

Solubility in:    other: alcohol
Descr.:           miscible


Reliability:      (2)  valid with restrictions
                  reliable Handbook
24-MAY-2004                                                    (35) (49)


Solubility in:    other: ether
Descr.:           slightly soluble (0.1-100 mg/L)


Reliability:      (2)  valid with restrictions
                  reliable Handbook
24-MAY-2004                                                    (35) (49)

2.6.2 Surface Tension
```

2.7 Flash Point

Value: = 165 degree C
Type: closed cup

Method: other: DIN EN 22719 (method according to Pensky-Martens)
GLP: no
Test substance: other TS: thiodiglycol, no further data

Reliability: (2) valid with restrictions
Meets national standard methods with acceptable restrictions.
Restrictions: No GLP study. No data on the TS.
24-MAY-2004 (23)

Value: = 110 degree C

Reliability: (2) valid with restrictions
reliable Handbook
22-JUN-2004 (51)

Value: = 160 degree C
Type: open cup

Reliability: (2) valid with restrictions
reliable Handbook
22-JUN-2004 (35)

Value: = 160 degree C
Type: open cup

Reliability: (2) valid with restrictions
reliable Handbook
22-JUN-2004 (72)

Value: = 174 degree C
Type: closed cup

Method: other: Pensky-Martens
GLP: no
Test substance: other TS: thiodiglycol, no further data

Reliability: (2) valid with restrictions
Comparable to national guideline study with acceptable restrictions.
Restrictions: No GLP study. No data on the TS.
22-JUN-2004 (24)

Value: = 160 degree C

Method: other: DIN 51 758
Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)

Value: = 160 degree C
Reliability: (4) not assignable
Collection of data
21-JUN-2004 (77)

Value: = 160 degree C

Test substance: other TS: thiodiglycol, no further data

Remark: No further details.
Reliability: (4) not assignable
Documentation insufficient for assessment.
15-JUN-2004 (59)

2.8 Auto Flammability

Value: = 245 degree C

Method: other: DIN 51794
Test substance: other TS: thiodiglycol, no further data

Remark: Ignition temperature
Reliability: (2) valid with restrictions
Meets national standard methods with acceptable restrictions.
Restrictions: No GLP study. No data on the TS.
10-MAR-2004 (24)

Value: = 245 degree C

Remark: Ignition temperature
Reliability: (2) valid with restrictions
reliable Handbook
11-AUG-2003 (51)

Value: = 245 degree C

Remark: Ignition temperature
Reliability: (4) not assignable
Collection of data
21-JUN-2004 (77)

Value: 260 degree C

Method: other: DIN 51 794

Remark: Ignition temperature
Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (21)

2.9 Flammability

2.10 Explosive Properties

Result: not explosive

Remark: because of chemical structure

Reliability: (2) valid with restrictions
Expert judgement
24-MAY-2004 (22)

Result: other: Explosion limits 1.2-5.2 vol.%

Reliability: (2) valid with restrictions
reliable Handbook
24-MAY-2004 (51)

Result: other: Explosion limits 1.2-5.2 vol.%

Reliability: (4) not assignable
Manufacturer/producer data without proof
24-MAY-2004 (20) (21)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: because of chemical structure
Reliability: (2) valid with restrictions
Expert judgement
02-MAY-2000 (22)

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Memo: Refractive index

Result: nD20 = 1.519
Reliability: (2) valid with restrictions
reliable Handbook
29-JAN-2004 (35)

Memo: Refractive index

Result: nD20 = 1.5215
Reliability: (4) not assignable
Collection of data
24-MAY-2004 (77)

3.1.1 Photodegradation

Type: air
Light source: other
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .000000000028 cm³/(molecule * sec)
Degradation: = 50 % after 13.8 hour(s)

Method: other (calculated): with AOP Program v1.90
Year: 2004
Test substance: other TS: thiodiglycol, no further data

Remark: Calculation based on an overall OH rate constant of 0.5E+6 OH radicals/cm³ for a 24 h day.
Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method.
Flag: Critical study for SIDS endpoint
29-JUN-2004 (25)

Type: water
Light source: Sunlight

Method: other (measured): EPA 600/3-82-022 (1982)
Year: 1998
GLP: no
Test substance: other TS: thiodiglycol, purity >= 99%

Result: No detectable photolysis of the parent compounds; no additional compounds detected; statistical evaluation of triplicate studies indicated that the mean sample concentration is within the 95% confidence limit.

Photolysis after 14 d exposure

Sample	Concentration in mg/l		
	Initial	Dark control	Sunlight irradiated
TS	50	48.9	48.7
	20	19.4	19.3

Test condition: Aqueous samples of the TS prepared in borosilicate glass test tubes (no further details); concentration 20 or 50 mg/l; triplicate samples; samples exposed to rooftop sunlight in late spring weather (mostly sunny with little precipitation); identical control samples covered with aluminium foil and placed alongside the experimental samples; samples taken for analysis after 4, 9, 14 d of irradiation.
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions.
Restrictions: No GLP study.
Flag: Critical study for SIDS endpoint
28-JUN-2004 (56)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH4: hour(s)
t1/2 pH7: hour(s)
t1/2 pH 11 : hour(s)

Method: other: EPA 600/3-82-022 (1982)
Year: 1998
GLP: no
Test substance: other TS: thiodiglycol, purity >= 99%

Result: Hydrolysis of the TS

sample concentration in mg/l after 96h				
initial	control	pH4	pH7	ph11
50	49.8	49.4	49.7	50.1
20	not analysed	19.7	19.7	19.8

Nearly 100% recovery of the parent compounds after 48 and 96 h; no significant deviation; no additional compounds detected.
Conclusion: hydrolysis has no effect on the fate of the TS in environmental media.

Test condition: TEST TYPE: Hydrolysis in water
- Test system: buffers prepared with final pH 4, 7, or 11; addition of the TS; solution in PPCO centrifuge tubes; triplicate samples; no further data available including data on the temperature (but presumably 20-25 °C according to EPA methods).
- Concentration of test substance: 20 or 50 mg/l

DURATION:
- samples analysed after 48 and 96 h

REFERENCE SUBSTANCE: no
CONTROLS:
- 3 samples prepared 96 h after initiation of hydrolysis

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions.
Restrictions: No GLP study.
Flag: Critical study for SIDS endpoint
03-JAN-2005 (56)

3.1.3 Stability in Soil

Type: laboratory

Method: other: see test condition
Year: 1998
GLP: no
Test substance: other TS: thiodiglycol, purity >= 99%

Result: The amount of TS recovered in the aqueous phase was 99-100% in 5 out of 6 soils; the maximum amount of TS that can be absorbed (Qmax) was less than 10 mg/kg.
In the 6th soil (TS1) the TS partly degraded to thiodiglycolic acid.

Sorption of the degradation product thiodiglycolic acid varied: Qmax in DPG reached 427 mg/kg, all other soils 19.9 to 36.6 mg/kg. In DPG high amount of manganes oxid (0.2%) and higher surface area. Effect of manganes oxid confirmed in further experiments (sorbed also TS at low pH value).

Conclusion: TS potentially very mobile in environments; the degradation product is potentially less mobile.
Test condition: Sorption of the TS onto 6 different soils determined.

Soil	sand (%)	silt (%)	clay (%)	soil pH	Organic matter (%)	surface area (m2/g)
DPG	53	14	33	8.5	0.5	39.2
FMC	43	21	36	4.7	0.4	14.6
RMA	66	16	18	8.4	0.1	16.0
TS1	88	4	8	6.6	0.4	1.72
TS2	46	28	26	7.9	2.6	10.0
WSL	74	16	10	4.5	1.3	1.9

20 ml TS solution (1-50 mg TS/l) added to a tube containing 1 g soil; soil to solution ratio has negligible effects on analysis, sorption and transformation (no further data); suspension shaken horizontally (50 strokes/min) in the dark for 24 h, constant temperature 25+/-0.2°C; aqueous phase analysed (TS concentration, detection limit 0.5 mg/l) after filtration; solid phase concentration calculated by mass balance;
sorption isotherms fit to Langmuir isotherm model;
triplicate experiments.

Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented and acceptable for assessment.
Restrictions: No GLP or guideline study.

Flag: Critical study for SIDS endpoint

28-JUN-2004 (56)

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: Calculation according Mackay, Level I
Year: 2004

Result: air: 0.04%; water: 99.95%; soil: 0.0014%; sediment: 0.0014%; susp. sediment: 9.13E-06%; fish 8.89E-07%; aerosol 5.07E-07%

Test condition: Calculation using the Level I V 2.11 Model.
Calculation basis:
molecular mass 122.18 g/mol
temperature 25°C
Log Kow -0.75
water solubility 1.0E+06 g/m3
Henry's Law constant 1.23E-03 Pa x m3/mol
vapour pressure 10.1 Pa
melting point -10°C

PHASE PROPERTIES

	Air	Water	Soil	Sedmt.	Susp. Sedmt.	Fish	Aerosol
VOLUME (m3)	6.0E+9	7.0E+6	45000	21000	35.0	7.00	0.120

Density (kg/m3)	1.185	1000	1500	1300	1500	1000	1500
Organic Carbon (g/g)	-	-	0.02	0.05	0.167	-	-
Fish lipid (g/g)						0.05	

Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method.
Flag: Critical study for SIDS endpoint
28-JUN-2004 (27)

Media: water - air
Method: other (calculation): with HENRY (v3.10) Program
Year: 2004

Result: 1) Henry's Law constant at 25°C = 1.85E-9 atm x m3/mole = 1.87E-6 hPa x m3/mole (Bond estimation method).

2) Henry's Law Constant at 25°C = 2.74E-13 atm x m3/mole = 2.77E-10 hPa x m3/mole (Group estimation method).
Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method.
Flag: Critical study for SIDS endpoint
28-JUN-2004 (25)

Media: water - soil
Method: other (calculation): according to the program PCKOCWIN v1.66
Year: 2002

Result: Koc = 1; log Koc = 0
"Very low" potential for geoaccumulation (Blume scale).
Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method.
Flag: Critical study for SIDS endpoint
29-JUN-2004 (26)

Media: water - soil
Method: other (calculation)

Result: Log Koc = 0.96
No further data.
Reliability: (4) not assignable
Secondary literature
29-JUN-2004 (61)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 49 mg/l related to Test substance
20 mg/l related to DOC (Dissolved Organic Carbon)
Contact time: 21 day(s)
Degradation: 90 - 100 % after 21 day(s)
Result: readily biodegradable
Kinetic: 7 day(s) = 9 %

10 day(s) = 95 %
14 day(s) = 92 %
20 day(s) = 94 %
21 day(s) = 98 %

Control Subst.: Aniline
Kinetic: 3 day(s) = 72 %
5 day(s) = 97 %

Method: other: OECD Guide-line 301 A (new version); 1993
Year: 1999
GLP: yes
Test substance: other TS: thiodiglycol, data on purity documented in: BASF AG, Report of the Analytical Laboratory No. 99L00159

Method: Also according to Directive 92/69/EEC (1992) and to ISO 7827 (1994)
Result: Duration of the adaptation phase: 7 days.
Duration of the degradation phase: 3 days.
Degradation of the test substance at the end of the 10-day window: 90-100% DOC.
Degradation degree of the test substance at the end of the test: 90-100% DOC.
Physico-chemical (abiotic) elimination of the test substance: <10% DOC at the end of the test.
Elimination of the test substance by adsorption: <10% DOC after 5 days.
Degradation of the reference substance (aniline) after 14 days: 90-100% DOC.
Degradation in the inhibition control after 14 days: 90-100% DOC.

The validity criteria as laid down in OECD TG 301 were fulfilled.
Test condition: INOCULUM
- activated sludge from laboratory waste water plants fed with municipal sewage.

TEST CONDITIONS
- TS stock solution 775.8 mg/l
- total test volume 1000 ml [919 ml deionized water, 13 ml inorganic medium (A-D, no further details), 63 ml stock solution of the TS, 5 ml inoculum (6 g/l dry matter)]
- pH value (before adding the inoculum) before and after correction: 7.8 / 7.4 (in all samples)

REFERENCE SUBSTANCE

- aniline (20 mg/l nominal, DOC), 1 sample
Conclusion: The test substance is in this test readily biodegradable according to OECD criteria.
Reliability: (1) valid without restriction
Guideline study with GLP
Flag: Critical study for SIDS endpoint
29-JUN-2004 (5)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Degradation: ca. 0 - 30 % after 28 day(s)

Method: other: OECD Guide-line 301 C, 1974

Year: 1992
GLP: no
Test substance: other TS: thiodiglycol, no further data

Test condition: Concentration of activated sludge: 30 mg/l
Reliability: (2) valid with restrictions
Guideline study without detailed documentation.
Flag: Critical study for SIDS endpoint
29-JUN-2004 (60)

Type: anaerobic
Inoculum: anaerobic sludge
Concentration: 1 g/l related to Test substance
Degradation: = 42 % after 185 day(s)
Result: other: slowly biodegraded under anaerobic conditions

Method: other: see test condition
Year: 1999
GLP: no
Test substance: other TS: thiodiglycol, no further data

Result: The TS was slowly biodegraded; Lag period 52 d.
In further experiments the addition of cosubstrates (1st exp.: TS 0.25 g of COD/l plus glucose 0.25 g of COD/l; 2nd exp.: TS 0.25 g of COD/L plus volatile fatty acids 0.25 g of COD/l) resulted in accelerated biodegradation of the TS in the presence of the cosubstrates:
1st exp. 48% degradation within 25 d incubation without lag phase and 2nd exp. 100% within 32 d incubation with a short (if any) lag period.
Test condition: INOCULUM
Sludge from the laboratory upflow anaerobic sludge blanket reactor treating liquid hen manure fraction was used (methanogenic activity ca. 0.4 g COD).
BASAL MEDIUM (pH 7.2)
280 mg/l NH_4Cl; 10 mg/l $CaCl_2 \times 2H_2O$; 250 mg/l K_2HPO_4; 100 mg/l $MgSO_4 \times 7H_2O$; 1 mg/l EDTA; 0.2 mg/l resazurin; 5 g/l $NaHCO_3$; 0.05 mg/l H_3BO_3; 2 mg/l $FeCl_3 \times 4H_2O$; 0.05 mg/l $ZnCl_2$; 0.05 mg/l $MnCl_2 \times 4H_2O$; 0.03 mg/l $CuCl_2 \times 2H_2O$; 2 mg/l $AlCl_3 \times 6H_2O$; 0.05 mg/l $NiCl_2 \times 6H_2O$; 0.1 mg/l $Na_2SeO_3 \times 5H_2O$;
Sludge (1 ml/flask, final concentration 1 g of volatile suspended solids per l) plus basal medium (final volume of a liquid phase was 25 ml) in 120 ml glass flasks flushed with argon and sealed, temperature 30 degree C, no stirring; incubated overnight to deplete organic compounds introduced with sludge;
TS used as sole carbon source (concentration 1 g/l), addition after a 24 h starvation; CH_4, H_2, and CO_2 in the gas phase and volatile fatty acids and alcohols in the liquid phase monitored.
Further exp. with addition of cosubstrates and similar experimental design (see results).
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented.
Restrictions: No guideline or GLP study. No data about the TS.
Flag: Critical study for SIDS endpoint
29-JUN-2004 (75)

Type: aerobic
Inoculum: other bacteria: Alcaligenes xylosoxidans (SH91)

Method: other: see freetext
Year: 1996
GLP: no
Test substance: other TS: thiodiglycol, no further data

Result: 40 mM TS:
TS concentration decreased rapidly to 10 mM during the exponential growth phase (70-80h) and continued to decrease during the stationary phase, but at slower rate (5 mg/l TS after 120h).
50 mM TS: similar results (13 mM TS after 250h).
100 mM TS:
similar results but in the stationary phase higher TS concentration (78 mM after 95 h; end of experiment).
Test condition: INOCULUM/TEST ORGANISM
- Species/strain: gram negative bacteria that utilizes the TS as its sole carbon source
TEST SYSTEM
- Culturing apparatus: batch fermentations performed in a 5-L BioFlow III fermenter
INITIAL TEST SUBSTANCE CONCENTRATION: 40, 50 or 100 mg/l
DURATION OF THE TEST: up to 250h
ANALYTICAL PARAMETER: optical density (growth rate) and TS concentration
SAMPLING: 5 ml samples from the fermenter
TEST CONDITIONS
- Test temperature: 30°C
- pH value: 8.0
- Aeration rate: 2.5 l/min
- agitation: 250 rpm

CONTROLS: no data
REFERENCE SUBSTANCE: no data

Reliability: (2) valid with restrictions
Meets generally accepted scientific standard.
Restrictions: No guideline or GLP study. No data about the TS.
29-JUN-2004 (63)

Type: aerobic
Inoculum: other: Gluconobacter suboxydans

Remark: Thiodiethylene glycol was oxidized slowly by resting cells of Gluconobacter suboxydans ATCC 621. No biodegradation degree given; end product(s) not determined.
Reliability: (4) not assignable
Documentation insufficient for assessment, only short abstract.
29-JUN-2004 (41)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

BCF: = 3.16

Method: other: calculation according to Bcfwin v2.15

Result: Based on a measured log Kow of -0.75 (see chapter 2.5), the estimated logBCF is 0.50 (BCF = 3.162).
Reliability: (2) valid with restrictions
Data obtained by a recognized calculation method
Flag: Critical study for SIDS endpoint
29-JUN-2004 (30)

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type:	static
Species:	Leuciscus idus (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: no
NOEC:	= 10000 -
LC50:	> 10000 -
LC100:	> 10000 -
Method:	other: DIN38412, part L15; 1982
Year:	1987
GLP:	no
Test substance:	other TS: thiodiglycol, purity 97.5%

Result:
RESULTS: EXPOSED
- no mortality at any dose level
- LC50 (1h, 4h, 24h, 48h, 72h, 96h) > 10000 mg/l (1% significance level)

- symptoms: no symptoms detectable

RESULTS: CONTROL
- No animals showed adverse effects in negative control
- Positive control conducted with Chloroacetamide, LC50 (48h) = 24 mg/l (normal sensitivity)

Test condition:
DILUTION WATER
according to DIN 38412, part 11 (Oct. 1982); prepared from fully demineralized tap water, conductivity 10 µMHO, resalted.

Test water ready for use: total hardness 2.5 mmol/l, acid capacity 0.8 mmol/l, ratio Ca ions/Mg ions =4:1, ratio Na+/K+ = 10:1, pH ca. 8.0

TEST ANIMALS
- Golden Orfe (Leuciscus idus L.)
- supplier: Paul Eggers, Hohenwestedt, Germany
- mean length 5.7 cm, mean body weight 2.8 g

TEST SYSTEM
- 3 days adaptation to test water and test temperature
- withdrawal of food 1 day before exposure
- nominal concentrations: 0, 5000, 10000 mg/l; TS added to the test water without any pretreatment
- Number of animals per test concentration: 10
- photoperiod 16 h light and 8 h darkness
- Loading: 2.8 g fish/l test water, test volume 10 l
- Test temperature: 20-21 degree C during exposure in all groups, measured after 1, 24, 48, 72, 96 h
- pH 7.7-8.0 during exposure in all groups, measured after 1, 24, 48, 72, 96 h
- Oxygen content during exposure: 7.4-8.7 mg/l in all groups, measured after 1, 24, 48, 72, 96 h

- Stability of the test substance solution: assumed to be stable
- Test parameter: mortality and symptoms recorded after 1, 4, 24, 48, 72 and 96 h
- positive control with chloroacetamide; LC50 determined

ca. 3 weeks before the test

STATISTICS
- Determination or calculation of median lethal concentration; the probit analysis was used (Finney, 1971)

Reliability: (2) valid with restrictions
Meets national standard methods with acceptable restrictions.
Restrictions: No GLP study. No analytical monitoring.
Flag: Critical study for SIDS endpoint
10-MAR-2005 (15)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: = 500 -
EC50: > 500 -
EC100: > 500 -

Method: other: directive 79/831/EEC, C.2; 1984
Year: 1988
GLP: no
Test substance: other TS: thiodiglycol, purity > 99%

Method: comparable to OECD 202
Result: RESULTS: EXPOSED
- exposure time 3h, 6h, 24h, 48h:
  EC0 = 500 mg/l
  EC50 > 500 mg/l
  EC100 > 500 mg/l

  2 out of 20 animals immobilized at 250 mg/l after 24 and 48h; no further effects.

RESULTS CONTROL:
valid negative control (immobility 0% after 48 h)

Test condition: TEST ORGANISMS
- Strain: Daphnia magna Straus.
- Source/supplier: derived 1978 from a culture received from the Institut National de Recherche Chimique Apliquee, France
- Age: 2-24 hours
- Feeding: yeast and green algae (no data about feeding during exposure)

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- stock solution 500 mg TS/l
- stock solution diluted to the below mentioned concentrations with test medium
- prepared nominal concentrations:
  control, 62.5, 125, 250, 500 mg/l

TEST MEDIUM (aerated)
- total hardness: 2.7+-0.5 mmol/l
- Ka to pH 4.3: 0.80+-0.1 mmol/l
- ratio Ca:Mg: 4 to 1
- ratio Na:K: 10 to 1
- conductivity: 550-650 µSiemens/cm

- pH value: 7.7-8.3

TEST SYSTEM
- Number of replicates (individuals/vessel): 4 (5 animals)
- test volume 10 ml (no renewal)
- Test temperature: 292.0-294.0 °K
- Dissolved oxygen: 8.45-9.65 mg/l (start of exposure)
  7.91-8.81 mg/l (after 48h)
- pH: 8.08-8.22 (start of exposure), 7.78-7.99 (after 48h)
- Stability of the test substance solutions: assumed to be stable
- mortality/immobility scored 0, 3, 6, 24, 48 h after start of experiment
- negative control (dilution water)

MONITORING OF TEST SUBSTANCE CONCENTRATION:
-Test performed without concentration control analysis.

STATISTICS:
-no data about methods used for calculation

Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions.
Restrictions: No GLP study; no analytical monitoring
Flag: Critical study for SIDS endpoint
10-MAR-2005 (8)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: other algae: Scenedesmus subspicatus SAG 86.81; new name: Desmodesmus subspicatus
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no
EC10: > 500 -
EC50: > 500 -
EC90 : > 500 -

Method: other: comparable to DIN 38412, part 9
Year: 1989
GLP: no
Test substance: other TS: thiodiglycol, no further data

Remark: No further data available
Result: CONTROL
- Valid negative control; valid results in uninoculated samples

INHIBITION AFTER 0h
- no effect, in treatment groups 93-102% of control value

INHIBITION AFTER 24h
- in treatment groups lower growth rate than in control (except dose 31.25 mg/l), but no dose dependent effect (low dose 81% of control and high dose 86% of control); presumably cultures were not shaken before removal of the sample for measurement)

INHIBITION AFTER 48h
- EC50 (48h) > 500 mg/l
- EC90 (48h) > 500 mg/l

RESULTS AFTER 72h
Growth rate calculated from data on chlorophyll fluorescence obtained after 0 and 72 h exposure:

Con.	0	3.91	7.81	15.63	31.25
0h	45	47	47	43	46
72h	2299	2325	2276	2306	2103
GR	1,311189	1,300442	1,293342	1,327356	1,274159
%C	100	99.18	98.64	101.23	97.18

Con.	62.5	125	250	500
0h	46	45	45	45
72h	2183	2144	2027	1783
GR	1,286604	1,287922	1,269216	1,226463
%C	98,12	98,23	96,80	93,54

Con.: concentration given in mg/l
GR: growth rate
%C: per cent of control

Test condition: STOCK SOLUTION AND DILUTION

- nominal concentrations: control, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, 500 mg/l (no further details reported)

TEST MEDIUM
- prepared according to OECD guideline

PERFORMANCE OF THE TEST
- 4 cultures per concentration and exposure time (inoculated; 2 cultures in uninoculated tests); no renewal
- test temperature 293°K;
- pH values in uninoculated samples 8.7 (all concentrations including control; stock solution pH 8.3) at start of experiments and pH 8.0-8.2 after 72 h;
  in inoculated tests pH 9.0-9.5 after 72 h;
- oxygen: no data
- test parameter:
  in vivo chlorophyll fluorescence after 0, 24, 48, 72 h;
- Test volume 10 ml
- Stability of the TS solution: assumed to be stable
- Illumination: no data

STATISTICS
- EC values calculated (no further details);
- standard deviation calculated from 4 individual samples (inoculated)

Reliability: (2) valid with restrictions
Comparable to national guideline study with acceptable restrictions.
Restrictions: No GLP study. No data about the TS. No analytical monitoring.

Flag: Critical study for SIDS endpoint

10-MAR-2005 (4)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic

```
Species:           activated sludge, domestic
Exposure period:   30 minute(s)
Unit:              mg/l                    Analytical monitoring: no
EC20 :             > 1000 -

Method:            other: OECD Guide-line 209, 1993
  Year:            1999
   GLP:            yes
Test substance:    other TS: data on purity documented in: BASF AG, Report of the
                   Analytical Laboratory ZAX No. 99L00159

Method:            Test according to directive 88/302/EEC (1987), corresponds
                   to OECD guideline 209 (1993) and ISO standard 8192-1986 (E)
                   (Method B)
Result:            RESULTS CONTROL
                   - deviation of blank control < 15% (valid)
                   - valid positive control (3,5-dichlorphenol)

                   RESULTS EXPOSED
                   - no significant inhibition of respiration measured up to
                     the tested concentration of 1000 mg/l (nominal)
                   - reduction of oxygen consumption rate at 1000 mg/l: 18%
                     compared with blank control
Test condition:    TEST ORGANISMS
                   - activated sludge from laboratory wastewater plants
                     treating municipal sewage

                   TEST CONDITIONS
                   - inoculum concentration 1 g/l dry substance
                   - OECD medium
                   - oxygen concentration during aeration > 2.5 mg/l and
                     immediately before measurement > 6.5 mg/l
                   - pH values before adding the inoculum (after correction)
                     7.1-7.3; after 30 min incubation pH 7.2 (TS)
                   - tested concentrations: control, 1000 mg/l (nominal)
                   - tested parameter: inhibition of oxygen consumption rate
                   - positive control 5-30 mg/l 3,5-dichlorphenol
Reliability:       (1)  valid without restriction
                   GLP guideline study
Flag:              Critical study for SIDS endpoint
18-MAY-2004                                                              (6)


Type:              aquatic
Species:           other bacteria: Pseudomonas putida DSM 50026
Exposure period:   17 hour(s)
Unit:              mg/l                    Analytical monitoring: no
EC10:              > 10000 -
EC50:              > 10000 -
EC90 :             > 10000 -

Method:            other: DIN 38412, part 8 (Draft); Inhibition of cell
                   multiplication
  Year:            1986
   GLP:            no
Test substance:    other TS: thiodiglycol, no further data

Result:            CONTROL
                   - valid negative control
                   - valid results in uninoculated samples
Test condition:    TEST ORGANISMS
```

- The test strain of Pseudomonas putida DSM 50026 as obtained in regular intervals from DSM.
- growth period: 7 +/- 1 hour

PRECULTURE & STOCK SOLUTION
- Preculture in 100 ml volume; medium according to DIN 38412, part 8; temperature 297+-1 °K
- stock solution of the TS: 12500 mg/l

TEST CULTURE
- 4 inoculated parallels, 1 uninoculated per concentration
- test volume 10 ml
- temperature 293°K
- nominal TS concentrations tested: 0, 156, 312, 625, 1250, 2500, 5000, 7500, 10000 mg/l
- pH values 7.0-7.1 at the start of exposure in uninoculated samples, after 17 h pH 7.0 (all concentrations); in inoculated samples after 17 h pH 4.8-4.9, control pH 4.8
- measured parameter: optical density at 436 nm

Year of the study: 1988

Reliability: (2) valid with restrictions
Meets national standard methods with acceptable restrictions.
Restrictions: No GLP study, no data about the TS, no analytical monitoring.

Flag: Critical study for SIDS endpoint

02-FEB-2004 (16)

Type: aquatic
Species: anaerobic microorganisms
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 4200 -

Method: other: see freetext
GLP: no
Test substance: other TS: thiodiglycol, no further data

Result: Inhibition of methane production.
Test condition: INOCULUM
Sludge from the laboratory upflow anaerobic sludge blanket reactor treating liquid hen manure fraction was used (methanogenic activity ca. 0.4 g COD).

BASAL MEDIUM (pH 7.2)
280 mg/l NH_4Cl; 10 mg/l $CaCl_2 \times 2H_2O$; 250 mg/l K_2HPO_4; 100 mg/l $MgSO_4 \times 7H_2O$; 1 mg/l EDTA; 0.2 mg/l resazurin; 5 g/l $NaHCO_3$; 0.05 mg/l H_3BO_3; 2 mg/l $FeCl_3 \times 4H_2O$; 0.05 mg/l $ZnCl_2$; 0.05 mg/l $MnCl_2 \times 4H_2O$; 0.03 mg/l $CuCl_2 \times 2H_2O$; 2 mg/l $AlCl_3 \times 6H_2O$; 0.05 mg/l $NiCl_2 \times 6H_2O$; 0.1 mg/l $Na_2SeO_3 \times 5H_2O$;

TEST CONDITION
Sludge (1 ml/flask, final concentration 1 g of volatile suspended solids per l) plus basal medium (final volume of a liquid phase was 25 ml) in 120 ml glass flasks flushed with argon and sealed, temperature 30 degree C, no stirring; incubated overnight to deplete organic compounds introduced with sludge; after 24 h TS added to the flasks (0, 0.5, 1, 2, 5, 7.5, 10 g/l); incubation for 24 h;
then addition of 1 ml acetate solution (2 g COD/l); methane production monitored; IC50 estimated from concentration dependent specific aceticlastic activities; triplicate

experiments.

Year of the study: 1999
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented and acceptable for assessment.
Restrictions: No guideline or GLP study. No data about the TS or analytical monitoring.
Flag: Critical study for SIDS endpoint
10-MAR-2005 (75)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

Type: other: biotransformation by microorganisms

Remark: No further data available, abstract.
Result: The metabolites [(2-hydroxyethyl)thio]acetic acid and thiodiglycolic acid were identified.
Test condition: Degradation by gram negative Alcaligenes xylosoxydans ssp. (SH91) investigated; microorganisms isolated from wastewater; concentration up to 60 mM TS; batch fermentation;
13-FEB-2002 (57)

Type: other: biotransformation in soil suspension

Result: Soils showed a decrease in aqueous thiodiglycol, an increase in [(2-hydroxyethyl)thio]acetic acid followed by an decrease and an increase in thiodiglycolic acid;
differences in transformation kinetics of the TS between the investigated soils: transformation started immediately (soil amended with fertilizers), transformation started after a lag period (48, 90, or 200h; no fertilizers) or no transformation occurred (soil with high pH);
kinetic data fit the zero-order rate model, rate coefficient for TS degradation k=6.26 x 10E-6 mol/l/h (most active soil) or k= 9.41 x 10E-7 mol/l/h (soil with a lag period of 90h).
Biological toxins like sodium azide and mercuric chloride prevented degradation significantly.
Test condition: Transformation kinetics determined in soil suspensions of 6 different soils; 1 g soil suspended in 20 ml solution containing 5-40 mg TS/l (3 concentrations tested); samples (in duplicate) shaken for desired duration (1, 2, 3, 6, 12, 24h and then every 12-24h for the next 2 weeks); aqueous phase analysed.
Test substance: thiodiglycol, purity >= 99%
10-MAR-2005 (56)

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Metabolism
Species:	rat
No. of animals, males:	16
Doses, males:	see freetext TC
Doses, females:	not tested
Route of administration:	i.p.
Method:	other: see freetext
Year:	1993
GLP:	no
Test substance:	other TS

Result: 1) Approximately 60% of the administered dose was excreted in the urine within 6 h and ca. 90% of the administered within 24 h, independently of the amount applied; after 8 days virtually all of the dose had been excreted via urine (93-99%, no dose dependency); no significant excretion in the faeces.

2) Four metabolites were isolated by HPLC and identified by MS (structural assignment by comparison with authentic synthetic standards).
Thiodiglycol sulphoxide was the major metabolite accounting for ca. 90% of the excreted radioactivity following the i.p. injection of 13C4,35S-thiodigylcol;
S-(2-hydroxyethylthio)acetic acid was present in significant quantities up to 10%; thiogylcol sulphone and S-(2-hydroxyethylsulphinyl)acetic acid were identified as minor metabolites. Analysis for thiodigycol by GC-MS indicated that ca. 0.5-1.0% of the administered dose was excreted unmetabolized.

Authors discussion of putative pathways: TS is mainly oxidized at the sulphur atom resulting in thiodiglycol sulphoxide and (after further oxidation) the minor metabolites thiodiglycol sulphone and S-(2-hydroxyethylsulphinyl)acetic acid (further oxidation at the carbon atom) were observed;
another possible pathway is the oxidation of the TS at an carbon atom resulting in S-(2-hydroxyethylthio)acetic acid and (after further oxidation at the sulphur atom) also S-(2-hydroxyethylsulphinyl)acetic acid.

Test condition: The metabolism of the TS studied in male Porton rats; n=4 per group; samples of pooled rat urine investigated; samples analysed 6h, 24h and then daily up to 8 days after injection.

1) The 35S-radiolabeled TS administered i.p. at doses of 0.2, 1, 5, and 328 umol/kg (ca. 24.2, 122.2, 610.9 ug/kg bw and 40 mg/kg bw) for the determination of the excretion profile.

2) The high dose group of rats in 1) was injected i.p. with 328 umol/kg (40 mg/kg) of 13C4,35S-thiodiglycol to isolate and identify the metabolites.

Test substance: 1) 35S-labelled thiodigylcol, activity ca. 6 mCi/mM
2) doubly-labelled thiodiglycol (35S & 13C4; ratio 1:1)

Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions.

Restrictions: No GLP study.
Flag: Critical study for SIDS endpoint
18-MAY-2004 (33)

In Vitro/in vivo: In vitro
Type: Toxicokinetics

Method: other: see freetext
Year: 2000
Test substance: other TS: thiodiglycol, no further data

Result: No or only a low specific activity (12 nmol/min/mg) was measured with a class II and III ADH isoenzymes. The specific activity of class I ADH isoenzymes varied between 79 and 647 nmol/min/mg. The highest activity was observed with a class IV ADH: 1630 mmol/min/mg.
Class I and IV ADH isoenzymes were inhibited by addition of 1 mM pyrazole (inhibition varied between 56 and 100%).
Test condition: Oxidation of thiodiglycol by different purified alcohol dehydrogenases (ADH) was studied; purified ADH isoenzymes of class I to IV were tested; thiodiglycol oxidation by ADH at saturating concentrations of thiodiglycol was determined at 30°C by measuring the change in absorbance at 340 nm.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented and acceptable for assessment.
Restrictions: Limited to the specific activity of alcohol dehydrogenase in vitro.
18-MAY-2004 (42)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: other: approximate lethal dose (ALD)
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 16
Vehicle: other: neat test substance
Doses: 8 doses: 579, 869, 1304, 1956, 2933, 4400, 6600, 9900 mg/kg
Value: > 9900 mg/kg bw

Method: other: Toxicology Programs SOP 17.97, Approximate lethal dose procedures, USACHPPM, 1997
Year: 1997
GLP: yes
Test substance: other TS: purity>=95%

Result: No mortality; only the male rat receiving 9900 mg/kg bw was slightly lethargic 1 h after gavage, but recovered within 4 hours. No other effects were noted.
Test condition: Determination of the approximate lethal dose; 1 rat/sex/dose; 14 days post exposure observation period; rats observed daily; body weight determined at initiation and at days 7 and 14 post-dosing; necropsy performed.
Reliability: (1) valid without restriction

```
                GLP guideline study
Flag:           Critical study for SIDS endpoint
18-MAY-2004                                                    (1)

Type:           LD50
Species:        rat
Value:          ca. 11800 mg/kg bw

Method:         other: BASF-Test
  Year:         1966
   GLP:         no
Test substance: other TS: thiodiglycol, no further data

Remark:         No further data available
Result:         Symptoms: dyspnoe, dizziness
                Necropsy: several rats with pancreas bleeding
Test condition: Application of a 30-40% watery solution; post exposure
                observation period 7 d.
Reliability:    (4)  not assignable
                Documentation insufficient for assessment.
Flag:           Critical study for SIDS endpoint
07-MAR-2005                                                    (14)

Type:           LD50
Species:        rat
Strain:         Wistar
Sex:            male
Vehicle:        water
Value:          = 6610 mg/kg bw

Method:         other: see freetext
  Year:         1941
   GLP:         no
Test substance: other TS: thiodiglycol, no further data

Remark:         No further data available
Result:         LD50 range of 95% probability 6100-7160 mg/kg bw, slope
                15.19.
Test condition: 10 male rats (weighing 90-120 g) per dose received a max.
                concentration of 10% TS in water; enough dose levels
                administered to include those at which no animal died and
                those at which all rats died; post exposure observation
                period 14 days; autopsy of rats, deaths due to infection not
                included in the calculation; data calculated by the method
                of probits (Bliss, C.I., Ann. Appl. Biol. 22, 134-167
                (1935)).
Reliability:    (4)  not assignable
                Documentation insufficient for assessment.
07-MAR-2005                                                    (76)

Type:           LD50
Species:        guinea pig
Strain:         no data
Sex:            male/female
Vehicle:        water
Value:          = 3960 mg/kg bw

Method:         other: see freetext
  Year:         1941
   GLP:         no
Test substance: other TS: thiodiglycol, no further data
```

Remark: No further data available
Result: LD50 range of 95% probability 3440-4560 mg/kg bw, slope 8.92.
Test condition: 10 male or female animals (weighing 250-300 g) per dose received a max. concentration of 10% TS in water; enough dose levels administered to include those at which no animal died and those at which all guinea pigs died; post exposure observation period 14 days; autopsy of guinea pigs, deaths due to infection not included in the calculation; data calculated by the method of probits (Bliss, C.I., Ann. Appl. Biol. 22, 134-167 (1935)).
Reliability: (4) not assignable
Documentation insufficient for assessment.
07-MAR-2005 (76)

5.1.2 Acute Inhalation Toxicity

Type: other: Inhalation hazard test
Species: rat
Strain: no data
Sex: male/female
No. of Animals: 12
Exposure time: 8 hour(s)

Method: other: BASF-Test, see freetext
Year: 1966
GLP: no
Test substance: other TS: thiodiglycol, no further data

Remark: The nominal concentration could not be calculated because the test substance weight slightly increased during the generation process (1.5 to 1.8 g per 8 hours). This means that the test substance was not very volatile and the evaporated portion, if any, was substituted by the uptake of humidity or CO2 by the test substance.
Result: No mortality in the 12 rats.
Symptoms: Immediately after the start of exposure, the animals showed attempts to escape, after 1 hour an irritation (slight irritation; BASF AG, 1966) of mucous membranes (BASF AG, 2004; no further details). No clinical signs and findings from the first post observation day onward.
Necropsy: 3 out of 12 animals showed chronic bronchitis. This finding is judged to be caused by the breeding and housing conditions and not to represent an exposure related effect. No macroscopic pathologic abnormalities were noted in the other animals.

Conclusion: No mortality was observed when 12 rats were exposed for 8 hours to an atmosphere saturated at 20 °C with the volatile fraction of the compound.
Test condition: 6 male and 6 female rats were exposed to the vapors, generated by bubbling 200 l/h air at 20°C through a substance column of about 5 cm above a fritted glass disc in a glass cylinder for 8 hours.
Necropsy after a post exposure observation period of 7 days.
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, acceptable for assessment.
Restrictions: No guideline or GLP study. No data about the TS.

Flag: Critical study for SIDS endpoint
20-JAN-2005 (2) (14)

Type: LCLo
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 10
Doses: 5.4 mg/l (containing 0.125 mg/l thiodiglycol)
Exposure time: 1 hour(s)
Value: > 5.4 mg/l

Method: other: US Department of Transportation guidelines desribed in CFR49, part 173.132-173.133 (10/1/94 edition)
Year: 2000
GLP: yes
Test substance: other TS: see freetext

Result: No toxic signs during and after exposure; also no irritation of the eyes. Normal increase in body weight.
Test substance: Sulfur mustard was neutralized by hot water (90°C) and the neutralized product used for the acute inhalation toxicity test. The test solution contained 2.36% thiodiglycol in water; sulphur mustard was below detection limit (<4 ppb).
Test condition: 5 male and 5 female rats inhaled for 1 h a water/thiodiglycol aerosol with a nominal concentration of 5.4 mg/l, particle size average 3.27 µm, chamber flow 534 l/min. The mean thiodiglycol concentration was 125 µg/l (analysed). Post exposure observation period 14 days.
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions. Restrictions: 1 h exposure; aerosol test substance primarily water containing only 2.4% thiodiglycol.
18-MAY-2004 (62)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Value: 23600 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS: thiodiglycol, no further data

Remark: original value: LD50 = 20 ml/kg
Reliability: (4) not assignable
Secondary literature
27-MAY-2003 (71)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: s.c.
Value: = 4000 mg/kg bw

Method: other: no data

Year: 1948
GLP: no
Test substance: other TS: thiodiglycol, no further data

18-MAY-2004 (70) (74)

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: ca. 4130 mg/kg bw

Method: other: BASF-Test
Year: 1966
GLP: no
Test substance: other TS: thiodiglycol, no further data

Remark: No further data available
Test condition: Application of a 30-40% watery solution.
18-MAY-2004 (14)

Type: LD50
Species: mouse
Route of admin.: s.c.
Value: = 4000 mg/kg bw

Method: other: no data
Year: 1948
GLP: no
Test substance: other TS: thiodiglycol, no further data

18-MAY-2004 (70)

Type: LD50
Species: rabbit
Route of admin.: i.v.
Value: = 3000 mg/kg bw

Method: other: no data
Year: 1948
GLP: no
Test substance: other TS: thiodiglycol, no further data

18-MAY-2004 (70) (74)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Semiocclusive
Exposure Time: 4 hour(s)
No. of Animals: 3
Result: slightly irritating
EC classificat.: not irritating

Method: other: OECD Guide-line 404, 1992
Year: 1995
GLP: yes
Test substance: other TS: Elf Aquitaine Production, batch D251BB, purity

99.83%

Method: Also in compliance with EC Directive No. 92/69/EEC B4, 31. July 1992.
Result: A very slight erythema (score 1) was noted in 1 out of 3 animals 1 hour after treatment until day 4 but no further effects (mean irritation score in this animal on day 2, 3, and 4: 1.0). The effect resolved on day 5. No cutaneous reactions were observed during the study in the 2 other animals.
Conclusion:
Thiodiglycol is not irritant when administered by the cutaneous route in rabbits.
Test condition: TEST ORGANISMS
3 male New Zealand White rabbits used;
breeder Elevage Cunicole de Val de Selle, Prouzel, France; average weight 2.2+-0.1 kg; 5 days acclimatization; food and water (analysed for contaminants) ad libitum; animals did not show any signs of cutaneous irritation or cutaneous defects.
EXPOSURE
A single dose of 0.5 ml of the undiluted test substance on a hydrophilic gauze pad (6 cm2) applied to a clipped area of the skin of rabbits. Gauze pad held in contact with the skin by an adhesive hypoallergenic aerated semi-occlusive dressing. Dressing removed after 4 h.
SCORING
Cutaneous reactions were scored approximately 1, 24, 48 and 72 hours after removal of the dressing.
No residual test substance was observed after removal of the dressing.
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
18-MAY-2004 (46)

Species: rabbit
Result: not irritating

Method: other: BASF-Test
Year: 1966
GLP: no
Test substance: other TS: thiodiglycol, no further data

Remark: No further data available
Result: Rabbit back after 24 h: questionable reddening;
ear after 24 h: no effects.
No irritation recorded after 8 days.
Test condition: Application of undiluted TS to the skin of the back or the ear; exposure duration 20 h.
Reliability: (4) not assignable
Documentation insufficient for assessment.
Details of the study confined to the above.
18-MAY-2004 (14)

Species: guinea pig
Concentration: undiluted
Exposure: Occlusive

Method: other: see freetext
Year: 1991
Test substance: other TS: thiodiglycol, purity 98.4%

Result: Minimum irritant concentration was found to be the undiluted TS; maximum nonirritant concentration: 75% aqueous TS preparation (48 h after the beginning of application).
Test condition: "Pretest" in Maximization Test of Glyezin A in guinea pigs for determination of irritant concentration;
filter paper strips soaked with ca. 0.15 g TS applied to the skin under occlusive dressing; exposure period 2 times for 24 h within a period of 96 h; 4 animals per concentration (no further data); readings 24 and 48 h after the beginning of application.
Reliability: (3) invalid
Unsuitable test system
18-MAY-2004 (9)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 3
Result: slightly irritating
EC classificat.: not irritating

Method: other: OECD Guide-line 405, 1981
Year: 1995
GLP: yes
Test substance: other TS: thiodiglycol, purity 99.83%, Elf Aquitaine Production, batch D251BB

Method: Also in compliance with EC guideline 92/69/EEC.
Result: No effects observed on cornea and iris in all 3 rabbits.

CONJUNCTIVA
No effects on conjunctiva in rabbit No.1.

	grade after observation period			
	1h	1d	2d	3d
conjunctiva				
rabbit No.2				
redness	0	1	1	0
chemosis	2	1	1	0
discharge	#	3	0	0
rabbit No.3				
redness	1	2	1	0
chemosis	0	1	0	0
discharge	#	1	0	0

#: evaluation obscured by residual test substance

Modified maximum average score: 5.3 (maximum possible score = 110; this value was calculated for comparison of different test substances in the eye irritation reference chemicals data bank, prepared by ECETOC, 1998).

The mean scores calculated for animals over 24, 48 and 72 hours were 0.0, 0.7 and 0.3 for chemosis, 0.0, 0.7 and 1.0 for conjunctival redness.

Conclusion:

Thiodiglycol is not irritating.
Test condition: TEST ORGANISMS
3 male New Zealand White rabbits used;
breeder Elevage Cunicole de Val de Selle, Prouzel, France;
average weight 2.5+-0.2 kg; 5 days acclimatization; food and water (analysed for contaminants) ad libitum; animals did not show any signs of ocular irritation/defects or pre-existing corneal injury.
EXPOSURE
0.1 ml of the undiluted test substance (pH=5) was instilled into the conjunctival sac of the left eye of rabbits. Eyelids were held together for ca. 10 sec. The eyes were not rinsed after administration of the test substance.
SCORING
Effects scored ca. 1, 24, 48 and 72 hours after the administration.
Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
17-JUN-2004 (43) (44)

Species: rabbit
Concentration: undiluted
Dose: .05 ml
Comment: not rinsed
No. of Animals: 2
Vehicle: none
Result: slightly irritating

Method: other: BASF-Test
Year: 1966
GLP: no
Test substance: other TS: thiodiglycol, no further data

Result: Irritation Scores

Effect	redness		chemosis		corneal opacity		iritis	
rabbit No.	1	2	1	2	1	2	1	2
time after treatment								
24 h	1	1	2	0	1	0	0	0
48 h	1	1	1	0	1	0	0	0
72 h	1	0	0	0	1	0	0	0
6 days	0	nd	0	nd	1	nd	0	nd
8 days	0	nd	0	nd	0	nd	0	nd

nd: not determined

Slight effects and max. moderate conjunctival edema; effects reversible; no effects detected in the control eye.

Conclusion: the TS caused no relevant irritation in the rabbit eye.
Test condition: 1 male and 1 female White Vienna; 50 µl/animal of unchanged TS applied to the conjunctival sac; observation times see results; BASF scoring system converted to OECD Draize scores; control eye saline-treated.
Reliability: (2) valid with restrictions
Comparable to Draize test with acceptable restrictions.
Restrictions: No GLP study, no data about the TS, 2 animals,

eyes not washed out, 50 µl applied, data confined to the above.
Flag: Critical study for SIDS endpoint
21-MAY-2004 (13)

Species: rabbit
Result: irritating

Method: other: see freetext
GLP: no
Test substance: other TS:

Result: TS application resulted in injury grade 2: 0.5 ml undiluted TS yielded scores over 1.0 up to 5.0 points (highest severity: injury grade 10).
Test condition: Study on 180 different substances; TS applied to the center of the cornea (lids retracted) in different concentrations and volumes and scored 18-24 h later, usually 5 rabbits; symptoms scored before fluorescein staining (cornea opacity, max 6 points; keratoconus 6 points; iritis, max 2 points) and after staining (necrosis of cornea, max. 6 points); max. level 20 points; level of >= 5 points representative of severe injury.
10 injury grades.
Reliability: (4) not assignable
Documentation insufficient for assessment. Scoring only after 24 h.
17-JUN-2004 (36)

5.3 Sensitization

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction 5 % intracutaneous
2nd: Induction undiluted occlusive epicutaneous
3rd: Challenge 75 % occlusive epicutaneous
No. of Animals: 15
Vehicle: other: 0.9% physiol. saline for intradermal induction; no vehicle for percutaneous induction
Result: not sensitizing
Classification: not sensitizing

Method: other: Directive 84/449/EEC, B.6; 1989
Year: 1991
GLP: yes
Test substance: other TS: thiodiglycol, purity 98.4%, stability of TS preparations confirmed by analysis

Method: Comparable to OECD TG 406
Result: RESULTS OF PILOT STUDY:
- see section 5.2.1
RESULTS OF TEST
- Intradermal induction resulted in well defined erythema (grade 2) and slight edema (grade 2) in experimental design a) and c) in TS treated and in control animals; no such effects were observed in controls of exp. design b); but TS treated animals in exp. design b) showed erythema grade 2 and 3 out of 10 animals in exp. design c) revealed TS treatment related necrotic

skin changes.
- Percutaneous induction resulted in erythema and edema grade 2, but these effects are related to intradermal induction at the same site, dito with necrotic skin changes.
- Challenge resulted in no skin reaction neither in TS treated animals nor in controls
- Sensitization reaction:
  Control group 1 0/5
  Test group 0/10
- valid positive control (positive reaction in 20/20)

Test condition: TEST ANIMALS
- Strain: Pirbright White, Dunkin Hartley HOE DHPK [SPF-LAC]BÖ
- Sex: female
- Source: Hagemann GmbH, D-4923 Extertal
- Weight at study initiation: 291-350 g
- Number of TS treated animals: 10
- Number of controls: 5 per control group (2 groups)

HOUSING during acclimatization and study period
- animals housed 5/cage, temperature 20-24°C, relative humidity 30-70%, light dark cycle 12h/12h
- diet (Kliba 341.4mm) and tape water (vitamin C added, 2 g per 10 l twice weekly) ad libitum, no contaminants (analysed) in water, diet, or sawdust

ADMINISTRATION/EXPOSURE
- Preparation of TS for intradermal induction:
  5% TS in 0.9% aqueous NaCl solution resp. in Freund's adjuvant/0.9% aqueous NaCl solution (1:1)
- Preparation of TS for percutaneous induction: unchanged (minimum irritant concentration)
- Preparation of TS for challenge: 75% TS in aqua bidest. (nonirritant concentration)
- Intradermal induction schedule:
  total of 6 intradermal injections
  a) 2 injections each of 0.1 ml Freund's adjuvant without TS emulsified with 0.9% aqueous NaCl-solution (1:1; left and right shoulder)
  b) 2 injections each of 0.1 ml 5% TS in 0.9% NaCl (left and right shoulder)
  c) 2 injections each of 0.1 ml 5% TS in Freund's adjuvant/0.9% NaCl (1:1)
  Readings 24 h after application (grading see below)
  Controls same exp. design without TS
- Percutaneous induction one week after intradermal induction:
  filter paper strips soaked with ca. 0.3 g undiluted TS under occlusive dressing for 48 h; same area (shoulder) as with intradermal induction; readings 48 h after beginning of exposure (grading see below).
  Controls untreated (undiluted TS, no solvent used)
- Challenge schedule:
  21 d after intradermal induction,
  filter paper strip soaked with ca. 0.15 g 75% TS applied for 24 h to the skin of intact clipped flank, occlusive; readings 24 and 48 h after removal of the patch (grading see below).
  Control group 1 treated with the TS and group 2 remained untreated.

- Positive control (historical):
  1-chloro-2,4-dinitrobenzene (n=20), intradermal and
  percutaneous induction, challenge: 1% in ethanol

EXAMINATIONS
- Grading system for assessment of skin findings:
Erythema

no erythema	0
very slight erythema (barely perceptible)	1
well-defined erythema	2
moderate to severe erythema	3
severe erythema to slight eschar formation	4

Edema

no edema	0
very slight edema (barely perceptible)	1
slight edema (edges of area well defined by definite raising)	2
moderate edema (raised ca. 1 mm)	3
severe edema (raised more than 1 mm and extending beyond exposure area)	4

- Pilot study: see section 5.2.1 for details

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
10-MAR-2005 (9)

Type: Guinea pig maximization test
Species: guinea pig
Concentration 1st: Induction 10 % intracutaneous
2nd: Induction undiluted occlusive epicutaneous
3rd: Challenge undiluted occlusive epicutaneous
No. of Animals: 30
Vehicle: physiol. saline
Result: not sensitizing
Classification: not sensitizing

Method: other: OECD Guide-line 406, 1992
Year: 1998
GLP: yes
Test substance: other TS: purity 99.78%; batch number: Elf Aquitaine Production 47956

Method: Study was conducted also in compliance with EC Directive No. 92/69/EEC, B6, 31. July 1992
Result: Preliminary tests have shown that the undiluted TS revealed no irritation 24 or 48 h after removal of the dressing.

MAIN STUDY
No clinical signs and no deaths were noted during the study.
No cutaneous reactions were observed after the challenge application.
The species and strain which were used showed a satisfactory sensitization response in 90% animals treated with DNCB and in 30% animals treated with MERCAPTOBENZOTHIAZOLE.
Conclusion:
According to the maximization method of Magnusson and Kligman, the test substance THIODIGLYCOL does not induce delayed contact hypersensitivity in guinea pigs.

Test condition: TEST ANIMALS

- Strain: Dunkin Hartley
- Sex: male and female
- Source: Charles River France
- acclimatization: at least 5 days
- Weight at study initiation: mean weight of males 340 g, females 341 g
- Number of TS treated animals: 10 males and 10 females
- Number of controls: 5 males and 5 females

HOUSING during acclimatization and study period
- animals housed individually, temperature 19-23°C, relative humidity 30-70%, light dark cycle 12h/12h, ventilation 12 cycles/h filtered air
- diet (106 pelleted diet) and filtered tape water (filter 0.22 µm) ad libitum, no contaminants (analysed) in water, diet, or sawdust

ADMINISTRATION/EXPOSURE
- On day 1, totally 6 injections of 0.1 ml into the dermis of the interscapular area, 3 on each side: a) 50% Freund's complete adjuvant (FCA) in vehicle, b) 10% TS in vehicle c) 10% TS in a mixture of FCA and vehicle 1:1). Same treatment in controls without TS.
- On day 7, the same region received a topical application of sodium lauryl sulfate in vaseline (10% w/w) in order to induce local irritation.
- On day 8, this same test site received a cutaneous application of 0.5 ml undiluted TS (treated group) or the vehicle (control group) and was then covered by an occlusive dressing for 48 hours.
- On day 22, after a rest period of 12 days, all animals of the treated and control groups were challenged by a cutaneous application of 0.5 ml test substance to the right flank. The left flank served as control and received 0.5 ml vehicle only. Test substance and vehicle were maintained under an occlusive dressing for 24 hours.
- Skin reactions were evaluated approximately 24 and 48 hours after removal of the dressing.

EXAMINATION
The grading system for assessment of skin findings is the same as described in the study above.
At the end of the study, animals were killed without examination of internal organs. No skin samples were taken from the challenge application sites.
The sensitivity of the guinea-pigs in C.I.T. experimental conditions was checked with positive sensitizers DNCB and MERCAPTOBENZOTHIAZOLE.
During the induction period, the test substance DNCB was applied at the concentrations of 0.1% (w/w) (day 1) and 1% (w/w) (day 8). The test substance MERCAPTOBENZOTHIAZOLE was applied at the concentrations of 1% (w/w) (day 1) and 20% (w/w) (day 8).
For the challenge application, the test substance DNCB was applied at the concentration of 1% (w/w). The test substance MERCAPTOBENZOTHIAZOLE was applied at the concentration of 20% (w/w).

Reliability: (1) valid without restriction
GLP guideline study

Flag: Critical study for SIDS endpoint

10-MAR-2005 (45)

5.4 Repeated Dose Toxicity

Type:	Sub-acute	
Species:	rat	Sex: male/female
Strain:	Wistar	
Route of administration:	gavage	
Exposure period:	28 days	
Frequency of treatment:	once daily	
Post exposure period:	3 days	
Doses:	0 or 1000 mg/kg bw/d	
Control Group:	no	
NOAEL:	= 1000 mg/kg bw	
LOAEL:	> 1000 mg/kg bw	

Method:	other: OECD Guide-line 407, 1981
Year:	1991
GLP:	yes
Test substance:	other TS: thiodiglycol, purity >= 98.4%

Result: NOAEL: 1000 mg/kg bw

ANALYSIS
- analytical check confirmed the correct concentration and stability, food and water not contaminated

TOXIC RESPONSE/EFFECTS
- no significant effects were observed (exceptions see below) at any parameter listed in the freetext "test condition".
- Exceptions:
  a) in males significant decrease in red blood cell counts, hemoglobin level and hematocrit; effect within the range of variation, values in control males unusually high; effect considered to be incidental
  b) in males significant decrease in bilirubin and albumin concentrations; effect within the range of variation (laboratory historical control), clinical and histopathological examinations revealed no findings in accordance with these changes; effects considered to be of no toxicological significance
- pathology: no changes related to the treatment

CONCLUSION
- In the presented study no changes were observed related to the test substance administered.

Test condition:
TEST ORGANISMS
- 38 days old Wistar rats received from Karl Thomae, Biberach, Germany
- acclimatization period 4 days

HOUSING AND DIET
- rats singly housed
- temperature 20-24°C, relative humidity 30-70%, day/night rythm 12h/12h
- room desinfected before use
- food (Kliba 343 feed) and water ad libitum

ANALYSIS
- test substance, stability of the test substance, and solution of the test substance (stability, homogeneity) were analysed as well as food and drinking water

TEST ORGANISMS at initiation of experiment
- Age: 42 days

- Weight at study initiation: males 164-169 g, females 138-155 g
- Number of animals: 5 males and 5 females per group

ADMINISTRATION / EXPOSURE
- Vehicle:
  bidistilled water
- Concentration in vehicle:
  0 or 100 mg/ml
- Volume applied:
  all animals received 10 ml/kg bw

CLINICAL EXAMINATIONS:
- Clinical signs and mortality checked twice daily
- Body weight determined on day 0 and then in weekly intervals
- Food consumption determined weekly (over a period of 7 d)
- Samples for hematology and clinical chemistry:
  Blood sampling on day 31 (sampling in a randomized sequence) from retroorbital venous plexus
- Hematological parameters
  leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, differential blood count, blood clotting analysis
- Clinical chemistry parameters
  Enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum-gamma-glutamyltransferase;
  blood chemistry: Na, K, Cl, Ca, Mg, inorganic phosphate, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, cholesterol;
  hormones: total triiodothyronine (T3), total thyroxine (T4)

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- according to OECD guideline 407 (1981)

STATISTICAL METHODS
- for clinical examinations, hematology and clinical chemistry analysis done via the MANN-WHITNEY-U-Test, marked level of significance $p < 0.05$

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
19-MAY-2004 (17)

Type: Sub-chronic
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 91-92 days
Frequency of treatment: once daily, 5 days per week
Post exposure period: no
Doses: 0, 50, 500, 5000 mg/kg bw/d
Control Group: other: controls treated with an empty gavage needle (no vehicle used)
NOAEL: = 500 mg/kg bw
LOAEL: = 5000 mg/kg bw

Method: other: comparable to OECD Guide-line 408
Year: 1997

GLP: yes
Test substance: other TS: thiodiglycol, samples analysed by gas chromatography before, during, and after the study; purity >= 95%

Result: NOAEL: 500 mg/kg bw/d
LOAEL: 5000 mg/kg bw/d

ANALYSIS OF THE DOSE
- analytical check confirmed the stability (purity >= 95%) of the test substance

TOXIC RESPONSE/EFFECTS
- Several deaths and unscheduled sacrifices occurred during the study in controls and treated groups (males: 2 controls, 1 mid dose rat; females: 1 control, 2 high dose rats), none of which appeared to be not compound related (e.g. irreversible malocclusion, oesophagus perforated)
- No significant effects were observed (exceptions see below) at any parameter listed in the freetext "test conditions".
- Exceptions:
  a) in the high dose group the body weights were in both genders significantly lower ($p<0.05$) than in controls: in treated females in exposure week 10, 11 and 13 and in males in exposure week 9, 11, 12, 13; at termination the mean body weight was in the high dose females 298 g versus 338 g in control, and in males 505 g versus 587 g in control; the total body weight gain in both genders of the high dose group was significantly lower ($p<0.01$); however, the food consumption was significantly reduced only on day 3 (males) or day 1 (females)
  b) the absolute and the relative mean kidney weights of males and females in the high dose group were significantly higher
  c) the urine analysis revealed in both genders of the high dose group significantly increased urine volume (ca. 3-fold of the control value) and significantly decreased urine ph (in females also significant in the mid dose group); in the high dose males there was also a slight but significant increase in urine specific gravity (no historical data available) and a significant reduction in triple phosphate (crystals per field measured); granular casts in the urine were only observed in the high dose group, significant in females
  d) due to the decreased body weight the mean relative organ weights of liver, brain and testes were significantly higher in males of the high dose group; however, no significant effects were seen with the mean absolute organ weights (no toxicological relevance, no changes in histopathology); the same was observed with the mean adrenal weight in females of the high dose group;

- Pathology/histopathology: no changes related to the test substance in any organ

CONCLUSION
- In the presented study no changes of toxicological relevance were observed in the low and mid dose group. In the high dose group effects on body and kidney weight were observed in males and females as well as changes in urine suggesting a LOAEL of 5000 mg/kg bw/d

Test condition: ANALYSIS

- purity and stability of the test substance

TEST ORGANISMS
- Age: 7-8 weeks (obtained from Charles River Lab, Wilmington, MA; acclimatization for 3-4 weeks before start of experiment, randomized)
- Weight at study initiation: males ca. 270 g, females ca. 205 g
- Number of animals: 10 males and 10 females per group
- rats in a satelite group (n=6 per sex) housed in the same room were screened for serology, bacteriology, pathology, parasitology at termination of the main study. Results: rats were in good health

HOUSING AND DIET
- rats singly housed
- 40-70% relative humidity, temperature 65-78 °F, light/dark cyclus 12h/12h
- pesticide-free rodent chow and drinking water ad libitum

ADMINISTRATION / EXPOSURE
- Vehicle:
  neat thiodiglycol administered

EXAMINATIONS:
- Clinical signs checked daily
- Body and feeder (food consumption determined) weight of each rat determined on test day -3, -1, 0, 1, 3, 7 and then in weekly intervals
- Ophthalmic examination of control and high dose group prior to commencment of the study and several days before termination
- Samples for urine analysis collected from all rats towards the end of the study
- Samples for hematology and clinical chemistry:
  Blood sampling at termination by intracardiac puncture
- Hematological parameters
  white blood cell count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, mean platelet volume, differential white count
- Clinical chemistry parameters:
  alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine kinase, lactic dehydrogenase, Ca, blood urea, creatinine, glucose, total bilirubin, total protein, triglycerides, cholesterol
- Urine analysis: volume, color, appearance, pH, specific gravity, glucose, bilirubin, urobilinogen, ketone, blood, protein, nitrite, leukocytes, microscopic examination
- Complete necropsy
- Organ weight determined of liver, kidney, brain, spleen, adrenals, gonads
- Histopathology of all organs (except rectum) listed in OECD guideline 408 (histopathology)

STATISTICAL METHODS
- food consumption, body weights, weight gains, organ/body and organ/brain weight ratio: one-way analysis of variance, when significance was observed data further analysed by Dunnett's post hoc test
- for hematology, urine analysis and clinical chemistry

analysis done via one-way analysis of variance and Bonferoni's post hoc test
- level of significance: p<0.05

Reliability: (1) valid without restriction
Comparable to guideline study

Flag: Critical study for SIDS endpoint

19-MAY-2004 (1)

Type: Sub-acute
Species: rat Sex:
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 2 weeks
Frequency of treatment: once daily, 5 days per week
Post exposure period: no
Doses: 0, 157, 313, 625, 1250, 2500, 5000, 10000 mg/kg bw/d
Control Group: other: controls treated with an empty gavage needle (no vehicle used)

Method: other: see freetext
Year: 1997
GLP: no
Test substance: other TS: thiodiglycol, purity >= 95%

Result: TOXIC EFFECTS
- in the high dose group 4/6 males and 5/6 females died within 1-3 days after start of exposure period; mortality was preceeded by lethargy of increasing severity
- at 5000 (males) and 10000 mg/kg bw (males and females) food consumption was depressed with corresponding decrease in body weight (see also lethargy)
- there was a dose-related trend (but not significant) to higher absolute kidney weights in males at >= 1250 mg/kg bw and in females at >= 2500 mg/kg bw; absolute kidney weights were significantly higher in males and females at >= 5000 mg/kg bw
- no further effects were detected in the determined parameters (see test condition).

CONCLUSION
- 5000 mg/kg bw/d was selected as the highest dose level in the 90-day oral study

Test condition: Dose-range-finding study
TEST ORGANISMS
- Age: 8-9 weeks
- Number of animals: 6 males and 6 females per group

ADMINISTRATION / EXPOSURE
- Vehicle:
neat thiodiglycol administered, no vehicle used

EXAMINATIONS:
- Clinical signs checked daily
- Body and feeder (food consumption determined) weight of each rat determined on test day -3, -1, 0, 1, 3, 7, 14
- Rats that died during the study were submitted gross necropsy
- Samples for hematology and clinical chemistry:
Blood sampling at termination by intracardiac puncture
- Hematological parameters

white blood cell count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration,

platelets, mean platelet volume, differential white count
- Clinical chemistry parameters:
alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine kinase, lactic dehydrogenase, Ca, blood urea, creatinine, glucose, total bilirubin, total protein, triglycerides, cholesterol
- Complete necropsy
- Organ weight determined of liver, kidney, brain, spleen, adrenals, gonads

STATISTICAL METHODS
- food consumption, body weights, weight gains, organ/body and organ/brain weight ratio: one-way analysis of variance, when significance was observed data further analysed by Dunnett's post hoc test
- for hematology, urine analysis and clinical chemistry analysis done via one-way analysis of variance and Bonferroni's post hoc test
- level of significance $p<0.05$

Reliability: (2) valid with restrictions
Meets generally accepted scientific standards, acceptable for assessment.
Restrictions: Dose-range-finding study. No histopathology.
19-MAY-2004 (1)

Type: Sub-acute
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 14 days
Frequency of treatment: once daily, 5 days per week
Post exposure period: 24 h
Doses: 1250, 2500, 5000 mg/kg bw/d
Control Group: other: controls treated with an empty gavage needle (no vehicle used)

Method: other: see freetext
Year: 1999
GLP: no
Test substance: other TS: thiodiglycol, purity 99%

Result: Males:
Activity of GSH transferase significantly increased in all treatment groups but no dose dependency.
Same results with glutathione reductase but significance only in the high dose group.
No significant effects on other parameters tested.

Females:
Glutathione reductase activity significantly reduced in the high dose group.
Oxidized glutathione significantly reduced in mid and high dose group.
No further effects.

Authors comment: no deleterious effects on the glutathione antioxidant system.

Test condition: The objective of this study was the evaluation of effects on enzymes in blood samples.
TEST ORGANISMS
- Age: 7 to 8 weeks old
- Weight at study initiation: no data
- Number of animals: 10 per group per sex
ADMINISTRATION / EXPOSURE
- Concentration in vehicle: neat TS
- Vehicle: no vehicle, undiluted TS administered

- Blood biochemistry: hemolysates used for determination of GSH transferases, glutathione reductase, oxidized and reduced glutathione content and protein.

STATISTICAL METHODS: ANOVA, level of significance p <= 0.05

Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented and acceptable for assessment concerning biochemical effects.
Restrictions: No guideline or GLP study.

18-MAY-2004 (82)

Type: Sub-chronic
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 90 days
Frequency of treatment: once daily, 5 days per week
Post exposure period: rats sacrificed 24 h after the last dose
Doses: 0, 50, 500, 5000 mg/kg bw/d
Control Group: other: controls treated with an empty gavage needle (no vehicle used)

Method: other: see freetext
Year: 1999
GLP: no
Test substance: other TS: thiodiglycol, purity 99%

Result: TOXIC RESPONSE/EFFECTS
- Clinical signs: no consistent signs of toxicity, several rats displayed irritable behavior during dosing (not dose dependent; no further details)
- Body weight gain: significantly decreased in both sexes in the high dose group
- Food consumption: no significant effect
- Organ weights: significant increase in kidney weight in both sexes in the high dose group (no further data)
- liver biochemistry (only significant effects described here)
  female rats: no effects observed except an increase in cytochrome-P450 content in the mid dose group (no dose dependency)
  male rats: cytochrome-b5 decreased in mid & high dose group, PROD increased in high dose group, reduced GSH decreased in mid and high dose group, activity of GSH-T decreased in all groups, GSH-Px activity reduced in the high dose group.
- blood biochemistry: no significant effects.

AUTHORS CONCLUSION
Effects not detrimental; minimal treatment related effects without toxicological relevance.

Test condition: The objective of this study was the evaluation of effects on hepatic enzyme systems and enzymes in blood samples.
TEST ORGANISMS
- Age: 7 to 8 weeks old
- Weight at study initiation: no data
- Number of animals: 10 per group per sex; for investigation of biochemical parameters 5 per group per sex

ADMINISTRATION / EXPOSURE
- Concentration in vehicle: neat TS
- Total volume applied: high dose ca. 1 ml
- Vehicle: no vehicle, undiluted TS administered

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs, data on body weight and food consumption reported in the result section of the study (no further details).
- Liver biochemistry: 24 h after the last dose rats sacrificed and livers excised and stored for biochemical analysis;
  tested parameters: cytochrome-P450 content, cytochrome-b5 content, ethoxyresorufin O-dealkylase (EROD), pentoxyresorufin O-dealkylase (PROD), reduced glutathione (GSH), oxidized glutathione, glutathione reductase (GSH-R), glutathione S-transferase (GSH-T), glutathione peroxidase (GSH-Px).
- Blood biochemistry: hemolysates used for determination of GSH transferases, glutathione reductase, oxidized and reduced glutathione content and protein.

STATISTICAL METHODS: ANOVA, level of significance p <= 0.05

Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, well documented and acceptable for assessment concerning biochemical effects.
Restrictions: No guideline or GLP study.

18-MAY-2004 (82) (83)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: 0, 20, 100, 500, 2500, 5000 µg/plate
Cytotoxic Concentration: no cytotoxicity except slight decrease in revertants observed only in TA100 with metabolic activation at >=2500 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: OECD Guide-line 471, 1983
Year: 1989
GLP: yes
Test substance: other TS: thiodiglycol, purity > 99%

Result: GENOTOXIC EFFECTS
- With and without metabolic activation: no positive results at any dose level in all tested strains.

CYTOTOXIC CONCENTRATION
- see above

CONTROLS
- spontaneous revertants in negative controls within the normal range;
- valid positive controls.

EVALUATION
- Under the condition of this study the TS did not cause an increase in the number of revertants of any tester strain either with or without metabolic activation.

Test condition: SYSTEM OF TESTING
- Type: standard plate test and additionally preincubation test performed
- Metabolic activation system: S9-mix, liver microsomes prepared from male Sprague-Dawley rats i.p. injected with 500 mg/kg Aroclor1254.
- number of plates per concentration/control: 3
- Solvent: aqua dest. (TS soluble)
- Controls: negative (solvent control and sterility control) and positive control (10 µg/plate 2-aminoanthracene for each tester strain with S9-mix; without S9-mix: 5 µg/plate N-methyl-N-nitro-N-nitrosoguanidine for TA100 and TA1535, 10 µg/plate 4-nitro-o-phenylendiamine for TA98, and 100 µg/plate 9-aminoacridine chloride x H2O for TA1537)
- Cytotoxicity: evaluated via bacterial background lawn and reduction in revertant colonies

CRITERIA FOR EVALUATING RESULTS:
- considered positive if the TS produced at least a 2-fold increase in revertants per plate over vehicle control
- a dose response to increasing concentrations
- reproducibility of the results

STATISTICS
- no details reported

Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions
Restrictions: TA102 or E. coli not tested; no GLP study.
Flag: Critical study for SIDS endpoint
18-MAY-2004 (12)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537 and E. coli WP2uvrA
Concentration: 0, 33, 100, 333, 1000, 3330, 5000 µg/plate
Cytotoxic Concentration: no cytotoxic effects
Metabolic activation: with and without
Result: negative

Method: other: OECD Guide-line 471, 1997
Year: 2001
GLP: yes
Test substance: other TS: thiodiglycol, Lot No. 05701EQ, further data available from the sponsor
Result: TEST SUBSTANCE HANDLING
- up to the high dose level the TS formed a transparent

colorless solution without precipitates

CYTOTOXICITY IN PRELIMINARY TEST
- no cytotoxic effects detected at any dose level

GENOTOXIC EFFECTS IN THE MAIN STUDY
- thiodiglycol did not induce any significant increase in the number of revertants, with or without S9 mix, in any of the 5 strains tested
- Negative and positive controls were valid.
- no cytotoxicity detected at any dose level

CONCLUSION
- The test substance did not show mutagenic activity in the Ames test under the conditions of this study

Test condition: SYSTEM OF TESTING
- 2 independent trials; in the 1st and 2nd trial the plate incorporation method was used; 3 plates per concentration; S9-mix and dilutions prepared immediately prior to use

- Metabolic activation system (MA): S9 fraction from liver homogenates of rats (induced with i.p. 500 mg/kg Aroclor 1254) plus cofactors

- vehicle: water (Quality Biological Lot No. 708589)

- Controls: sterility control; vehicle control (with and without MA); positive control (with MA: 2.5 µg/plate benzo(a)pyrene for TA98, 2,5 µg/plate 2-aminoanthracene for TA100, TA1535, TA1537 and 25 µg/plate 2-amino-anthracene for WP2uvrA; without MA: 1.0 µg/plate 2-nitrofluorene for TA98, 2 µg/plate sodium azid for TA100 and TA 1535, 2 µg/plate ICR-191 for TA1537, 1 µg/plate 4-nitroquinoline-N-oxide for WP2uvrA)

- Cytotoxicity: A preliminary toxicity test was performed to define the concentrations to be used for the mutagenicity study. TA100 and E. coli WP2uvrA exposed to 10 dose levels between 6.67 and 5000 µg/plate with and without MA; cytotoxicity evaluated by scoring the decrease in revertants and/or a thinning or disappearance of the bacterial background lawn; in the main study cytotoxicity scored in the same manner

CRITERIA FOR EVALUATION
- tester strain integrity and strain culture density demonstrated
- negative and positive controls within the range of historical controls
- positive controls exhibited at least 3-fold increase in revertants over vehicle control
- positive: in TA98, TA100, and WP2uvrA at least 2-fold increase in revertants accompanied by a dose response to increasing concentrations; same with TA1535 and TA1537 but increase in revertants at least 3-fold

STATISTICS
- mean revertants per plate and standard deviation calculated; no further data

Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions.

Restrictions: no details about the purity of the TS.
Flag: Critical study for SIDS endpoint
18-MAY-2004 (78)

Type: Cytogenetic assay
System of testing: Chinese hamster ovary (CHO) cells
Concentration: 1, 2, 3, 4, or 5 mg/ml
Cytotoxic Concentration: without metabolic activation at >= 1 mg/ml; with metabolic activation at >= 2 mg/l
Metabolic activation: with and without
Result: positive

Method: other: comparable to OECD guideline 473
Year: 1997
GLP: yes
Test substance: other TS: thiodiglycol, no further data

Result: PRELIMINARY CYTOTOXICITY TEST
- without MA: no significant change in osmolality, pH in the normal range; at 5 mg/ml TS the MI was 28% lower than the control value and the average generation time (AGT) increased by 14%; 5 mg/ml selected for maximum dose in the main study
- with MA: also no effect on osmolality and pH; at 5 mg/ml the MI was depressed by 63% the AGT increased by 25%; 5 mg/ml selected for maximum dose level

VALIDITY OF CONTROLS
- The frequency of cells with structural chromosome aberrations in the vehicle and positive controls was not compared with the range of the historical data; however, recorded data seem to be acceptable.

ABERRATIONS without MA
- clastogenicity evaluated at 3, 4, and 5 mg/ml; significant increase (p=0.004) in aberrations excluding gaps (chromatid and chromosome breaks, chromatid-type rearrangements) demonstrated in the trend analysis; significant also in the Fisher exact test at 5 mg/ml; no effect on PI but MI was significantly decreased (max. 30% at 5 mg/ml) at 1-5 mg/ml, except at the dose level of 4 mg/ml (questionable and not discussed by the authors); cell density was significantly decreased in ANOVA analysis (p<0.024) but not in the t-test analysis

Dose in mg/ml	%DC +gaps	%DC -gaps	MI(%)	PI(%)	Cell density(%)
0	7.5	3.5	7.95	0.5	100
1	not scored		5.85*	0.0	103
2	not scored		5.65*	0.0	102
3	8.0	4.0	6.05*	0.5	98
4	13.0	5.0	5.9	0.0	98
5	18.5	11.0*	5.55*	0.0	98
positive control	53.0	47.0*	4.65*	0.5	98

%DC= percentage of metaphase cells with at least 1 aberration, MI(%)= % of metaphase cells; PI(%)= % of polyploid metaphase cells; cell density in % of control; *: significant

ABERRATIONS with MA
- clastogenicity evaluated at 3, 4, and 5 mg/ml; using the trend test the TS induced a significant (p<0.001) increase in aberrations excluding gaps; using the Fisher's exact test the lowest effective dose was 4 mg/ml; chromatid/chromosome breaks and chromatid like rearrangements were detected; the positive control could not be evaluated because of mitotic depression (authors comment: test valid because the TS induced clastogenic effects); no effects on PI and cell density; MI significantly depressed (ANOVA), significant differences at 2, 3, and 5 mg/ml (Fisher's exact test)

Dose in mg/ml	%DC +gaps	%DC -gaps	MI(%)	PI(%)	Cell density in % of control
0	7.0	4.0	8.1	0.0	100
1	not scored		4.9#	0.0	103
2	not scored		5.4*	0.0	97
3	16.5	7.0	5.9*	0.0	103
4	21.5	10.0*	5.95	0.0	106
5	23.5	13.0*	4.15*	0.5	100
positive control	not scorable		0.15*	0.0	106

#: significance not determined; see also legend above

Authors conclusion:
The test substance did induce chromosome aberrations in cultured CHO cells in the presence and in the absence of a metabolic activation system.

Test condition: SYSTEM of TESTING
- exponentially growing CHO-K1 cells seeded in complete medium (2.4x 10E4 cells/cm²) at 37°C, 5% CO2

- Metabolic activation system (MA): S9 mix, prepared from a liver microsomal fraction (S9 fraction of rats induced with Aroclor1254) plus cofactors

- Vehicle: sterile distilled water; preparation of solutions on the day of experiment

- Controls: negative vehicle control and positive control using 0.05 µg/ml mitomycin C (without MA) or 20 µg/ml cyclophophamide (with MA)

- Preliminary toxicity test
  Cells exposed to 0, 10, 50, 100, 500, 1000, 5000 µg/ml for 28.5 h in the absence of MA and for 4 h in the presence of MA, 10 µM bromodeoxyuridine (BrdU) was added 4 h after addition of the TS; following 22.5 h BrdU exposure 0.1 µg/ml colcemid was added and cells harvested 2 h later and fixed; slides prepared and cells stained with Hoechst33258 and Giemsa; based on 100 metaphases per culture 1st, 2nd, 3rd, and subsequent cell divisions evaluated on duplicate cultures; mitotic index determined on 1000 cells per culture; osmolality and pH (phenol red indicator in the medium) measured after addition of TS

- Cytogenetic assay
  Cells exposed to the vehicle or to 1, 2, 3, 4, or 5 mg/ml

TS in duplicate trials at 37°C and 5% CO2; without MA: exposure period 20 h, 2 h before termination 0.1 µg/ml colcemid added; with MA: cells exposed to the TS plus MA for 4 h, then treatment medium removed, cells washed and cultured for additional 16 h in medium without the TS; harvest: cells treated with hypotonic solution, fixed in methanol followed by methanol:glacial acetic acid (3:1) fixative, cells on slides air dried and stained with 4% Giemsa

- Microscopic evaluation: 200 metaphases per dose level analysed; gaps, chromatid and chromosome breaks and rearrangements, multiple aberrations, and pulverisation recorded and tabulated; evaluation on a blind basis; cell density determined in each culture

- Cytotoxicity evaluated using the mitotic index (MI) based on 1000 cells per culture and the polyploidy index (PI) based on 100 metaphases per culture

EVALUATION CRITERIA
- positive: significant dose dependent increase in the frequency of cells with chromosome aberrations which is demonstrated in the trend test (see below) and a significant increase in at least one treatment group is demonstrated in the Fisher exact test (see below); if either, but not both, of these conditions are met, further evaluation by the authors depending on the effects
- negative: both conditions are not met (see above)

STATISTICS
- chromosomal aberration data analysed by a one-tailed Cochran-Armitage trend test and a one-tailed Fisher's exact test; MI, PI and cell density analysed by ANOVA followed by a two-tailed pairwise student's t-test; level of significance p=0.05

Reliability: (2) valid with restrictions
Comparable to national guideline study with acceptable restrictions.
Restrictions: no data about the TS
Flag: Critical study for SIDS endpoint
18-MAY-2004 (80)

Type: Mouse lymphoma assay
System of testing: L5178Y tk+/- cells
Concentration: 0, 50, 158, 500, 1580, 5000 µg/ml
Cytotoxic Concentration: see freetext
Metabolic activation: with and without
Result: negative

Method: other: OECD Guide-line 476, 1997
Year: 1998
GLP: yes
Test substance: other TS: thiodiglycol, no further data

Result: PRELIMINARY CYTOTOXICITY TEST
- with and without MA: no significant change in osmolality, pH in the normal range; no dose dependent decrease in RSG (not greater than 4.1% at any dose level without MA and not greater than 7.3% at any dose level with MA); 5 mg/ml

selected for maximum dose in the main study

VALIDITY OF CONTROLS
- without MA: valid negative and positive controls except high dose MMS (ACE < 50%), but low dose MMS valid;
- with MA: initial mutagenicity test was not valid because of unacceptable ACE for the positive control (data not shown); in the repeat test valid negative and positive controls were demonstrated

MUTAGENICITY ASSAY
without MA:
The RSG depression in TS treated cells was not greater than 10.7%; the TS did not induce a significant increase in mean MF compared with the negative control (47.7 xE-6), increase not greater than 1.1 fold at all dose levels; mutant colony sizing data on negative and positive controls showed small and large colony mutants (16% increase in small colony mutants at 5 µg/ml MMS), no data presented on TS treated cells.
with MA:
Little toxicity was seen after exposure to the TS; the TS did not induce a significant increase in mutations using the one-tailed trend test; no increase in mutations above vehicle control (29.4xE-6); data on mutant colony sizing similar to data without MA.

Summary Table for the main study

Dose in µg/ml	RSG	RCE	RTG	MF	IMF
without MA					
0	-	-	-	64	-
50	126	93	113	70	6
158	89	103	92	65	1
500	91	88	81	46	-18
1580	98	97	95	68	4
5000	96	92	89	54	-10
positive control					
5 MMS	81	82	66	411	348
10 MMS	65	27	16	805	741
with MA	RSG	RCE	RTG	MF	IMF
0	-	-	-	56	-
50	68	99	68	45	-11
158	66	98	66	55	-1
500	70	93	65	47	-9
1580	70	94	65	51	-5
5000	81	104	84	55	-1
positive control					
2.5 MCA	86	107	93	202	146
5.0 MCA	38	97	37	411	355

mean values of 2 trials; MF per million clonable cells

Authors conclusion:
The test substance did not induce mutations in the mouse lymphoma assay in the presence and in the absence of a metabolic activation system.

Test condition: SYSTEM of TESTING
- L5178Y cells, clone 3.7.2C cultered in complete medium

plus antibiotics at at 37°C, 5% CO2; cells cleansed of TK-/- mutants with methotrexate one week prior to testing

- Metabolic activation system (MA): S9 mix, prepared from a liver microsomal fraction (S9 fraction of rats induced with Aroclor1254) plus cofactors

- Vehicle and solutions: sterile distilled water; preparation of solutions on the day of experiment; standard dosing volume in all experiments 100 µl (vehicle concentration 1% in culture medium)

- Controls: negative vehicle control and positive control (dissolved in DMSO) using 5 and 10 µg/ml methylmethanesulfonate (MMS) (without MA) or 2.5 and 5 µg/ml methylcholanthrene (MCA)(with MA)

- Preliminary toxicity test
6x10E6 cells per tube (log phase growth) exposed to 0, 1, 5, 10, 50, 100, 500, 1000, 5000 µg/ml for 4 h in the absence and presence of MA (37°C and 5% CO2); cells washed and cultured for additional 20 or 44 h; cell density determined; duplicate trials; osmolality and pH (phenol red indicator in the medium) measured after addition of TS

- Mutagenicity assay
Cells exposed for 4 h to the vehicle or to 50, 158, 500, 1580, 5000 µg/ml TS or to substances for positive controls in duplicate trials at 37°C with and without MA; after exposure cells washed, resuspended in F10P (cell density 0.3xE6 cells/ml) and cultured at 37°C and 5% CO2; expression period 2 days;
mutant selection: on day 2 3xE6 cells resuspended in soft agar cloning medium containing 1 µg/ml trifluorothymidine (TFT) for detection of TFT resistant mutants, sample distributed into 3 plates at ca. 1xE6 cells;
cloning efficiency viable counts (VC): at the time of selection 200 cells/plate (3 plate per dose level) cultured without TFT at 37°C and 5% CO2 for 10-12 days, then colonies counted;
colony sizing: if TS induced mutants, the diameter of the TFT colonies was determined over a range of 0.2-2.0 mm

PARAMETER DETERMINED
TSG: total suspension growth
RSG: relative suspension growth (relative to vehicle)
number of mutant colonies per TFT plate
number of viable count colonies per VC plate
MF: mutant frequency
IMF: induced mutant frequency (MF-MF vehicle control)
ACE: absolute cloning efficiency
RCE: relative cloning efficiency (relative to vehicle)
RTG: relative total growth (relative suspension growth x relative cloning efficiency/100)
distribution of mutant colony sizes (for a positive response only)

EVALUATION CRITERIA
- valid negative control: absolute cloning efficiency not

< 50% and mutant frequency < 150 per million viable cells
- valid positive control: mutant frequency at least twice that of mean vehicle control
- positive response: significant dose dependent increase in the mutant frequency which is demonstrated in the trend test (see statistics) and a twofold increase in at least one treatment group;
if either, but not both, of these conditions are met, further evaluation by the authors depending on the effects
- negative: both conditions are not met (see above)

STATISTICS
- significance based on a positive dose response determined by a one-tailed trend test (StatMost32), level of significance p=0.05, with at least 1 dose 2 times above solvent control

Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions.
Restrictions: no details about the purity of the TS.
Flag: Critical study for SIDS endpoint
18-MAY-2004 (37)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse Sex: male/female
Strain: ICR
Route of admin.: gavage
Exposure period: single exposure
Doses: 500, 1000, 2000 mg/kg bw
Result: negative

Method: other: OECD Guide-line 474, 1997
Year: 2001
GLP: yes
Test substance: other TS: thiodiglycol, Lot No. 05701EQ, further data available from the sponsor

Result: - Preliminary toxicity test
no clinical signs at any dose level; 2000 mg/kg bw used for the main study

- Clinical signs in the main study
no clinical signs observed in any group

- Cytogenetic
no significant differences in MPE values between vehicle controls and TS treated males of all dose groups;
the PN/NE ratio was also not significantly altered in any TS treatment group; valid positive and negative control (also in comparison with historical data)

- Cytogenetic summary table

Dose in mg/kg bw and harvest time	% MPE (SE)	PE/NE ratio (SE)
vehicle 24 h	0.13 (0.02)	0.91 (0.03)
vehicle 48 h	0.09 (0.01)	0.84 (0.06)
500 24 h	0.09 (0.03)	0.79 (0.03)
1000 24 h	0.12 (0.03)	0.79 (0.04)

	2000	24 h	0.11 (0.02)	0.82 (0.05)
	2000	48 h	0.10 (0.02)	0.91 (0.04)
positive control		24 h	3.07 (0.35)**	0.67 (0.04)*

SE: standard error; *: p<0.05; **: p<0.01

CONCLUSION:
Under the condition of this study the test substance does not induce damage to the chromosomes or the mitotic apparatus of mouse bone marrow cells.

Test condition: TEST ORGANISMS
- Strain: Crl:CD-1(ICR) BR
- obtained from Charles River Lab, Raleigh (North Carolina) (preliminary study) or St. Constant (Quebec) (main study)
- at least 6 days acclimatization period
- randomization of animals
- at start of treatment period in the main study males ca. 8 weeks old, bw range 30.0-34.5 g; in the preliminary study males and females ca. 8 weeks old, bw range 30.2-34.8 g and 22.8-25.4 g, respectively

HOUSING and DIET
- animals housed in dose groups; polycarbonate cages used with hardwood chip laboratory bedding.
- temperature 18-26°C; 30-70% relative humidity; light/dark cycle 12h/12h; ventilation at least 10 air changes per h;
- certified rodent diet #5002 and tap water ad libitum; no contaminants in diet, water and wood chips (analysed)

TREATMENT
- Preliminary toxicity test
3 males and 3 females per group gavaged once with 500, 1000, 2000 mg/kg bw (dosing volume 10 ml/kg; vehicle: sterile deionized water), clinical signs of toxicity recorded daily (no data about post exposure observation period, presumably 48 h).

- Experimental design (main study)
only males used because no differences in clinical observations between the sexes in the preliminary study; 6 males per group treated (ca. 8 weeks old), but 5 males per group used for final evaluation; test groups gavaged once at dose levels of 500, 1000, or 2000 mg/kg bw, same treatment in negative controls receiving the vehicle; positive controls gavaged once with 80 mg/kg bw cyclophosphamide;
all animals examined for clinical signs after dosing, ca. 1 h after dosing, and at least daily for the duration of the test;

animals killed 24 h after treatment, additional groups killed after 48 h (only negative control and at the high dose level); bone marrow smears prepared (air dried, fixed with methanol, stained with May-Grünwald followed by Giemsa staining) for microscopic examination.

- Formulation procedure (main study)
test substance dissolved in the vehicle (sterile deionized water) immediatly before use; concentrations of 0, 50, 100, 200 mg/ml TS or 8 mg/ml cyclophosphamide (positive control); administration volume 10 ml/kg in all groups.

MICROSCOPY
Evaluation of slides on a blind basis; for each mouse, the number of micronucleated polychromatic erythrocytes (MPE) counted in 2000 polychromatic erythrocytes (PE); the ratio of PE versus normochromatic erythrocytes (NE) determined by scoring 500 erythrocytes per mouse; historical background frequency of micronuclei in this strain at this lab is 0.0 to 0.4%.

CRITERIA FOR EVALUATION
A statistical significant increase in the frequency of MPE must be demonstrated for at least one dose level, and a statistically significant dose-related response; historical data and other considerations of biological relevance were taken into account.

STATISTICS
data analysed by using an analysis of variance (Winer, 1971) on untransformed proportions of cells with micronuclei per mouse and on untransformed PE:NE ratios when the variances were homogeneous; ranked proportions used for heterogeneous variances; differences from control analysed by Dunnett's t-test; parametric and nonparametric tests used for trend analysis.

Reliability: (2) valid with restrictions
Guideline study with acceptable restrictions.
Restrictions: no details about the purity of the TS.
Flag: Critical study for SIDS endpoint
19-MAY-2004 (48)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

Type:	other: sub-chronic gavage study comparable to OECD TG408 with data relating to fertility
Species:	rat
Sex:	male/female
Strain:	Sprague-Dawley
Route of administration:	gavage
Exposure Period:	91-92 days
Frequency of treatment:	once daily, 5 days per week
Doses:	0, 50, 500, 5000 mg/kg bw/day
Control Group:	other: controls treated with an empty gavage needle (no vehicle used)
Result:	see freetext

Method: other: comparable to OECD Guide-line 408
Year: 1997
GLP: yes
Test substance: other TS: thiodiglycol, samples analysed by gas chromatography before, during, and after the study; purity >= 95%

Result: Due to the decreased body weight the mean relative organ weights of testes were significantly higher in males of the high dose group; however, no significant effects were seen with the mean absolute testes weights (no toxicological relevance, no changes in histopathology). No effect on other

organ weights mentioned under test condition.

Pathology/histopathology: no changes related to the test substance in any organ mentioned under test condition.

Test condition: A detailed description of this study is given in chapter 5.4.

Organ weights: at necropsy testes and ovaries were removed and weighed for comparison among groups.

Histopathology of gonads and uterus, accessory genital organs were not examined.

Reliability: (1) valid without restriction
Comparable to guideline study

Flag: Critical study for SIDS endpoint

17-JUN-2004 (1)

5.8.2 Developmental Toxicity/Teratogenicity

Species:	rat	Sex: female
Strain:	Wistar	
Route of administration:	gavage	
Exposure period:	gestation day 6 to 15	
Frequency of treatment:	once daily	
Duration of test:	gestation day 20	
Doses:	0 or 1000 mg/kg bw/d	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	= 1000 mg/kg bw	

Method: other: OECD Guide-line 414, 1981
Year: 1991
GLP: yes
Test substance: other TS: thiodiglycol, purity >= 98.4%; stability tested by reanalysis

Method: LIMIT Test
Result: MATERNAL TOXIC EFFECTS
- Number of pregnant rats per dose level: 24 rats in each group
- None of the determined parameters (see freetext TC) revealed statistically significant or toxicologically relevant results; the significant decrease in bw of treated dams (only) on gestation day 3 occurred before the first gavage.

FETAL DATA
- No significant effects observed (determined parameters see freetext TC) except alterations on the fetal skeleton (see below)
- Skeletal abnormalities
  1) Significant increase in dumbbell ossification of thoracic vertebral bodies (12% versus 5.2% in control); this variation is also outside the historical control range (0.0-8.8%)
  2) Significant increase in rudimentary cervical ribs (variation; 7.1% versus 1.2% in control). Also total variations (concerning affected fetuses/litter) statistically increased (52.9 versus 38.6%).

ANALYSIS
- stability of the TS and TS solutions confirmed; food and tape water not contaminated

Test condition:

TEST ORGANISMS
- sexually mature, virgin Wistar rats
- supplied by Karl Thomae, Biberach, Germany
- acclimatization period at least 2 weeks

HOUSING AND DIET
- rats singly housed
- temperature 20-24°C, relative humidity 30-70%, day/night rythm 12h/12h
- room desinfected before use
- food (Kliba 343 feed) and tap water ad libitum

ANALYSIS
- test substance, stability of the test substance, and solution of the test substance (stability, homogeneity) were analysed as well as food and drinking water

MATING PROCEDURE
- virgin Wistar rats (mean weight 249 g; randomization) mated with untreated fertile males of the same breed
- if sperm was detected in the vaginal smear in the morning, this day was considered day0 (rats were 12-13 weeks old)

ADMINISTRATION / EXPOSURE
- Vehicle: bidistilled water
- Concentration in vehicle: 0 (control) or 10 g/100 ml
- Total volume applied: 10 ml/kg bw in both groups
- TS solution prepared twice during the study (stable solution)
- Number of animals per group: 25
- due to technical reasons, study carried out in 2 sections

PARAMETERS ASSESSED DURING STUDY
- Body weight gain: recorded on gestation day 0, 1, 3, 6, 8, 10, 13, 15, 17, 20 (corrected bw determined)
- Food consumption: determined on the same days than bw
- Clinical observations: clinical symptoms recorded once daily
- Examination of uterine content:
  measured parameters at termination are weight of uterus, No. of corpora lutea, live fetuses and dead implantations, early and late resorptions, dead fetuses; calculation of conception rate, preimplantation loss and postimplantation loss.
- Examination of fetuses:
  measured parameters are bw, sex, external findings, viability, placental weight; one half of the fetuses per dam prepared for soft tissue examination (method according to Barrow and Taylor, J Morph 127, 291-306, 1969), the other half for skeletal examination (method according to Dawson, Stain Tech 1, 123, 1926); detected changes differentiated in malformation, variation, retardation and unclassified observations.

ORGANS EXAMINED AT NECROPSY
- dams necropsied and assessed by gross pathology (no further details)

STATISTICAL METHODS
- two-sided DUNNETT-Test for comparison of one dose group with control
- one-sided FISHER's EXACT Test for a pairwise comparison of each dose group with control for hypothesis of equal proportions

- one-sided WILCOXON-Test for comparison of the dose group with control for the hypothesis of equal medians
- significance level p<0.05

Reliability: (1) valid without restriction

GLP guideline study
Flag: Critical study for SIDS endpoint
07-MAR-2005 (11)

Species:	rat	Sex: female
Strain:	Wistar	
Route of administration:	gavage	
Exposure period:	gestation day 6 to 15	
Frequency of treatment:	once daily	
Duration of test:	gestation day 20	
Doses:	0, 100, 400 or 1000 mg/kg bw d	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	= 400 mg/kg bw	
NOAEL Teratogenicity:	= 400 mg/kg bw	

Method: other: OECD Guide-line 414, 1981
Year: 1993
GLP: yes
Test substance: other TS: thiodiglycol, purity >= 98.4%; stability tested by reanalysis

Result: ANALYSIS
- stability of the TS and TS solutions was confirmed; food and drinking water not contaminated

MATERNAL TOXIC EFFECTS
- Number of nonpregnant rats: 1 rat in control group, 0 in low dose group, 4 rats in mid dose group and 0 in high dose group
- None of the determined parameters (see freetext TC) revealed statistically significant or toxicologically relevant results with exception of the bw of pregnant rats in the high dose group on gestation day 8 (32% lower than control value; transient, significant effect; authors comment: marginal effect but possibly treatment related)

FETAL DATA
- No statistical significant effects observed (compare with measured parameters in freetext TC) except the effects described below.
- Sex distribution: in the mid dose group statistically significant more females (no dose dependency), authors comment: no biological relevance.
- Placental weight: in the mid dose group significantly decreased placental weights of male fetuses, but value within laboratory historical control range.
- External malformations: 1 anophthalmia in low dose group and in high dose group 1 fetus with cleft palate and 1 with microphthalmia; considered to be spontaneous in nature by the authors (also low incidence in laboratory historical controls).
- Soft tissue malformations: significantly increased incidence of affected fetuses/litter (1.8%) in the mid dose group, but this value is within the laboratory historical control data (0-1.9%); considered by the authors to be spontaneous in nature and not treatment

related.
- Skeletal abnormalities
  1) Nonsignificant increase in dumbbell ossification of thoracic vertebral bodies (most often observed in the high dose group; 6.3% versus 3.6% in control), but this variation is outside the laboratory historical control concerning litter incidence (40% versus 19.5% in control); compare also with the LIMIT Test in section 5.9.
  2) Significant increase in number of affected fetuses/litter with accessory 14th rib in the high dose group (variation); this variation is regarded to be incidental in nature because litter and fetal incidences are within laboratory historical control range and this variation is not observed in the LIMIT Test (see this section).

CONCLUSION
No overt signs of teratogenicity observed up to 1000 mg/kg bw/day; however, a slight increase of dumbbell ossification of thoracic vertebral bodies was seen; this variation was significantly increased in a previously conducted LIMIT Test at the same dose level; a borderline effect due to TS treatment cannot be ruled out; at the same dose level marginal maternal toxicity (decreased body weight) occurred. The NOAEL for dams and fetuses is 400 mg/kg bw/day.

Test condition: TEST ORGANISMS
- sexually mature, virgin Wistar rats
- supplied by Karl Thomae, Biberach, Germany
- acclimatization period at least 2 weeks

HOUSING AND DIET
- rats singly housed
- temperature 20-24°C, relative humidity 30-70%, day/night rythm 12h/12h
- room desinfected before use
- food (Kliba 343 feed) and tap water ad libitum

ANALYSIS
- test substance, stability of the test substance, and solution of the test substance (stability) were analysed as well as food and drinking water

MATING PROCEDURE
- virgin Wistar rats (mean weight 242 g; randomization) mated with untreated fertile males of the same breed
- if sperm was detected in the vaginal smear in the morning, this day was considered day0 (rats were 88-90 days old)

ADMINISTRATION / EXPOSURE
- Vehicle: bidistilled water
- Concentration in vehicle: 0 (control), 1, 4, or 10 g/100 ml
- Total volume applied: 10 ml/kg bw in both groups
- TS solution prepared in intervals of 10 days (stable solution)
- Number of animals per group: 25
- due to technical reasons, study carried out in 2 sections

PARAMETERS ASSESSED DURING STUDY
- Body weight gain: recorded on gestation day 0, 1, 3, 6, 8, 10, 13, 15, 17, 20 (corrected bw determined)
- Food consumption: determined on the same days than bw

- Clinical observations: clinical symptoms recorded once daily
- Examination of uterine content:
measured parameters at termination are weight of uterus, No. of corpora lutea, live fetuses and dead implantations, early and late resorptions, dead fetuses; calculation of conception rate, preimplantation loss and postimplantation loss.
- Examination of fetuses:
measured parameters are bw, sex, external findings, viability, placental weight; one half of the fetuses per dam prepared for soft tissue examination (method according to Barrow and Taylor, J Morph 127, 291-306, 1969), the other half for skeletal examination (method according to Dawson, Stain Tech 1, 123, 1926); detected changes differentiated in malformation, variation, retardation and unclassified observations.

ORGANS EXAMINED AT NECROPSY
- dams necropsied and assessed by gross pathology (no further details)

STATISTICAL METHODS
- two-sided DUNNETT-Test for comparison of one dose group with control
- one-sided FISHER's EXACT Test for a pairwise comparison of each dose group with control for hypothesis of equal proportions
- one-sided WILCOXON-Test for comparison of the dose group with control for the hypothesis of equal medians
- significance level $p<0.05$

Reliability: (1) valid without restriction
GLP guideline study
Flag: Critical study for SIDS endpoint
07-MAR-2005 (10)

Species:	rat	Sex: female
Strain:	Sprague-Dawley	
Route of administration:	gavage	
Exposure period:	gestation day 5 to 19	
Frequency of treatment:	once daily	
Duration of test:	gestation day 20	
Doses:	0, 430, 1290, 3870 mg/kg bw d	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	= 1290 mg/kg bw	
NOAEL Teratogenicity:	= 3870 mg/kg bw	
NOAEL Fetotoxicity :	= 1290 mg/kg bw	

Method: other: see freetext
Year: 2001
GLP: no data
Test substance: other TS: thiodiglycol, purity 99,9%

Result: Maternal toxicity:
- At the high dose body weight and food consumption reduced.

Developmental toxicity:
- In the high dose group fetal weight was significantly reduced
- Increased incidence of variation in the high dose group

but not statistically significant
- no teratogenic effects

Test condition: 25 mated rats per group; litters examined for soft tissue and skeletal alterations; maternal body weight gain and food consumption recorded.

Reliability: (4) not assignable
Documentation insufficient for assessment.
Details of the study confined to the above.

Flag: Critical study for SIDS endpoint

18-MAY-2004 (52) (53) (64)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Human

Remark: Based on the structural similarity to ethylene glycol thiodiglycol may produce depression of the central nervous system, metabolic acidosis and renal failure in severe intoxication.

03-JAN-2005 (54)

5.11 Additional Remarks

Type: Biochemical or cellular interactions

Remark: The inhibiton of horseraddish peroxidase by the TS was investigated; the horseraddish peroxidase oxidation of 2,2-azino-di-(3-ethyl)benzthiazoline sulfonic acid was inhibited by TS; inhibition of this reaction followed a mixed-type inhibitory reaction mechanism; the Km and Vmax of the enzymatic reaction were significantly affected in the presence of TS; the Ki value of the TS was found to be in the range of 1.0x10E-4 M.

Test substance: thiodiglycol, no further data

14-FEB-2002 (87)

Type: Biochemical or cellular interactions

Result: The TS stimulated the differentiation of chick embryo myogenic cells. In the presence of the test substance, myoblasts fused, yielding myotubules with the same efficiency in standard media for chick embryo fibroblast-like cell
culture (4% bovine serum and 1% chick serum) as in media specially designed to promote myoblast fusion (10% horse serum, 5% chick serum). Furthermore, the myofibres formed in the presence of the test substance at a concentration of 0.1% morphologically resembled more closely myofibres formed in vivo than those formed in the presence of horse serum.

Test condition: The effects of the TS on the myogenesis in suboptimal tissue culture conditions were measured. Cell cultures containing myogenic and fibroblastic cells obtained from 11-day old

chicken embryos were incubated with the test substance at concentrations ranging from 0.02-0.2% at 37°C for 24, 48, 72, and 96 hours.
Test substance: thiodiglycol, no further data

14-FEB-2002 (65)

Type: other: background levels in unexposed humans

Result: Concentration in blood 6-16 ng/ml, in 2 subjects below detection limit of 1 ng/ml.
In urine concentration < 1 ng/ml (n=8), also < 1 ng/ml after treatment with beta-glucuronidase and conc. HCl (in urine of 3 subjects determined).
Test condition: In unexposed control subjects the background levels of the TS in blood (n=10) and urine (n=8) were determined (detection limit 1 ng/ml).

07-JUN-2002 (32)

Type: other: thiodiglycol as a metabolite

Remark: Thiodiglycol was detected in urine samples from 2 male subjects following an accidental cutaneous (predominantly) exposure to sulfur mustard from an 80-year old munition. Sulfur mustard was converted in humans to thiodiglycol and thiodiglycol sulfoxide by hydrolysis. TS not found in the urine of unexposed humans (detection limit 1 ng/ml). Similar results presented in a further case study of accidental human exposure to sulfur mustard (Jakubowski et al., 2000).
Test substance: thiodiglycol, no further data

21-MAY-2004 (31) (55)

Type: other: thiodiglycol as a metabolite

Remark: The urinary excretion profiles of some metabolites of sulfur mustard (thiodiglycol and other, derived from hydrolysis of sulfur mustard among others) were determined by GC/MS after cutaneous application of sulfur mustard in rats.
Concentrations of thiodiglycol detected increased up to 10-fold after treatment of the urine with hydrochloric acid, presumably because of the excretion fo acide-labile esters of thiodiglycol. Free thiodiglycol excreted over 8 days accounted for <0.3% of the applied dose of sulfur mustard (free thiodiglycol plus esterified thiodiglycol 1-1.5% of the applied dose).
Test substance: thiodiglycol, no further data

27-MAY-2003 (34)

Type: other: thiodiglycol as a metabolite

Remark: TS detected in blood samples collected from rats which had been intravenously intoxicated with the sulphur-mustard (2,2'-dichlorodiethyl sulfide).
Test substance: thiodiglycol, no further data

07-JUN-2002 (58)

Type: other: thiodiglycol as a metabolite

Result: Thiodiglycol was one of the metabolites of the chlorinated derivatives; however the metabolic profiles of the chlorinated compounds were different from that of thiodiglycol (no further data).

Test condition: The metabolism of radiolabeled S-mustard (35-S-di-2-chlorethylsulphide), half mustard (35-S-2-chloroethyl-2'-hydroxyethylsulphide) and their hydrolysis product, 35-S-thiodiglycol was investigated in rats. Rats were injected with the different test substances, urine samples were collected and analyzed autoradiographically by paper chromatography.

Test substance: 35S-thiodiglycol, no further data

07-JUN-2002 (66)

Type: other: thiodiglycol as a metabolite

Remark: The metabolism of S-mustard was investigated in rodents. Urine and tissues (brain, liver, kidney, fat and muscles) of rats, guinea pigs, and albino mice were examined by GCMS 48 hours after application of undiluted S-mustard. The TS was identified in the urine, only.

Test substance: thiodiglycol, no further data

07-JUN-2002 (81)

Type: other: thiodiglycol as a metabolite

Remark: The TS was detected in urine samples from several Iranian patients who were victims of an alleged attack with mustard gas. The concentration of the test substance ranged from 10 to 100 ng/ml. In 20 male controls the TS concentration in urine was not above 20 ng/ml; the difference between the 2 groups is significant.

Test substance: thiodiglycol, no further data

07-JUN-2002 (85)

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