FOREWORD INTRODUCTION

3-Methylbut-2-en-1-ol

CAS N° : 556-82-1

SIDS Initial Assessment Report

For

SIAM 16

Paris, France, 27 – 30 May 2003

1.	**Chemical Name:**	3-Methylbut-2-en-1-ol
2.	**CAS Number:**	556-82-1
3.	**Sponsor Country:**	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn- Bad Godesberg
4.	**Shared Partnership with:**	BASF AG, Germany; KURARAY CO., LTD
5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	BASF AG, Germany Contact person: Dr. Hubert Lendle, GUP/CL - Z570 D-67056 Ludwigshafen
•	Process used	see below
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): 08. December 2002 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 10. September 2002 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms
8.	**Quality check process:**	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
9.	**Date of Submission:**	19 February 2003
10.	**Date of last Update:**	

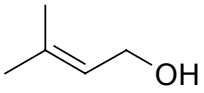
11. Comments:

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 o f 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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	556-82-1
Chemical Name	3-Methylbut-2-en-1-ol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The LD50 for the rat after oral administration of 3-methylbut-2-en-1-ol was 1591 mg/kg bw. The main symptoms described were apathy, dyspnea and reddened eyes and ears. A dose response was observed, with symptoms getting progressively worse with increasing dose and recovery occurred within 7 days in the two lowest doses tested (172 and 1376 mg/kg bw). After inhalation of vapors of the substance, a LC50 of > 16.8 mg/l/4 hrs can be estimated for rats using Haber's rule. A dermal LD50 in rats was found to be > 4000 mg/kg bw. In rabbits the substance was corrosive to the skin and highly irritant to the eyes.

In a maximization test in humans, the substance (10 % in petrolatum) caused no skin sensitization.

In a 90 days study (OECD guideline 408) with administration of the test substance in the drinking water up to concentrations of 5000 ppm (243.8 and 307.2 mg/kg bw/day for males and females), the only treatment related findings were reduction in food and water consumption at the high and mid dose which was accompanied by a decrease in body weight and body weight gain at the high dose. There were no other treatment related significant changes in clinical examinations, functional observational battery, opthalmoscopy, clinical chemistry, hematolgy, urinalyses, organ weights, pathology and histopathology. The no observed adverse effect level (NOAEL) was 1000 ppm for both sexes (65.4 and 82.1 mg/kg bw/day for males and females)

No mutagenic effect was found in the Ames Test (preincubation test and liquid suspension assay) and *in vivo* in the mouse micronucleus test.

Based on the results of the well conducted 90 days study in rats with administration of the test substance in the drinking water, 3-methylbut-2-en-1-ol does not have potential to damage the reproductive organs at least up to the highest tested concentration of 5000 ppm (243.8 and 307.2 mg/kg bw/day).

3-Methylbut-2-en-1-ol showed no evidence of developmental toxicity (including no teratogenicity) in an OECD TG 414 study when administered by gavage (up to 600 mg/kg bw/day) to pregnant rats from implantation to one day prior the expected day of parturition (days 6-19 after conception). The NOAEL for maternal toxicity was 200 mg/kg bw/day while the NOAEL for prenatal developmental toxicity was > 600 mg/kg bw/day.

Environment

3-Methylbut-2-en-1-ol is a colorless liquid, with high solubility in water (170 g/l at 20°C) and high vapor pressure (3.17 hPa at 25°C). The substance has a flash point at 51.5 °C and is flammable. The density of the substance (0.85 g/cm^3 at 20°C) is slightly lower than that of water. The boiling point of the substance is about 142 °C, the calculated melting point at –59.3 °C. The measured partition coefficient n-octanol water (log K_{OW}) is 0.91.

Distribution modelling using Mackay level I indicates water to be the main target compartment (95 %). The calculated Henry´s constant in the range of 0.73 to 1.4 $Pa*m^3/mole$ suggests a moderate volatilisation from water. According to OECD-criteria the substance is readily biodegradable (OECD 301F, 82 % after 28 d, 10d-window fulfilled). Hydrolysis is not expected according to the structure. In the atmosphere 3-methylbut-2-en-1-ol will be indirectly photodegraded by reaction with hydroxyl radicals (calculated half-life 4.25 hours) or ozone (calculated half-life 38 min). Calculations based on the log K_{OW} = 0.91 do not indicate a potential for bio- and geoaccumulation.

Acute aquatic toxicity has been determined for fish (*Leuciscus idus*: LC50 (96 h) 46 mg/l), for aquatic invertebrates (*Daphnia magna*: EC50 (48h) = 144 mg/l) and for green algae (*Scenedesmus subspicatus*: E_bC50 (72 h) > 500 mg/l). According to the EU Technical Guidance Document, the PNEC aqua can be calculated to 0.046 mg/l by applying an assessment factor of 1000 on the most sensitive species.

Exposure

The world-wide production of 3-methylbut-2-en-1-ol for the year 2001 was in the range of 6,000 to 13,000 tonnes, thereof 5,000 to 10,000 tonnes in Europe. It is produced in Europe and Asia by two producers, in the NAFTA it is processed at a range of 1,000 to 5,000 tonnes per year.

3-Methylbut-2-en-1-ol is mainly used as intermediate in the chemical industry for the synthesis of active ingredients (pharmaceuticals, aroma chemicals). A minor fraction, estimated to a maximum of 50 tons, is used as flavoring agent (1 - 10 ppm in final products) and in cosmetics at a maximum level of 0.1 %. There are no products containing the substance in the Swedish, Danish, Swiss and Norwegian product registers.

3-Methylbut-2-en-1-ol naturally occurs in citrus fruits, cranberry, bilberry, currants, grapes, raspberry, black berry, tomato, white bread, hop oil, coffee, Arctic bramble, cloudberry and passion fruit.

Releases into the environment may occur during production and processing of 3-methylbut-2-en-1-ol as an intermediate, as well as from the use of the substance as an ingredient in cosmetic products.

Exposure to workers is adequately controlled in the industry of the sponsor country (Germany).

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The substance is corrosive. Given the main use as a chemical intermediate in closed systems and the low content of the substance in consumer products in the Sponsor country, the substance is considered to be of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

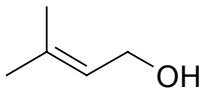
Environment: The substance possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 556-82-1
IUPAC Name: 3-methylbut-2-en-1-ol
Molecular Formula: $C_5 H_{10} O$
Structural Formula:



Synonyms: 2-buten-1-ol, 3-methyl-
3,3-dimethylallyl alcohol
3-methyl-2-buten-1-ol
3-methylcrotyl alcohol
dimethylallyl alcohol
prenyl alcohol
Prenol
Substance type: organic
Physical status: liquid

1.2 Purity/Impurities/Additives

Purity: ca. 98 % w/w

Impurities: 3-methylbut-3-en-1-ol, ca. 0.5% w/w

2-methylbut-3-en-2-ol, ca. 0.5% w/w

formaldehyde, < 400 ppm

1.3 Physico-Chemical properties

3-Methylbut-2-en-1-ol is a colorless liquid, with high solubility in water (170 g/l at 20°C) (BASF AG 2001a) and high vapor pressure (3.17 hPa at 25 °C, extrapolated from measured data at higher temperatures)(BASF AG 1979a). The substance has a flash point at 51.5 °C and is flammable (manufacturer data without proof). The density of the substance (0.85 g/cm^3 at 20°C) is slightly lower than that of water (BASF AG 1968). Flotation or stratification processes in surface waters in case of accidental losses are possible. The boiling point of the substance is about 142 °C (BASF AG 1973), the calculated melting point at –59.3 °C (BASF AG 2002a).

The measured partition coefficient n-octanol water (log K_{OW}) is 0.91 (BASF AG 1988a).

2 GENERAL INFORMATION ON EXPOSURE

The world-wide production of 3-methylbut-2-en-1-ol for the year 2001 was in the range of 6000 to 13,000 tons, thereof 5000 to 10,000 tons in Europe. It is produced in Europe by BASF AG

(Ludwigshafen) and in Asia by KURARAY CO., in the NAFTA it is processed at a range of 1000 to 5000 tons.

3-Methylbut-2-en-1-ol is manufactured in a two-step synthesis involving the reaction of isobutene and formaldehyde, followed by isomerisation of the resulting iso-Prenol (BASF AG 2002b).

3-Methylbut-2-en-1-ol is mainly used as intermediate in the chemical industry for the synthesis of active ingredients (pharmaceuticals, aroma chemicals). It is handled in a fully continuous process in closed systems. It is mainly consumed internally within the production site. Minor amounts are consumed at customer sites in Europe and overseas.

In addition to that, the use as ingredient in cosmetic products is limited. It can be estimated that at maximum 50 tons are directly used for the generation of flavor and fragrance compounds (BASF AG 2002b). In these products, there are varying levels: flavor compounds 1 - 10 ppm in final products, in fragrance compounds the maximum use levels are about 0.1 %. There are no products containing the substance in the Swedish, Danish, Swiss and Norwegian product registers (Danish Product Register 2002, Swedish Product Register 2002, Swiss Product Register 2002, Norwegian Product Register 2003).

3-Methylbut-2-en-1-ol naturally occurs in citrus fruits, cranberry, bilberry, currants, grapes, raspberry, black berry, tomato, white bread, hop oil, coffee, Arctic bramble, cloudberry and passion fruit (CIVO-TNO 1977).

Releases into the environment may occur during production and processing of 3-methylbut-2-en-1-ol as an intermediate, as well as from the use of the substance as ingredient in cosmetic products.

3-Methylbut-2-en-1-ol is measured in the influent and the effluent of the waste water treatment plant of BASF AG at regular intervals (24 h-mixing sample). 2001 the concentration in the influent as well as in the effluent was always found to be below the limit of quantitation (influent: 0.5 mg/l; effluent: 0.02 mg/l; BASF AG 2002f).

Based on the limit of quantitation and assuming worst case conditions, less than 7.9 kg per day of 3-methyl-2-en-1-ol were released to the River Rhine in that period.

During production and internal processing at BASF AG, Ludwigshafen (Germany), less than 25 kg/a (limit for notification at the German Emission Register) were emitted into the air in 2000. During production, internal processing and storage at BASF AG, exhaust gases are admitted to combustion (BASF AG 2002e).

Emission data from other production and processing sites are not available.

2.1 Environmental Exposure and Fate

Distribution modelling using Mackay level I indicates water to be the main target compartment (95 %). A minor part of the substance will distribute into the air (5 %). The underlying input parameters are described in the IUCLID data set. The calculated Henry´s constant (SRC-HENRY v3.10) of 0.73 to 1.4 Pa*m^3/mole suggests a moderate volatilisation from water. In the air the substance will be rapidly degraded according to the calculated half life of about 4.25 hours for the reaction with OH-radicals and 38 min for the reaction with ozone molecules (AOP v1.90)(BASF AG 2002a).

3-Methylbut-2-en-1-ol is readily biodegradable according to OECD-criteria (82 % BOD of ThOD in a respirometric test (OECD 301F), 10d-window-criterion fulfilled) (BASF AG 1988d). Hydrolysis is not to be expected according to the chemical structure.

The substance has no chromophores. A relevant absorption above 300 nm and thus direct photolysis is not expected (BASF AG 2004).

The estimated log K_{oc} of 0.58 indicates that 3-methylbut-2-en-1-ol will not adsorb on soil, sediments or suspended solids (BASF AG 2002a).

No data on bioaccumulation are available. Based on a measured log K_{ow} of 0.91, bioaccumulation is not expected in aquatic organisms.

2.2 Human Exposure

At the European production site, 3-Methyl-2-en-1-ol is used predominantly as a chemical intermediate for the production of Citral. The product is handled in closed systems except for drumming. Concerning the usage in cosmetics, no information about workplace exposure is available.

3-Methyl-2-en-1-ol has a limited use as ingredient in cosmetic products as flavor and fragrance compounds. In these products, there are varying levels: flavor compounds 1 - 10 ppm in final products, in fragrance compounds the maximum use levels are about 0.1 %.

As 3-Methyl-2-en-1-ol is readily biodegradable and has a low bioaccumulation potential, indirect human exposures via the environment is not expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No specific studies are available concerning kinetic or metabolic fate of the substance. Based on the acute and repeated dose studies it can be concluded that the substance can be absorbed by oral, dermal and inhalation routes. In vitro experiments indicate that 3-methylbut-2-en-1-ol is metabolized by the liver (Strubelt et al. 1999).

3.1.2 Acute Toxicity

Oral

In a non-guideline study an LD50 in rats was determined to be ca. 1591 mg/kg bw (BASF AG 1970) after a post-dosing observation period of 7 days. The symptoms reported were described as staggering, dyspnea, restlessness (172 mg/kg bw or higher), apathy, abdominal position, reddened eyes and ears (1376 mg/kg bw or higher), lateral and partly dorsal positions, secretion out of eyes and mouth (1720 mg/kg bw or higher). A dose response was observed, with symptoms getting progressively worse with increasing dose and recovery occurred within 7 days in the two lowest doses tested (172 and 1376 mg/kg bw).

The unassignable acute oral toxicity data in rat (LD50 810 mg/kg bw and mouse 1500 mg/kg bw) are broadly consistent with the original data reviewed by the sponsor.

Inhalation

LC50 rat after a 7 days post-observation period: > 16.8 mg/l/4 hrs; estimated by Haber's Rule from an Inhalation Risk Test which used a highly enriched/saturated vapor exposure system at 20°C, in

which rats were exposed to a vapor of the substance at a concentration of 8.4 mg/l for 8 hours (BASF AG 1970). One animal out of the 6 exposed rats died within the first 24 hrs after the exposure. Clinical symptoms were attempts to escape, strong secretion out of eyes and nose, and tremors after exposure.

Dermal

In a non-guideline study, a LD50 in rats was reported as > 4000 mg/kg bw (BASF AG 1979b). The clinical symptoms noted were slight apathy, irregular breathing, slight local skin irritation which were reversible in the post observation period.

Conclusion

The LD50 for the rat after oral administration of 3-methylbut-2-en-1-ol was 1591 mg/kg bw. The main symptoms described were apathy, dyspnea, redness of eyes and ears. After inhalation of vapors of the substance, a LC50 of > 16.8 mg/l/4 hrs can be estimated for rats using Haber's rule. A dermal LD50 in rats was found to be > 4000 mg/kg bw.

3.1.3 Corrosiveness and irritation

In non-guideline studies, 3-methylbut-2-en-1-ol was corrosive to the skin of rabbits after 1, 4 and 20 hours of occlusive exposure (BASF AG 1970, BASF AG 1979c). A Primary Irritation Index (PII) of 6.13 can be calculated for the 4 hour exposure (although not done in the original report).

Similar results were obtained in a further study when 3-methylbut-2-en-1-ol was tested for its skin irritation in a non-guideline study in rabbits. The substance was applied for 24 hours under occlusive conditions to intact and abraded skin. The substance was considered to be extremely irritating to the skin of rabbits under conditions of the study (TSCAT 1992).

In the eyes of rabbits, 3-methylbut-2-en-1-ol caused moderate corneal opacity, moderate conjunctival redness and chemosis when applied undiluted at a volume of 0.1 ml. The changes were not completely reversible within a post observation period of 8 days (BASF AG 1979d). In a further study, the substance applied at a volume of 50 µl led to slight corneal opacity and moderate redness and edema in the rabbit eye. The findings were reversible after 8 days except a slight conjunctival redness (BASF AG 1970).

Conclusion

3-Methylbut-2-en-1-ol was corrosive to the skin of rabbits. In the rabbit eye, the substance was highly irritating and has a risk of serious damage to the eyes.

3.1.4 Sensitisation

In a human maximization test, 3-methylbut-2-en-1-ol at a concentration of 10 % in petrolatum did not produce skin sensitization in 26 volunteers (Epstein 1977).

Conclusion

3-Methylbut-2-en-1-ol showed no skin sensitizing potential in a maximization test in humans at a test concentration of 10 % in petrolatum.

3.1.5 Repeated Dose Toxicity

A subchronic oral toxicity study with 3-methylbut-2-en-1-ol was recently conducted under GLP conditions and according to OECD protocol 408 (BASF AG 2002c). The scope of examinations was extended to cover also effects on reproductive organs (see also chapter 3.1.7).

3-Methylbut-2-en-1-ol was administered to groups of 10 male and 10 female Wistar rats in the drinking water at concentrations of 0, 200, 1000 and 5000 ppm for three months. These concentrations corresponded to dosages of 14.4 and 21.0 mg/kg bw/day, 65.4 and 82.1 mg/kg bw/day or 243.8 and 307.2 mg/kg bw/day for males and females. Food consumption, water consumption and body weights were determined weekly. The animals were examined for clinical signs of toxicity or mortality at least once a day. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. A functional observational battery (FOB) and measurement of motor activity was carried out towards the end of the administration period. Ophthalmological examinations were carried out prior to the start and towards the end of the administration period. Clinicochemical and hematological examinations as well as urinalyses and investigation of sperm parameters were carried out towards the end of the administration period. All animals were assessed by gross pathology, followed by histopathological examinations.

Substance related effects were seen at the high and mid dose level. Food consumption was significantly decreased in both sexes of the high dose group (up to –18.2 % below control in males and –21 % in females) and in females of the mid dose group (up to -9.4 %). Water consumption was significantly reduced in both sexes of the high dose group during the entire study (up to –49.9 % in males and –47.8 % in females) and the mid dose group (up to -25.1 in males and -28.9 % in females) which can be most likely be explained by the intensive taste and odor of the test substance solutions. Body weight was significantly impaired at the high dose (–12.2 % in males and –8.8 % in females on day 91). A significantly decreased body weight change was seen in the same dose group (–20.4 % in males and –19.2 % in females on day 91). In the high and mid dose male rats, the mean absolute liver weights were significantly decreased (–14.9 % and –7.9 %, respectively), but not the relative liver weights. This is regarded as a consequence of the significantly reduced body weights rather than a treatment related or adverse effect. Urinalysis revealed a reduced urinary volume with increased specific gravity in both sexes of the high dose animals. These findings were assessed as being compound related, but were mainly caused by the reduced water consumption.

There were no other treatment related significant changes in clinical examinations, opthalmoscopy, functional observational battery, clinical chemistry, hematology, urinalyses, organ weights, gross lesions, or microscopical examinations. As reduction in food and water consumption resulted in significant decrease of body weight only at the high dose level, the no observed adverse effect level (NOAEL) was assessed to be 1000 ppm (65.4 mg/kg bw/day in males, 82.1 mg/kg bw/day in females). The lowest observed adverse effect level (LOAEL) was 5000 ppm (243.8 and 307.2 mg/kg bw/day for males and females). No effects on reproductive organs or sperm parameters were observed.

Conclusion

The only treatment-related findings after subchronic oral exposure to 3-methylbut-2-en-1-ol were a reduction in food and water consumption which was accompanied by a decrease in body weight and body weight gain (NOAEL 65.4 mg/kg bw/day in males, 82.1 mg/kg bw/day in females; LOAEL 243.8 and 307.2 mg/kg bw/day for males and females).

3.1.6 Mutagenicity

In vitro Studies

3-Methylbut-2-en-1-ol was tested for its mutagenic potential at doses of up to 5000 µg/plate in Salmonella strains TA1535, TA100, TA1537 and TA98 with and without metabolic activation according to OECD guideline 471 (BASF AG 1989). The laboratory conducted the study under GLP working conditions, but was not yet GLP certified. An additional Salmonella mutagenicity test with a modified protocol (Liquid Suspension Assay) was carried out in the same laboratory in two bacterial strains (TA 98 and TA 100) (BASF AG 1991). In both studies, an increase in the number of his^+ revertants was not observed and consistently a negative result was obtained.

In vivo Studies

3-Methylbut-2-en-1-ol was tested for its ability to induce micronuclei in bone marrow erythrocytes in mice using two intraperitoneal doses up to 500 mg/kg bw/day under OECD guideline 474 and GLP conditions (BASF AG 2001b). This dose level produced evident toxicity. The test substance did not have a chromosome-damaging (clastogenic) effect and there were no indications of any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells in vivo.

Conclusion

3-Methylbut-2-en-1-ol gave no indication of a mutagenic effect in bacteria or a clastogenic potential in vivo in the bone marrow from mice.

3.1.7 Carcinogenicity

No specific study concerning the investigation of a carcinogenic potential is available.

3.1.8 Toxicity for Reproduction/Development

Reproduction

Studies specifically designed to assess reproductive toxicity were not available for an assessment; however, in a recently well conducted subchronic oral toxicity study, the scope of examinations was extended to cover also effects on reproductive organs (see also chapter 3.1.5; BASF AG 2002c).

In this study, methylbut-2-en-1-ol was administered to groups of 10 male and 10 female Wistar rats in the drinking water at concentrations of 0, 200, 1000 and 5000 ppm for 3 months (14.4 and 21.0 mg/kg bw/day, 65.4 and 82.1 mg/kg bw/day, 243.8 and 307.2 mg/kg bw/day for males and females). At necropsy, the weights of the reproductive organs of the males (testes, epididymides, prostate gland) and females (ovaries, uterus) were assessed by gross pathology and a histopathological examination of the testes, epididymides, prostate gland and, seminal vesicles, ovaries, uterus, oviducts and vagina was subsequently performed. Furthermore, immediately after necropsy, the right testis and cauda epididymis were taken from all male animals. Sperm motility, sperm morphology and sperm head count (cauda epididymis and testis) were examined.

No treatment related changes in sperm analysis were observed. The weights of the reproductive organs were not influenced by the exposure, except a significantly increased relative weight of the testes (+13.7 %) and epididymides (+12.7 %) in the high dose males (most likely as a result of the decreased mean terminal body weight in these animals) and a slightly (–13.6 %), but significantly ($p < = 0.05$) decreased absolute organ weight of the ovaries of the high dose females. The relative ovary weights were not affected. No histological abnormalities in the sex organs were detected and

no histological correlates were obtained for the changes in relative weights of the testes and epididymides and absolute weights of the ovaries. Considering the normal biological variation of these organ weight parameters in connection with the reduced terminal body weight of the high dose animals these observations were not regarded as adverse effects.

Conclusion:

Based on the results of the well conducted 90 days study in rats with administration of the test substance in the drinking water, 3-methylbut-2-en-1-ol does not have potential to damage the reproductive organs at least up to the highest tested concentration of 5000 ppm (243.8 and 307.2 mg/kg bw/day).

Developmental Toxicity

3-Methylbut-2-en-1-ol was recently tested for its prenatal developmental toxicity in Wistar rats according to OECD guideline 414 and under GLP conditions (BASF AG 2002d). The test substance was administered as an aqueous suspension to 25 time-mated female Wistar rats/group by stomach tube at doses of 50, 200 and 600 mg/kg/d bw on day 6 through day 19 post coitum (p.c.). A standard dose volume of 10 ml/kg body weight was used for each group. The control group, consisting of 25 females, was dosed with the vehicle only (0.5 % Carboxymethylcellulose CB 30,000 in doubly distilled water). 23 - 24 females/group had implantation sites at terminal sacrifice. Food consumption and body weights of the animals were recorded regularly throughout the study period. The state of health of the animals was checked each day.

On day 20 p.c., all surviving females were sacrificed and assessed by gross pathology (including weight determinations of the unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) were determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external findings. Thereafter, nearly one half of the fetuses of each litter was examined for soft tissue findings and the remaining fetuses for skeletal (incl. cartilage) findings.

The oral administration of 3-methylbut-2-en-1-ol to pregnant Wistar rats from implantation to one day prior to the expected day of parturition elicited clear signs of maternal toxicity at 600 mg/kg bw/day. Maternal toxicity was predominantly substantiated by adverse clinical findings (like salivation, lacrimation, abdominal position and piloerection), which could be at least partly observed throughout the treatment period. One dam died before schedule, which might be also substance-induced. After initiation of treatment, mean food consumption, mean body weight and mean body weight gain were statistically significantly lowered if compared to the controls. Moreover, the corrected body weight gain and the mean carcass weight were also impaired.

No signs of substance-induced maternal toxicity occurred at the low and the mid dose level (50 or 200 mg/kg bw/day). There were no substance-related influences on the gestational parameters up to and including the highest dose level (600 mg/kg bw/day). Conception rate, mean number of corpora lutea, total implantations, resorptions and live fetuses, fetal sex ratio or the values calculated for the pre- and the postimplantation losses were unaffected by treatment.

The test substance administration evoked no signs of developmental toxicity and in particular no indications for teratogenicity at any of the dose levels tested. Placental and fetal body weights were unaffected. The external, soft tissue and/or skeletal (including cartilage) examinations of the fetuses revealed no biologically relevant differences between the control and the substance-treated groups.

Based on the results of this developmental toxicity study, the no observed adverse effect level (NOAEL) for maternal toxicity is 200 mg/kg bw/day, while it is > 600 mg/kg bw/day (the highest dose tested) for developmental toxicity.

Conclusion:

3-Methylbut-2-en-1-ol showed no evidence of developmental toxicity or teratogenicity by oral administration.

3.2 Initial Assessment for Human Health

LD50 for the rat after oral administration of 3-methylbut-2-en-1-ol was 1591 mg/kg bw. The main symptoms described were apathy, dyspnea, reddened eyes and ears. A dose response was observed, with symptoms getting progressively worse with increasing dose and recovery occurred within 7 days in the two lowest doses tested (172 and 1376 mg/kg bw). After inhalation of vapors of the substance, a LC50 of > 16.8 mg/l/4 hrs can be estimated for rats using Haber's rule. A dermal LD50 in rats was found to be > 4000 mg/kg bw. In rabbits the substance was corrosive to the skin and highly irritant to the eyes.

In a 90 days study (OECD guideline 408) with administration of the test substance in the drinking water up to concentrations of 5000 ppm (243.8 and 307.2 mg/kg bw/day for males and females), the only treatment related findings were reduction in food and water consumption at the high and mid dose which was accompanied by a decrease in body weight and body weight gain at the high dose. There were no other treatment related significant changes in clinical examinations, functional observational battery, opthalmoscopy, clinical chemistry, hematology, urinalyses, organ weights, pathology and histopathology. The no observed adverse effect level (NOAEL) was 1000 ppm for both sexes (65.4 and 82.1 mg/kg bw/day for males and females; LOAEL 243.8 and 307.2 mg/kg bw/day for males and females).

No mutagenic effect was found in the Ames Test (preincubation test and liquid suspension assay) and in vivo in the mouse micronucleus test.

Based on the results of the well conducted 90 days study in rats with administration of the test substance in the drinking water, 3-methylbut-2-en-1-ol does not have potential to damage the reproductive organs at least up to the highest tested concentration of 5000 ppm (243.8 and 307.2 mg/kg bw/day).

3-Methylbut-2-en-1-ol showed no evidence of developmental toxicity (including no teratogenicity) in an OECD TG 414 study when administered by gavage (up to 600 mg/kg bw/day) to pregnant rats from implantation to one day prior the expected day of parturition (days 6 - 19 after conception). The NOAEL for maternal toxicity was 200 mg/kg bw/day while the NOAEL for prenatal developmental toxicity was > 600 mg/kg bw/day (the highest dose tested).

In a maximization test in humans, the substance (10 % in petrolatum) caused no skin sensitization.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

The following acute toxicity tests with aquatic organisms are available:

Leuciscus idus	LC50 (96h) 46 mg/l	BASF AG 1988b

Daphnia magna	EC50 (48h) 144 mg/l	BASF AG 1988c
Scenedesmus subspicatus	EbC50 (72h) >500 mg/l	BASF AG 1988c
	EbC10 (72h) 213 mg/l	

In addition, also effect values for microorganisms are available:

Pseudomonas putida	EC50 (17h) 3380 mg/l	BASF AG 1988c
Activated sludge, industrial	EC20 (0.5h) >2880 mg/l	BASF AG 1988d

All tests were performed in static, open test systems and the effect values are related to nominal concentrations. As 3-methylbut-2-en-1-ol is moderately volatile, a decrease in test concentration during the exposure period cannot be excluded. Therefore, volatility was measured under test conditions comparable to the fish, daphnia and algae tests, but without test organisms (BASF 2003). Based on TOC measurements the recovery rate at the end of the exposure period was 93 % for the fish test, 94 % for the daphnia test and 98 % for the algae test. This shows that the test substance concentration remained nearly constant under the conditions of the three ecotoxicity tests and therefore the effect values based on nominal concentrations can be used for the hazard assessment without limitations.

Results from prolonged or chronic studies are not available.

Based on the most sensitive data, *Leuciscus idus* LC50 (96h) 46 mg/l, a PNEC aqua of 0.046 mg/l can be derived by applying an assessment factor of 1000, according to the EU Technical Guidance Document.

4.2 Terrestrial Effects

There are no data for toxicity to soil dwelling organisms, terrestrial plants or other non-mammalian terrestrial organisms.

4.3 Initial Assessment for the Environment

Distribution modelling using Mackay level I indicates water to be the main target compartment (95 %). The calculated Henry´s constant in the range of 0.73 to 1.4 Pa*m^3/mole suggests a moderate volatilisation from water. According to OECD-criteria the substance is readily biodegradable. Hydrolysis is not expected according to the structure. The substance has no chromophores. A relevant absorption above 300 nm and thus direct photolysis is not expected.

In the atmosphere 3-methylbut-2-en-1-ol will be indirectly photodegraded by reaction with hydroxyl radicals (calculated half-life 4.25 hours) or ozone (calculated half-life 38 min). Calculations based on the log K_{ow} = 0.91 do not indicate a potential for bio- and geoaccumulation.

Acute aquatic toxicity has been determined for fish (*Leuciscus idus*: LC50 (96h) 46 mg/l), for aquatic invertebrates (*Daphnia magna*: EC50 (48h) = 144 mg/l) and for algae (*Scenedesmus subspicatus*: EbC50 (72h) > 500 mg/l). Results from prolonged or chronic studies are not available. According to the EU Technical Guidance Document, the PNEC aqua can be calculated to 0.046 mg/l by applying an assessment factor of 1000 on the most sensitive species.

5 RECOMMENDATIONS

Environment: The chemical is currently of low priority for further work. 3-Methylbut-2-en-1-ol possesses properties indicating a hazard for the environment. Based on data presented by the Sponsor country, exposure to the environment is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Human Health: The chemical is currently of low priority for further work. The substance is corrosive. Given the main use as a chemical intermediate in closed systems and the low content of the substance in consumer products in the Sponsor country, the substance is considered to be of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

6 REFERENCES

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ANNEX: DETAILS OF THE LITERATURE SEARCH USED

The data banks searched are indicated below.

Toxicology

Date of last literature search: 27 February 2002
JETOC
RTECS
AGRICOLA
CABA
CANCERLIT
TOXCENTER
TOXLINE
JICST-EPLUS
LIFESCI
TOXLIT
EMBASE
ESBIOBASE
EMBAL
HEALSAFE
CSNB
MEDLINE
IRIS
ATSDR TOX. PROFILES
atsdr TOX: FAQS
chemfinder
civs
gestis
ginc
nicnas
ntp

Ecology

Date of last literature search: 27 February 2002

AQUASCI
BIOSIS
EMBASE
ESBIOBASE.
LIFESCI
OCEAN
POLLUAB
SCISEARCH
TOXCENTER
TOXLINE
ULIDAT
datalog
chemfate
biodeg
aquire
HSDB

I U C L I D

D a t a S e t

Existing Chemical	ID: 556-82-1
CAS No.	556-82-1
EINECS Name	3-methylbut-2-en-1-ol
EC No.	209-141-4
Molecular Weight	86.132 g/mol
Molecular Formula	C5 H10 O

Producer Related Part

Company:	BASF AG
Creation date:	19-JUN-1996

Substance Related Part

Company:	BASF AG
Creation date:	19-JUN-1996

Status:	other: The consortium wants to state that this document is declared confidential within the framework of the ICCA/HPV-prog. and not ready for publication via OECD/WHO. This has to be derestricted by BASF before publication is allowed.
Memo:	master

Printing date:	02-SEP-2004
Revision date:	
Date of last Update:	**31-AUG-2004**

Number of Pages: **80**

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: BASF AG
Contact Person: Dr. Hubert Lendle **Date:**
GUP/CL - Z570
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Country: Germany
Phone: +49 621 60 44712
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Homepage: www.basf.com

Flag: Critical study for SIDS endpoint
03-APR-2002

Type: cooperating company
Name: KURARAY CO., LTD.
Contact Person: Environmental, Industrial **Date:**
Safety and Quality
Managment Dept.
c/o Taku Tanaka, Senior
Technical Staff

Town: 1-6,3-Chome, Nihonbashi, Chuo-ku, Tokyo 103-8254
Country: Japan
Phone: 81-3-3277-6683
Telefax: 81-3-3277-6718

Flag: Critical study for SIDS endpoint
26-MAR-2002

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

Mol. Formula: C5 H10 O
Mol. Weight: 86.132 g/mol

Flag: non confidential, Critical study for SIDS endpoint
13-AUG-2004

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: liquid
Purity: >= 98 % w/w

Colour: colourless
Odour: alcoholic

Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

.gamma.,.gamma.-Dimethylallyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

2-Buten-1-ol, 3-methyl- (7CI, 8CI, 9CI)

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3,3-Dimethylallyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3-Methyl-2-buten-1-ol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3-Methyl-2-butenol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3-Methyl-2-butenyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3-Methyl-buten-2-ol-1

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

3-Methylcrotyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

Dimethylallyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

Prenol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

Prenyl alcohol

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

1.3 Impurities

Purity type: typical for marketed substance
CAS-No: 763-32-6
EC-No: 212-110-8
EINECS-Name: 3-methylbut-3-en-1-ol
Mol. Formula: C5H10O
Contents: ca. .5 % w/w

Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (2)

Purity type: typical for marketed substance
CAS-No: 115-18-4
EC-No: 204-068-4
EINECS-Name: 2-methylbut-3-en-2-ol
Mol. Formula: C5H10O
Contents: ca. .5 % w/w

Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (2)

1.4 Additives

1.5 Total Quantity

Remark: Production volumes for the year 2001:

USA : 0 t
Germany: 5.000 - 10.000 t
Europe : 5.000 - 10.000 t
Asia : 1.000 - 3.000 t

World : 6.000 - 13.000 t
Flag: Critical study for SIDS endpoint
12-NOV-2002

1.6.1 Labelling

Labelling: provisionally by manufacturer/importer
Symbols: (C) corrosive
R-Phrases: (10) Flammable
(34) Causes burns
(22) Harmful if swallowed
S-Phrases: (36/37/39) Wear suitable protective clothing, gloves and eye/face protection

(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(45) In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

1.6.2 Classification

Classified: provisionally by manufacturer/importer
Class of danger: corrosive
R-Phrases: (34) Causes burns
Specific limits: no

Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

Classified: provisionally by manufacturer/importer
Class of danger: flammable
R-Phrases: (10) Flammable
Specific limits: no

Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed
Specific limits: no

Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

Type: industrial
Category: Chemical industry: used in synthesis

Remark: Intermediate in the synthesis of citral from Isobutene and Formaldehyde.
Flag: non confidential, Critical study for SIDS endpoint
05-APR-2002 (4)

Type: use
Category: Cosmetics

Remark: The use as ingredient in cosmetic products is limited. Use in

cosmetics as flavor and fragrance compounds.
Flag: non confidential, Critical study for SIDS endpoint
27-AUG-2004

Type: use
Category: Intermediates

Flag: non confidential, Critical study for SIDS endpoint
19-JUN-1996

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: Prenol is manufactured in a two-step synthesis involving the reaction of isobutene and formaldehyde, followed by isomerisation of the resulting iso-Prenol.
Flag: non confidential, Critical study for SIDS endpoint
29-JAN-2003

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

Type of limit: MAK (DE)
Limit value: other: no MAK value established

Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (5)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

Classified by: other: VwVwS (Germany), Annex 2
Labelled by: other: VwVwS (Germany), Annex 2
Class of danger: 1 (weakly water polluting)

Remark: ID-number: 1158
Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (6)

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: EINECS No. 209-141-4

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: ENCS
Additional Info: ENCS No. 2-2393X

Remark: For ENCS chemical class or category name, refer to ENCS No. 2-2393
Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: ECL
Additional Info: ECL Serial No. KE-23623

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (7)

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

Memo: German "Flammable Liquids" classification (VbF): A II

Flag: non confidential, Critical study for SIDS endpoint
17-FEB-2003 (3)

Memo: Hazardous reactions: reacts with acids

Flag: non confidential, Critical study for SIDS endpoint
17-FEB-2003 (3)

1.12 Last Literature Search

Chapters covered: 1
Date of Search: 31-MAR-2003

Flag: non confidential, Critical study for SIDS endpoint
25-APR-2003

Chapters covered: 8
Date of Search: 31-MAR-2003

Flag: non confidential, Critical study for SIDS endpoint
25-APR-2003

Chapters covered: 3, 4, 5
Date of Search: 27-FEB-2002

Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 13-NOV-2002

07-FEB-2003

1.13 Reviews

2.1 Melting Point

Value: -59.3 degree C

Method: other: calculated: SRC-MPBWIN v1.40
Year: 2002

Result: The value selected by the program is the mean melting point from the two following methods:
adapted Joback Method: -85.27 °C
Gold and Ogle Method: -33.23 °C
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint
28-JAN-2003 (8)

2.2 Boiling Point

Value: = 139 - 141 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (9)

Value: = 141 degree C at 1013 hPa

Method: other: measured

Test substance: 3-Methylbut-2-en-1-ol pure
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
17-NOV-1999 (10)

Value: = 141.9 degree C at 1013 hPa

Method: other: measured

Test substance: 3-Methylbut-2-en-1-ol no further data
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
Flag: Critical study for SIDS endpoint
17-NOV-1999 (11)

2.3 Density

Type: density
Value: .8517 g/cm³ at 20 degree C

Method: other: no data
Year: 1968
GLP: no
Test substance: no data

Reliability: (2) valid with restrictions

basic data given, acceptable restrictions
Flag: Critical study for SIDS endpoint
27-JAN-2003 (12)

Type: density
Value: .86 - .88 g/cm³ at 20 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: 3.15 hPa at 25 degree C

Method: other (calculated): SRC-MPBPWIN v1.40
Year: 2002

Result: The value selected by the program is a mean value of Antoine and Grain methods.
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
28-JAN-2003 (8)

Value: = 11.8 hPa at 50 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

Method: other (measured)

Result: temperature (°C) / vapour pressure (torr): 35.0/4.0; 41.9/6.6; 49.2/10.6; 58.8/19.8; 68.2/33.5; 78.3/56.6; 89.7/98.8; 102.7/175.8; 120.8/361.9; 133.5/569.0; 141.9/760.0

The extrapolated vapour pressure at 25 °C using the Clausius-Clapeyron equation with the Trouton rule is calculated as 3.13 hPa.
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
17-NOV-1999 (11)

Method: other (measured)

Result: temperature (°C) / vapour pressure (torr): 20/1.4; 30/3.0; 40/6.1; 50/11.8; 60/21.4; 70/37.8; 80/64.3; 90/103; 100/161; 110/244; 120/358; 130/518; 140/735; 141/760

The extrapolated vapour pressure at 25 °C using the Clausius-Clapeyron equation with the Trouton rule is calculated as 3.04 hPa.
Test substance: 3-Methylbut-2-en-1-ol pure
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
17-NOV-1999 (10)

Method: other (measured)
Test substance: as prescribed by 1.1 - 1.4

Remark: This study is the newest of a set of tests all resulting in almost the same value for the vapour pressure and therefore has been chosen as critical study for the SIDS endpoint.
Result: temperature (°C) / vapour pressure (hPa): 31.8/4.57; 48.4/14.12; 69.1/47.22; 89.8/131.8; 116.5/402.3; 142.9/1022.0

The extrapolated vapour pressure at 25 °C using the Clausius-Clapeyron equation with the Trouton rule is calculated as 3.17 hPa.
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
Flag: Critical study for SIDS endpoint
31-JAN-2003 (13)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = .91 at 25 degree C

Method: other (measured)

Result: The prescribed value is a mean of 3 measurements. The concentrations of the substance have been derived by GC.
Reliability: (2) valid with restrictions
basic data given, acceptable restrictions
Flag: Critical study for SIDS endpoint
28-JAN-2003 (14)

2.6.1 Solubility in different media

Solubility in: Water
Value: 170 g/l at 20 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
Flag: Critical study for SIDS endpoint
11-JUN-2002 (3)

2.6.2 Surface Tension

Result: 28 mN/m at 0 °C
24 mN/m at 40 °C
20 mN/m at 80 °C
Test substance: 3-Methylbut-2-en-1-ol no further data
Reliability: (4) not assignable
Secondary quotation
17-NOV-1999 (15)

2.7 Flash Point

Value: = 51.5 degree C
Type: closed cup

Method: other: DIN 51 755

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

2.8 Auto Flammability

Value: = 305 degree C

Method: other: DIN 51 794

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

2.9 Flammability

Result: flammable

Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

2.10 Explosive Properties

Result: not explosive

Remark: evaluation derived from chemical structure
Reliability: (2) valid with restrictions
Expert judgement
16-NOV-1999 (16)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: evaluation derived from chemical structure
Reliability: (2) valid with restrictions
Expert judgement
16-NOV-1999 (16)

2.12 Dissociation Constant

2.13 Viscosity

Value: 3 mPa s (dynamic) at 25 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
14-JUN-2002 (3)

2.14 Additional Remarks

Remark: Explosion limits: 2.7 - 16.3 Vol.%
Hazardous reactions: Reaction with: acids
Reliability: (4) not assignable
Manufacturer / producer data without proof
16-NOV-1999 (3)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Degradation: = 50 % after 4.3 hour(s)

Method: other (calculated): SRC-AOP, v 1.90
Year: 2002

Result: Calculation of T1/2 based on 24 hour-day.
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint
30-AUG-2004 (8)

INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 1500000 molecule/cm³
Rate constant: = .000000000090581 cm³/(molecule * sec)
Degradation: = 50 % after 1.4 hour(s)

Method: other (calculated): SRC-AOP, v 1.90
Year: 2002

Result: Calculation of T1/2 based on 12 hour-day.
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint
30-AUG-2004 (8)

INDIRECT PHOTOLYSIS
Sensitizer: O3
Conc. of sens.: 700000000000 molecule/cm³
Rate constant: = .00000000000000043 cm³/(molecule * sec)
Degradation: = 50 % after 38.4 minute(s)

Method: other (calculated): SRC-AOP, v 1.90
Year: 2002

Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint
30-AUG-2004 (8)

Type: water

Result: DIRECT PHOTOLYSIS in water
The substance has no chromophores. A relevant absorption above 300 nm and thus direct photolysis is not expected.
Reliability: (2) valid with restrictions
Expert judgement
Flag: Critical study for SIDS endpoint
30-AUG-2004 (17)

3.1.2 Stability in Water

Type: abiotic

Method: other

Remark: No hydrolysis is to be expected because of the chemical structure.

28-JAN-2003

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

Medium: food

Remark: 3-Methyl-2-buten-1-ol was identified as additional volatile in pineapple essence.

19-JUN-1996 (18)

Medium: food

Result: 3-Methyl-2-buten-1-ol has been identified as a volatile in beer.

28-JAN-2003 (19)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - soil
Method: other: SRC-PCKOCWIN v1.66
Year: 2002

Result: Koc: 3.78, log Koc: 0.58
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint

30-AUG-2004 (8)

Type: volatility
Media: water - air
Method: other: calculated: SRC-HENRY v3.10
Year: 2002

Result: The following values have been calculated:
Bond contribution method: 1.4 Pa*m3/mol
Group contribution method: 0.73 Pa*m3/mol
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint

31-JAN-2003 (8)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation):Calculation according Mackay, Level I v 2.11
Year: 2002

Remark: Data basis:
Log Pow: 0.91,
Water solubility: 170 g/l,
Vapour pressure: 315 Pa; calculated value. The values extrapolated from studies performed at higher temperatures are at exactly the same range.
Melting point: -59.25, calculated value
Result: Distribution at 25°C
Water: 94.7 %, air: 5.2 %, soil: 6.1e-2 %, sediment: 6.2e-2 %, biota: <0.001 %
Reliability: (2) valid with restrictions
Calculated value in accordance with generally accepted standard methods
Flag: Critical study for SIDS endpoint
31-JAN-2003 (8)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 85 mg/l related to Test substance
Degradation: 82 % after 28 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: lag-phase: 2 days, log-phase: 8 days, TOC: 689 mg/g, DOC: 1050 mg/g (direct), BOD5 = 1343 mg/g, ThOD: 2605 mg/kg
Test condition: concentration of activated sludge: 30 mg/l, reference substance: aniline, pH values in the assays at the end of the test:
pH 6.5 (test substance), pH 7.4 (control substance), pH 7.0 (blank control)
Reliability: (2) valid with restrictions
Comparable to guideline study with acceptable restrictions.
Flag: Critical study for SIDS endpoint
30-JAN-2003 (20)

3.6 BOD5, COD or BOD5/COD Ratio

B O D 5

Method: other
BOD5: = 1343 mg/l

C O D

Method: other
Year:
COD: = 2418 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = .55
Method:
Result: BOD5: 1343 mg/g
06-AUG-2002 (21)

3.7 Bioaccumulation

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: 22
LC0: 22
LC50: 46
LC100: 100

Method: other: DIN 38412 part 15
Year: 1982
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: The method used closely followed the guideline of DIN 38 412 ["Testverfahren mit Wasserorganismen (Gruppe L). Allgemeine Hinweise zur Planung, Durchführung und Auswertung biologischer Testverfahren (L1) und Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische - Fischtest (L15)"], June 1982, using a static procedure.

Remark: Volatility screening test (for details see chapter 4.9):
Based on TOC measurements the recovery rate at the end of the exposure period was 93 % for the fish test.
This shows that the test substance concentration remained nearly constant under the conditions of the ecotoxicity test and therefore the effect values based on nominal concentrations can be used for the hazard assessment without limitations.

Test condition: Fish: golden orfe (Leuciscus idus L., golden variety)
body length: 5.7 - 7.2 cm
body weight: 1.5 - 4.4 g
Ten animals were used per test group; fish loading: 2.9 g/l

Test temp.: 21 °C
Photoperiod: 16 h light and 8 h dark
Water total hardness: approx. 2.5 mmol/l
Acid capacity: approx. 0.8 mmol/l
pH: approx. 8

Test concentrations: 10, 21.5, 46.4, 100 , 215, and 464 mg/l following a range finding study, the test substance was directly added to test water .

Results refer to nominal concentrations.

Determination of LC50 by Probit Analysis if possible. In this study, the Probit Analysis has not been possible for determination of the LC50 after 96 hours. An approximation was therefor used (60% mortality at 46.4 mgl/l was taken as LC50).

Reliability: (1) valid without restriction
Test method comparable to guideline study, in accordance with accepted national standards

Flag: Critical study for SIDS endpoint
30-AUG-2004 (22) (23)

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: = 62.5
EC50: = 144
EC100: = 500

Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1984
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Volatility screening test (for details see chapter 4.9):
Based on TOC measurements the recovery rate at the end of the exposure period was 94 % for the daphnia test.
This shows that the test substance concentration remained nearly constant under the conditions of the ecotoxicity test and therefore the effect values based on nominal concentrations can be used for the hazard assessment without limitations.

Result: EC values (24 and 48 hours) were calculated according to the procedure of Spearman-Kaerber.

Results after 24 h were as follows:
EC0 = 125 mg/l
EC50 = 234 mg/l
EC100 = 500 mg/l

Test condition: Age of test organism: < 24h

Test water: pH value: 7.7 - 8.0;
total hardness: 2.6 mmol/l;
alkalinity up to pH 4.3: 0.77 mmol/l;
conductivity: 620 µS/cm; ;
O2 content: 7.75 - 8.45 mg/l
Illumination: artificial light, day:night-rhythm = 16:8 hours
light intensity: 5 µE at a wave of 400 - 750 nm.

Test temperature: 20.7 °C;
Test volume: 10 ml, volume/animals: 2 ml,
number of animals/vessel: 5,
total number of animals/concentration: 20.

Check of the study: visually after 0, 3, 6, 24, and 48 h.
Nominal test concentrations:
15.6, 31.2, 62.5, 125, 250, and 500 mg/l.

Reliability: (1) valid without restriction
Test method comparable to guideline study, in accordance with accepted national standards

Flag: Critical study for SIDS endpoint

30-AUG-2004 (22) (24)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass

Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC10: = 213
EC50: > 500
EC90 : > 500

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Volatility screening test (for details see chapter 4.9):
Based on TOC measurements the recovery rate at the end of the exposure period was 98 % for the algae test.
This shows that the test substance concentration remained nearly constant under the conditions of the ecotoxicity test and therefore the effect values based on nominal concentrations can be used for the hazard assessment without limitations.
Result: Results after 96 h were as follows:

EC10 = 225 mg/l
EC50 = >500 mg/l
EC90 = >500 mg/l
Test condition: Inoculum density: approx. 10,000 cells/ml;
Determination of cell density after 0, 24, 48, 72, and 96 h (fluorescence at 685 nm).
Duration of test: 96 h, test temperature: 21 - 25 °C;
test vessel: reagent tube with flat bottom, volume 10 ml);
test volume: 8 ml,
initial pH 8.0.
Illumination: artificial light, permanent,
illumination intensity: 120 µE/m2s.

Nominal test concentrations, made from a stock solution with 1 g/l:
31.25, 62.5, 125, 250, and 500 mg/l.
Reliability: (2) valid with restrictions
Test method comparable to guideline study, in accordance with accepted national standards
Flag: Critical study for SIDS endpoint
30-AUG-2004 (22) (25)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge, industrial
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:** no
EC0: >= 2880

Method: OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions

Comparable to guideline study with acceptable restrictions.
Flag: Critical study for SIDS endpoint
29-JAN-2003 (26)

Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:**
EC10: = 1880
EC50: = 3380
EC90 : = 4850

Method: other: Pseudomonas-Zellvermehrungs-Hemmtest, DIN 38412 Teil 8, zum Gelbdruck verabschiedet, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Bakterien
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Test procedure according to national standards (DIN).
Flag: Critical study for SIDS endpoint
28-JAN-2003 (27)

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

4.9 Additional Remarks

Memo: Examination of the volatility of Prenol: algae test

Method:
- Test vessel: 250 ml Erlenmeyer flasks, plugged with gas permeable siliconesponge caps
- Test volume: 100 ml
- Medium: OECD-Medium T 9
- Incubator: Ecophyt with circulating air
- Test temperature: 23 °C ± 2 °C
- agitation: laboratory shaker: about 85 rpm
- Illumination: artificial light, permanent illumination (about 120 µE/(m2*s))
- test preparations: one flask for each measuring time
- Test concentration: 100,7 mg/l
- Test parameter: TOC-Concentration

Result:
- Concentration at test initiation: 100,7 mg/l
- Results of the measurement:

Time [h]	TC [mg/]			TIC [mg/]			TOC [mg/l]	[%]	
	1.	2.	Mean	1.	2.	Mean			
0	75,0	75,4	75,2	6,8	6,8	6,8	68,4	100	
24	74,4	74,7	74,6	6,6	6,7	6,7	67,9		99,3
48	73,8	74,2	74,0	6,8	6,9	6,9	67,1		98,1
72	73,2	73,5	73,4	6,7	6,7	6,7	66,7		97,5

TC = total carbon,
TIC = total inorganic carbon,
TOC = total organic carbon

- Interpretation:

Recovery rate:
about 98 % (on the basis of the 72 h value)
about 99 % (mean value of the 0 h and 72 h value)

Reliability: (2) valid with restrictions

screening test meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2004 (22)

Memo: Examination of the volatility of Prenol: daphnia test

Method:
- Test vessel: 20 ml test tubes (glass) with flat bottom, unplugged
- Test volume: 10 ml
- Medium: M4-Medium
- Test temperature: 20 °C ± 2 °C
- Illumination: artificial light (16 h day, 8 h night)
- test preparations: one flask for each measuring time
- Test concentration: 500 mg/l
- Test parameter: TOC-Concentration

Result:
- Concentration at test initiation: 500 mg/l
- Results of the measurement:

Time [h]	TC [mg/l] 1.	2.	Mean	TIC [mg/l] 1.	2.	Mean	TOC [mg/l]	[%]
0	338	343	341	8,7	8,6	8,7	332	100
24	331	334	333	9,6	9,5	9,6	323	97,3
48	322	324	323	10,0	10,0	10,0	313	94,3

TC = total carbon,
TIC = total inorganic carbon,
TOC = total organic carbon

- Interpretation:

Recovery rate:
about 94 % (on the basis of the 72 h value)
about 97,2 % (mean value of the 0 h and 72 h value)

Reliability: (2) valid with restrictions
screening test meets basic scientific principles
Flag: Critical study for SIDS endpoint
30-AUG-2004 (22)

Memo: Examination of the volatility of Prenol: fish test

Method:
- Test vessels: glass aquarium
- Test volume: 10 l
- Medium: artificial fresh water:
  deionised water
  26,1 mg/L CaCl2 x 2 H2O
  17,7 mg/L MgSO4 x 7 H2O
  1,1 mg/L K2SO4
  25,0 mg/L NaHCO3
- Test temperature: 25°C ± 2
- Aeration: no
- Test concentration: 464,1 mg/l
- Test parameter: TOC-Concentration

Result:
- Concentration at test initiation: 464,1 mg/l
- Results of the measurement:

Time	TC [mg/l]	TIC [mg/l]	TOC

[h]	1.	2.	Mean	1.	2.	Mean	[mg/l]	[%]
0	377	379	378	63,1	63,0	63,5	315	100
24	366	370	368	60,3	60,5	60,4	308	97,8
48	359	358	359	54,0	53,8	53,9	305	96,8
72	351	352	352	49,0	48,9	49,0	303	96,2
96	334	334	334	41,6	41,7	41,7	292	92,7

TC = total carbon,
TIC = total inorganic carbon,
TOC = total organic carbon

- Interpretation:

Recovery rate:
about 93 % (on the basis of the 72 h value)
about 96,4 % (mean value of the 0 h and 72 h value)

Reliability: (2) valid with restrictions
screening test meets basic scientific principles

Flag: Critical study for SIDS endpoint

30-AUG-2004 (22)

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: other: Gassner
Sex: male/female
No. of Animals: 20
Vehicle: other: aqueous solution of tragacanth
Doses: 172, 1376, 1720, 2150, 2752 and 5504 mg/kg bw
Value: = 1591 mg/kg bw

Method: other
GLP: no
Test substance: other TS

Method: Similar to former OECD 401. Restrictions: reduced post observation time (7 days instead of 14)

Year study performed: 1970

Result: MORTALITY
No deaths occurred at the lower doses up to 1.6 ml/kg bw. All animals died at 2.0 ml/kg bw and above.

Time of death and number of deaths at each dose:

6.4 ml/kg bw: 10/10 males and 10/10 females died within 24 hrs
3.2 ml/kg bw: 10/10 males and 10/10 females died within 24 hrs
2.5 ml/kg bw: 9/10 males and 10/10 females died within 24 hrs
2.0 ml/kg bw: 7/10 males and 10/10 females died within 24 hrs
1.6 ml/kg bw: 0/10 males and 0/10 females died within 7 days
0.2 ml/kg bw: 0/10 males and 0/10 females died within 7 days

From these data a LD50 value was estimated to be 1.85 ml/kg bw (= 1591 mg/kg bw) after 7 days

CLINICAL SIGNS
At 6.4 to 2.0 ml/kg bw: Immediately after application, staggering, abdominal and lateral position, partly dorsal position, apathy, laboured and irregular breathing, secretion out of eyes and mouth, reddened eyes and ears. In the post observation days, calm behavior of the survivors and piloerection.

At 1.6 ml/kg bw: Immediately after application, staggering, slight abdominal position, apathy, laboured and irregular breathing, reddened eyes and ears. In the post observation days, quiet behavior, slightly increased breathing and piloerection. At the 7th post observation day without clinical symptoms.

At 0.2 ml/kg bw: Immediately after application, restlessness, staggering, irregular and slightly increased breathing. During

the the post observation days, calm behavior and piloerection. At the 7th post observation day, animals were without clinical symptoms.

NECROPSY FINDINGS
In 2 animals that died after application of 2.5 ml/kg bw, stomach dilated and filled with liquid, all other animals without findings in the inner organs.

Test condition: TEST ORGANISMS
Per dose group 10 male and 10 female Gassner rats of weight range 160-260 g, no control animals were included.

ADMINISTRATION
The substance was applied at dosages of 6.4, 3.2, 2.5, 2.0, 1.6 and 0.2 ml/kg bw by gavage as aqueous emulsions in tragacanth at concentrations of 30, 20, and 2% (v/v) (5504, 2752, 2150, 1720, 1376 and 172 mg/kg bw). These were volumes of 8-21.4 ml/kg bw for the respective doses. Post observation period: 7 days

EXAMINATIONS
Animals were inspected for signs of pharmacologic or toxicologic effects during a 7 days post observation period. Body weight was measured before dosing. At the end of the observation period, survivors were sacrificed and necropsied as were animals that died.

The LD50 value was estimated (calculation method not mentioned in the raw data).

Test substance: 3-Methylbut-2-en-1-ol, purity 95%
Reliability: (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions. Chosen as key study for SIDS dossier.
Flag: Critical study for SIDS endpoint
12-JUN-2003 (28)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 810 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Remark: The acute LD50 in rats was reported as 0.81 g/kg bw (0.55-1.18 g/kg bw).
Test substance: 3-Methyl-2-buten-1-ol; no further data on purity
Reliability: (4) not assignable
4b: Secondary literature
06-JUN-2003 (29) (30) (31)

Type: LD50
Species: mouse
Strain: no data

Sex: no data
Vehicle: no data
Doses: no data
Value: = 1500 mg/kg bw

Method: other
GLP: no
Test substance: other TS

Test substance: 3-Methyl-2-buten-1-ol; no further data on purity
Reliability: (4) not assignable
4b: Secondary literature
06-JUN-2003 (32)

5.1.2 Acute Inhalation Toxicity

Type: other: Inhalation Risk Test
Species: rat
Strain: no data
Sex: male/female
No. of Animals: 6
Exposure time: 8 hour(s)

Method: other: BASF-Test
GLP: no
Test substance: other TS

Method: Similar to OECD 403
Restrictions: reduced animal number (3 animals per sex instead of at least 5 per sex) and reduced post observation time (7 days instead of 14 days).

Year study performed: 1970
Result: MORTALITY
No mortality was observed when 12 rats were exposed for 3 hours to an atmosphere that has been saturated at 20 degree centigrade with the volatile part of the compound. Mortality in 1 animal out of 6 occurred after exposure of 8 hours during the first 24 hrs.

CLINICAL SIGNS
Attempt to escape, strong secretion out of the eyes and the nose, after the exposure tremor.

NECROPSY FINDINGS
In the animal that died multifocal congestion of the lungs, all other animals were without abnormalities.

Using Haber's Rule a LC50 > 7.7 mg/l/4 hrs (3 hrs exposure) and > 16.8 mg/l/4 hrs (8 hrs exposure) can be estimated.
Test substance: 3-Methylbut-2-en-1-ol, purity 95%, no further data on impurities
Test condition: TEST ORGANISMS
Rats (male/female) weighing 200 - 250 g (strain not mentioned in the raw data).

EXPOSURE
12 rats were exposed for 3 hrs to an atmosphere that has

been saturated at 20 degree centigrade with the volatile part of the compound. 6 rats were exposed for 8 hrs. Nominal concentrations of the test substance in the atmosphere were calculated to be 10.25 mg/l (3 hrs) and 8.4 mg/l (8 hrs) by using the weight loss of test substance and the amount of air used during the exposure.

EXAMINATION
Animals were inspected for signs of pharmacologic or toxicologic effects during a 7 days post observation period. Body weight was measured before dosing. At the end of the observation period survivors were sacrificed and necropsied as were animals that died.

Reliability: (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment. Chosen as key study for SIDS dossier.

Flag: Critical study for SIDS endpoint

06-JUN-2003 (28)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 6
Vehicle: other: undiluted substance was applied
Doses: 2000 and 4000 mg/kg bw
Value: > 4000 mg/kg bw

Method: other
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: similar to OECD 402. Restrictions: reduced animal number (3 animals per dose and sex instead of 5 animals per dose and sex)

Year study performed: 1979

Result: MORTALITY
No deaths occurred at both dosages.

A LD50 value of > 4000 mg/kg bw was determined.

CLINICAL SIGNS
Slight apathy, staggering, irregular breathing, slight local skin irritation, which was reversible during the post observation period.

NECROPSY FINDINGS
All examined animals were without abnormal findings.

Test condition: TEST ORGANISMS
Per dose group 3 male and 3 female Sprague-Dawley rats, no control animals were included

ADMINISTRATION
The substance was applied undiluted at dosages of 2000 and

4000 mg/kg bw onto the clipped flank or back skin of the animals (area: about 42 sqcm) The treated skin area was covered with a aluminium wrap which was fixed with an adhesive tape. The dressing was removed 24 hrs after application of the test substance. Subsequently, the remaining test substance was removed with warm water or a water/Lutrol (polyethyleneglycol) mixture.

EXAMINATIONS
Animals were inspected for signs of pharmacologic or toxicologic effects during a 14 days post observation period. Signs of local irritation were recorded. Body weight was measured before dosing. At the end of the observation period survivors were sacrificed and necropsied as were animals that died.
A LD50 value was determined.

Test substance: 3-Methylbut-2-en-1-ol, purity ca. 99%
Reliability: (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions. Chosen as key study for SIDS dossier.
Flag: Critical study for SIDS endpoint
28-JAN-2003 (33)

Type: LD50
Species: rabbit
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 3900 mg/kg bw

Method: other
GLP: no data
Test substance: other TS

Result: The acute dermal toxicity in rabbits was reported as 3.9 g/kg bw (2.5-6.0 g/kg bw).
Test substance: 3-Methyl-2-buten-1-ol; no data on purity
Reliability: (4) not assignable
4b: Secondary literature
27-FEB-2002 (29) (30) (31)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Strain: other: Kisslegg
Sex: male/female
No. of Animals: 10
Vehicle: other: aqueous emulsion with tragacanth
Doses: 172, 344, 430, 550, 688 and 1376 mg/kg bw
Route of admin.: i.p.
Value: = 413 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: other TS

Method: Similar to former OECD 401 with exception of administration route (intraperitoneal).

Year study performed: 1970

Result: MORTALITY (after 14 days)

1.6 ml/kg bw: 5/5 (males), 5/5 (females)
0.8 ml/kg bw: 5/5 (males), 5/5 (females)
0.64 ml/kg bw: 5/5 (males), 3/5 (females)
0.5 ml/kg bw: 5/5 (males), 2/5 (females)
0.4 ml/kg bw: 0/5 (males), 0/5 (females)
0.2 ml/kg bw: 0/5 (males), 0/5 (females)

LD50 after 14 days (estimated): 0.48 ml/kg bw (413 mg/kg bw)

CLINICAL SIGNS
Abdominal, lateral and dorsal position, dyspnoea, staggering

NECROPSY
Adhesions in the abdomen, other organs without abnormalities

Test condition: TEST ORGANISMS
Per dose group 5 male and 5 female Kisslegg-mice of weight range 28-38 g, no control animals were included

ADMINISTRATION
The substance was applied at dosages of 1.6, 0.8, 0.64, 0.5, 0.4 and 0.2 ml/kg bw (1376, 688, 550, 430, 344 and 172 mg/kg bw) as intraperitoneal injections as aqueous emulsions in tragacanth at concentrations of 20, 8, 4 and 2%. Post observation period: 14 days

EXAMINATIONS
Animals were inspected for signs of pharmacologic or toxicologic effects during a 14 days post observation period. Body weight was measured before dosing. At the end of the observation period survivors were sacrificed and necropsied as were animals that died.

The LD50 value was estimated (calculation method not mentioned in the raw data).

Test substance: 3-Methylbut-2-en-1-ol, purity 95%, no further data on impurities

Reliability: (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment.

06-JUN-2003 (28)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Route of admin.: i.p.
Value: = 700 mg/kg bw

Method: no data
GLP: no
Test substance: other TS

Test substance: 3-Methyl-2-buten-1-ol; no data on purity
Reliability: (4) not assignable
4b: Secondary literature
27-FEB-2002 (32)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 20 hour(s)
No. of Animals: 8
Vehicle: other: none
Result: corrosive

Method: other: similar to Draize method
GLP: no
Test substance: other TS

Method: Similar to Draize method.
Deviations: 20 hours exposure (Draize method: 24 hours), only intact skin used (Draize: abraded and intact skin), 2 application sites (Draize: 3 application sites)

Year study performed: 1970
Result: LOCAL EFFECTS
1 and 5 min. exposure: slight erythema after 24 hrs; slight scaling after 8 days
15 min exposure: moderate erythema, slight edema after 24 hrs; moderate scaling after 8 days
20 hrs exposure: moderate erythmea, slight edema, necrosis after 24 hrs; necrosis after 8 days

SYSTEMIC TOXICITY
No mortality occurred. There were no signs of clinical toxicity from the dermal exposure.

CONCLUSION
The test substance was corrosive to the rabbit skin after 20 hrs of occlusive exposure.
Test condition: TEST ANIMALS
Strain: White Vienna rabbits
Number of animals: 8

ADMINISTRATION/EXPOSURE
Preparation of test substance: test substance was used as delivered
Total volume applied: approximately 0.5 ml, applied with a cotton pad saturated with the test substance
Exposure condition: occlusive
Exposure times: 1, 5, 15 min, 20 hrs
Animals per exposure time: 2

EXAMINATION:
Observation period: 24 hrs, 8 days

Scoring system:
Erythema, edema and necrosis were scored according to the below described system. Although the results in the report were originally not given as Draize scores the data can be transferred into the Draize scorings system (in brackets).

(+) = none - negligible effect (0)
+ = slight effect (1)
++ = moderate effect (2)
+++ = severe effect (3)
N = Necrosis

Test substance: 3-Methylbut-2-en-1-ol, purity 95%, no further data on impurities

Reliability: (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment.

Flag: Critical study for SIDS endpoint

06-JUN-2003 (28)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 4 hour(s)
No. of Animals: 4
Vehicle: other: none
PDII: 6.13
Result: corrosive
EC classificat.: corrosive (causes burns)

Method: other: 4-hour corrosivity test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: similar to OECD 404

Year study performed: 1979
Result: LOCAL EFFECTS

Immediately after termination of exposure (individual score):
Erythema: 2, 4 (necrosis), 2, 2
Edema: 3, 3, 4, 4

24 hrs after exposure:
Erythema: 2, 4 (necrosis), 3, 3 (mean 3.0)
Edema: 3, 2, 4, 4 (mean 3.25)

48 hrs after exposure:
Erythema: 3, 4 (necrosis), 3, 3 (mean 3.25)
Edema: 3, 2, 3, 3 (mean 2.75)

8 days after exposure:
Erythema: 2, 4 (necrosis), 4 (necrosis), 4 (necrosis)
Edema: 2, 1, 2, 1

A primary irritation index (sum of combined erythmea and edema values at 24 and 48 hrs divided by the number of observations) can be calculated (although not done in the original report): 6.13

SYSTEMIC TOXICITY
No mortality occurred. There were no signs of clinical toxicity from the dermal exposure.

CONCLUSION
The test substance was corrosive to the rabbit skin after 4 hrs of occlusive exposure.

Test condition: TEST ANIMALS
Strain: White Vienna rabbits
Sex: 2 males, 2 females
Source: M. Gaukler, Offenbach, Germany
Weight at study initiation: about 2.9 kg

ADMINISTRATION/EXPOSURE
Preparation of test substance: test substance was used as delivered
Area of exposure: 2 cm x 2 cm, back of the animals
Vehicle: not used
Total volume applied: 2 cm x 2 cm cotton patch was saturated with the substance (approximat. 0.5 ml). The patch was covered with a gummed linen pad which was fixed with an adhesive tape.
Exposure time: 4 hrs
Removal of test substance: shortly after exposure substance remnants were removed with water or a 50% Lutrol (polyethylenglykol) dilution
Postexposure period: 8 days

EXAMINATION
Observation period: after exposure, 24, 48 hrs and 8 days
Scoring system: Draize score
Signs of clinical toxicity

Test substance: 3-Methylbut-2-en-1-ol, purity ca. 99%
Reliability: (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions. Chosen as key study for SIDS dossier.
Flag: Critical study for SIDS endpoint
06-JUN-2003 (34)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 24 hour(s)
Vehicle: no data
Result: moderately irritating

Method: Draize Test
GLP: no
Test substance: other TS

Result: Prenol applied full strength to intact or abraded rabbit skin for 24 hrs under occlusion was moderately to severly irritating.
Test substance: 3-Methyl-2-buten-1-ol; no data on purity
Reliability: (4) not assignable
4b: Secondary literature
27-FEB-2002 (29) (30)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Vehicle: other: none
Result: highly irritating

Method: other
GLP: no
Test substance: other TS

Method: EPA proposed guidelines, April 1978; sec. 162-81-5 (similar to Draize method)

Year study performed: 1978
Remark: Prenyl alcohol is considered to be extremly irritating to the skin of albino rabbits.
Result: SYSTEMIC TOXICITY
No animal died. Clinical signs of toxicity were not reported.

LOCAL EFFECTS
The following mean Draize scores were obtained:

Erythema and eschar formation (intact and abraded skin):
24 hrs: reading not possible due to grey black discoloration of the skin
72 hrs: 4; 25 days: 4

Edema formation (intact and abraded skin):
24 hrs: 0; 72 hrs: 0; 25 days: 0

Conclusion:
According to the authors of the study, the test substance is considered to be extremely irritating to the skin of albino rabbits.
Test condition: TEST ANIMALS
Strain: New Zealand albino rabbits
Number: 6 animals
Source: Davidson's Mill Farm, Jamesburd, New Jersey, USA
Weight at study initiation: 2-3 kg

ADMINISTRATION/EXPOSURE
Preparation of test substance:
Test substance was used as delivered
Area of exposure:
24 hrs before treatment, the backs were carefelly clipped free of hair. The clipped area was large enough to accomodate four 2.5 cm x 2.5 cm application sites.
Abrasion:
Two of the application sites were abraded with a firm nylon toothbrush and the other two were left intact. The abrasions were through the stratum corneum but not the dermis.
Total volume applied:
0.5 ml of the test material was applied directly to the application sites under a 2.5 cm x 2.5 cm gauze pad placed over each site. The pads were held securely in place with adhesive tape lined with parafilm. The entire shaved area

was covered with an impervious rubberized cloth to prevent evaporation.
Exposure time: 24 hrs
Postexposure period: 25 days

EXAMINATION
Observation period: 24, 72 hrs, 25 days
Scoring system: Draize Score
After 24 hrs the sites were wiped (not washed) and the resulting reactions evaluated and scored. Half of the animals were sacrifced, photographs taken and skin samples taken and half of the animals were held for an additional 3 week observation period, and photographs and skin samples taken.

Test substance: Prenol, (2-Buten-1-ol, CAS 556-82-1), purity > 99%, no further data on impurities

Reliability: (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment.

Flag: Critical study for SIDS endpoint

06-JUN-2003 (35)

Species: rabbit
Concentration: undiluted
Exposure: Occlusive
Exposure Time: 1 hour(s)
No. of Animals: 4
Result: corrosive

Method: other: 1 hour corrosivity test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 1979
Result: LOCAL EFFECTS

Immediately after termination of exposure (individual score):
Erythema: 2, 2, 2, 2
Edema: 2, 0, 3, 4

24 hrs after exposure:
Erythema: 3, 2, 3, 4 (necrosis); (mean 3.0)
Edema: 3, 2, 3, 3 (mean 2.75)

48 hrs after exposure:
Erythema: 3, 2, 3, 4 (necrosis) (mean 3.0)
Edema: 3, 2, 2, 3 (mean 2.5)

8 days after exposure:
Erythema: 4 (necrosis), 1, 2, 4 (necrosis)
Edema: 2, 0, 1, 1

SYSTEMIC TOXICITY
No mortality occurred. There were no signs of clinical toxicity from the dermal exposure.

CONCLUSION
The test substance was corrosive to the rabbit skin in 2 out

of 4 animals after 1 hrs of occlusive exposure.

Test condition: TEST ANIMALS
Strain: White Vienna rabbits
Sex: 4 females
Source: M. Gaukler, Offenbach, Germany
Weight at study initiation: about 2.7 kg

ADMINISTRATION/EXPOSURE
Preparation of test substance: test substance was used as delivered
Area of exposure: 2 cm x 2 cm, back of the animals
Vehicle: not used
Total volume applied: 2 cm x 2 cm cotton patch was saturated with the substance (approximat. 0.5 ml). The patch was covered with a gummed linen pad which was fixed with an adhesive tape.
Exposure time: 1 hr
Removal of test substance: after exposure substance remnants were removed with water or a 50% Lutrol (polyethylenglykol) dilution
Postexposure period: 8 days

Test substance: 3-Methylbut-2-en-1-ol, purity ca. 99%

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

Flag: Critical study for SIDS endpoint

06-JUN-2003 (34)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: .1 ml
Comment: not rinsed
No. of Animals: 3
Vehicle: none
Result: highly irritating
EC classificat.: risk of serious damage to eyes

Method: other: Federal Register 38, No. 187, § 1500.42
Year: 1973
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Federal Register 38, No. 187, § 1500.42, 1973

Year study performed: 1979

Result: At the observation points, the following effects were observed (individual Draize scores):

Cornea
Opacity: 24 hrs: 1,1,1; 48 hrs: 1,1,1; 72 hrs: 1,1,1; 8 days: 2,0,0
Area affected: 24 hrs: 4,4,4; 48 hrs: 4,4,4, 72 hrs: 4,4,4; 8 days: 4,0,0

Iris:
24 hrs: 0,0,0; 48 hrs: 0,0,0; 72 hrs: 0,0,0; 8 days:

0,0,0

Conjunctiva
Redness: 24 hrs: 2,2,2; 48 hrs: 2,2,2; 72 hrs; 2,1,2; 8 days: 1,0,1
Chemosis: 24 hrs: 2,2,2; 48 hrs: 1,1,1; 72 hrs: 1,1,1; 8 days: 1,0,0

Overall irritation score: about 28.7 (maximal score 110)
The treatment led to slight to moderate corneal opacity, moderate conjunctival redness and chemosis. The findings were not completely reversible within 8 days of observation time.

CONCLUSION
The substance is highly irritating to the eyes with a risk of serious damage to the eyes.

Test condition: TEST ANIMALS
Strain: White Vienna rabbits
Sex: 2 males, 1 female
Source: M. Gaukler, Offenbach, Germany
Weight at study initiation: about 3.4 kg
Controls: untreated left eye served as control

EXPOSURE
Postexposure period: 8 days

EXAMINATION
Observation period: 24, 48, 72 hrs and 8 days
Scoring method used: Draize score
Irritation score:
Cornea: 0-4 (opacity and area affected); Iris: 0-2;
Conjunctiva: 0-3 (redness), 0-4 (chemosis)

Test substance: 3-Methylbut-2-en-1-ol, purity ca. 99%

Reliability: (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions
Chosen as key study for SIDS dossier.

Flag: Critical study for SIDS endpoint

20-JAN-2003 (36)

Species: rabbit
Concentration: undiluted
Dose: .05 ml
Comment: not rinsed
No. of Animals: 3
Vehicle: none
Result: irritating

Method: other
GLP: no
Test substance: other TS

Method: BASF method

Year study performed: 1970

Result: The following findings were obtained (mean scores; Draize score in brackets):

Cornea
opacity: 1 hr: + (Draize score 1); 24 hrs: + (1); 8 days: none (0)

Conjunctiva
Redness: 1 hr: ++ (Draize score 2); 24 hrs: ++ (2); 8 days: + (1)
chemosis: 1 hr: +++ (Draize score 3); 24 hrs: ++ (2); 8 days: none (0)

The treatment led to slight corneal opacity, moderate conjunctival edema and redness. All findings were reversible after 8 days of observation period except a slight conjunctival redness.

The control eyes which were treated with sodium chloride did not show any reactions.

CONCLUSION
The substance showed a irritating potential to the eyes of rabbits.

Test condition: TEST ANIMALS
2 White Vienna rabbits
Controls: Sodium chloride into the untreated left eye

EXPOSURE
50 µl undiluted substance were applied into the conjuncticval sac
Postexposure period: 8 days

EXAMINATION
Observation period: 1 hr, 24 hrs and 8 days
Scoring system:
Conjunctival redness, chemosis and corneal opacity were scored according to the below described system. Although the results in the report were originally not given as Draize scores the data can be transferred into the Draize scoring system (in brackets).

(+) = negligible - no effect (Draize score 0)
+ = slight effect (1)
++ = moderate effect (2)
+++ = severe effect (> = 3)

Test substance: 3-Methylbut-2-en-1-ol, purity 95%
Reliability: (2) valid with restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment.
Flag: Critical study for SIDS endpoint
30-JAN-2003 (28)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Wistar

Route of administration: drinking water
Exposure period: 90 days
Frequency of treatment: continuously
Post exposure period: none
Doses: 200, 1000 and 5000 ppm
Control Group: yes, concurrent vehicle
NOAEL: = 1000 ppm
LOAEL: = 5000 ppm

Method: OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
Year: 1998
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 2001
Result: ANALYSES
Stability of test substance in vehicle: was demonstrated over a period of 4 days at room temperature
Concentration control of test substance in vehicle: correctness of the concentrations were confirmed. The recovery rates were within a range of 92.1% - 101.1% of the target concentrations.

CLINICAL EXAMINATIONS
- Mortality: No animal died during the administration period.

- Clinical signs: No treatment related abnormal clinical signs were observed.

- Food consumption
was significantly decreased in males of the high dose group from days 7-28 and 42-91 (up tp 18.2 % below control), in males of the mid dose group on days 7 and 91 (up to -9.4 %) and in females of the high dose group on days 7-28 and 42-91 (up to -21 %). This was assessed as being treatment related.

- Water consumption
was significantly decreased in males and females of the high dose group during the entire study (up to -49.9 % and -47.8 %, respectively) and in males (days 7-14, 28-63, 77-91) and females (days 7-14, 42, 63-77) of the mid dose group (up to -25.1 % and -28.9 %, respectively). This was assessed as being treatment-related.

- Body weight data
Body weight was significantly decreased in high dose males on days 14 to 91 (-12.2 % on day 91) and in females of the same group from days 14 to 21, 42, 56 to 70 and 84 to 91 (-8.8 % on day 91).
A significantly decreased value of body weight change was seen in males of the high dose group from days 7 to 91 (-20.4 % on day 91) and in females of the same group from days 14 to 28, 42 to 70 and 84 to 91 (-19.2 % on day 91). This was assessed as being treatment-related.

- Food efficiency
was significantly decreased in males from days 7 to 14, 56 and

77 to 84 and in females on day 42 of the high dose group.

- Substance intake
The mean daily test substance intake in mg/kg bw over the entire study period was calculated:

200 ppm group: 14.4 (males) and 21.0 mg/kg bw/d (females)
1000 ppm group: 65.4 (males) and 82.1 mg/kg bw/d (females)
5000 ppm group: 243.8 (males) and 307.2 mg/kg bw/d (females)

- Ophthalmoscopy
No substance-related effects were obtained.

- Functional observational battery and motor activity measurement
All findings were assessed as being incidental, as they occurred in single animals, only, or were equally distributed between treated groups and controls.

CLINICAL PATHOLOGY
- Hematology
no treatment-related changes

- Clinical chemistry
Compound-related differences in clinical chemistry parameters were not evident at any dose level in either males or females.

- Urinalyses
Urine examinations revealed decreased amounts of urine with increased specific gravity in the high dose males and females. No treatment-related changes were found in the other urine parameters examined.

- Sperm analysis
No treatment-related changes were observed in sperm parameters.

PATHOLOGY
- Absolute organ weights
In male rats, the mean terminal body weight was significantly decreased in the high dose group (-11.7 %). Also in female rats of the high dose group, the mean terminal body weight was slightly but significantly decreased (-6.4 %). This was regarded treatment-related.
In male rats, the mean weight of the liver was significantly decreased in the high dose group (-14.9 %) and in the mid dose group (-7.9 %). The mean weight of thymus in the low dose group was slightly although significantly increased in males (+16.3 %). This was regarded incidental as there was no dose-response relationship.

In female rats of the high dose group, the mean weight of the ovaries was slightly although significantly decreased (-13.6 %, $p <= 0.05$). The absolute mean ovary weights are tabulated in the following.

Dose Group mean absolute ovary weights (mg +/- SD)

Controls 94.9 +/- 10.5
200 ppm 91.5 +/- 23.2
1000 ppm 100.5 +/- 16.1
5000 ppm 82.0 +/- 9.4 (* p < = 0.05)

The other mean absolute weight parameters did not show significant differences when compared to the control group.

- Relative organ weights (related to terminal body weight)
The mean relative weights of testes (+13.7 %), epididymides (+12.7%) and brain (+10.7 %) were significantly increased in males of the high dose group. This was regarded to be the consequence of the decrease of the mean terminal body weight (-11.7 %). In females of the high dose group, the mean weight of the kidneys was slightly but significantly increased (+10.8 %), most likely for the same reason. The relative ovary weights of the high dose females did not show statistically significant changes compared to the controls:

Dose Group Mean relative Ovary Weights

Controls 0.045 +/- 0.005
200 ppm 0.043 +/- 0.012
1000 ppm 0.05 +/- 0.009
5000 ppm 0.042 +/- 0.004

An incidentical finding was the slight although significant decrease (-7.5 %) of relative weight of the heart in males of the low dose group as there no dose-relationship was evident. The other mean relative weight parameters did not show significant differences when compared to the control group.

- Gross lesions
Only a few gross lesions were noted in the glandular stomach (erosion/ulcer, focus, hyperemia), liver (enlarged), kidneys (granular surface, pelvic dilation) and skin (lesion, sparse hair). With one exception (erosion/ulcer in 2 low dose groups) these findings occured only once per group and they were hence interpreted to have developed spontaneously and unrelated to treatment.

- Histopathology
Some grossly noted lesions lacked a microscopic correlate. However, regardless of whether or not they had a microscopic correlate, all the gross lesions were considered to have developed spontaneously and to be unrelated to treatment. No histological correlates were obtained for the significantly decreased absolute weights of liver in the male high dose group and in mid dose group.
Further, no morphologic correlate was obtained for the significantly increased mean relative weights of the testes, epididymides and brains in male high dose group. The increase of the relative weight of brain in male high dose group as well as the increase of the relative weights of kidneys in the female high dose group were considered to have developed spontaneously and to be unrelated to treatment.
Finally, no microscopic finding was obtained that may account for the significant decreased mean absolute weight of the ovaries in the high dose females which was most likely caused

by the decreased body weight of these animals.
All microscopic findings recorded were either single observations, or they were recorded at a low incidence, or they occurred in control animals only, or at comparable incidence and graded severity in control and high dose males and/or females.

CONCLUSION
Substance related effects were seen at the high and mid dose level (decreased food and water consumption, decreased body weight data). There were no other treatment related significant organ weight changes, gross lesions, or microscopic changes. As reduction in food an water consumption did result in significant decrease of body weight only at the high dose level, the no observed adverse effect level (NOAEL) in this study was 1000 ppm (65.4 mg/kg bw/d in males, 82.1 mg/kg bw/d in females). No effects on reproductive organs or sperm parameters were observed.

Test condition: PALATABILITY STUDIES

3-Methylbut-2-en-1-ol was administered for 2 weeks to groups of Wistar rats (3 per sex) in drinking water at concentrations of 0, 5000 and 15000 ppm (1st study) and 0, 2500, 5000 and 7500 ppm (2nd study). The following results were obtained:

- 15000 ppm: water intake refused in males and females, animals sacrificed after 5 days
- 7500 ppm: water consumption reduced by -25% and -41% (m/f), food consumption reduced by -19% and -25% (m/f), body weight reduced by -14% and -15% (m/f)
- 5000 ppm: water consumption reduced by -52% and -30% (m/f) (1st study) and -21% and -26% (m/f) (2nd study), food consumption reduced by -20% and -14% (m/f) (1st study) and -12% and -13% (m/f) (2nd study), body weight reduced by -11% and -8% (m/f) (1st study) and by -5% and -7% (m/f) (2nd study)
- 2500 ppm: water consumption reduced by -16% and -25% (m/f), food consumption reduced by -7% and -17% (m/f), body weight reduced by -6% and -13% (m/f)

No treatment related mortality occurred. Based on these results (drastically reduced water consumption at 7500 and 15000 ppm), test concentrations of 5000, 1000 and 200 ppm were selected for the main study.

MAIN STUDY

TEST ORGANISM
Strain: CRL:WI (GlX/BRL/HAN) IGS BR (Supplier: Charles River, Germany)
Age at study initiation (day 0): 41 - 43 days
Weight at study initiation: males: 148.7 - 171.1 g (mean 159.2 g), females: 111.1 - 136.4 g (mean 123.5 g)
Number of animals per group: 10 per dose and sex

ADMINISTRATION / EXPOSURE
Duration of test/exposure: 90 days
Test substance purity: 99.1% (gas chromatography)

Vehicle: drinking water
Preparation of test formulation: appropriate amount of test substance was weighed, then drinking water was filled up to the desired volume and subsequently mixed using a magnetic stirrer. The test substance preparations were prepared twice a week.
Stability of test substance in vehicle: was determined over a period of 4 days at room temperature at the start of the study. As the preparations were solutions in water, no homogeneity analyses were carried out. Concentration control analyses of the test substance preparations were performed in all concentrations at the start and the end of the administration period.

CLINICAL OBSERVATIONS
- Clinical signs: Daily after application of test substance. Detailed clinical observations outside the home cage in an open field (50x37.5 cm with sides of 25 cm high) were performed prior to the start of the administration period and weekly thereafter. The findings were ranked according to the degree of severity, if applicable.
The following parameters were examined: behavior during "handling", fur, skin, posture, salivation, respiration, activity/arousal level, tremors, convulsions, abnormal movements, impairment of gait, lacrimation, palpebral closure, exophthalmus, feces (appearance/consistency), urine and pupil size.

- Mortality: twice daily (monday - friday), once daily (saturday and sunday)
- Body weight: before the start of administration, thereafter once weekly. On days 86, 87 and 90 an additionally body weight, for the FOB animals of these days, was determined.
- Food consumption: once weekly
- Water consumption: daily
- Food efficiency: was calculated based upon individual values for body weight and food consumption.
- Intake of test substance: was calculated based upon individual values for body weight and water consumption.

- Ophthalmoscopic examination: Prior to the start of the administration period the eyes of all animals were examined for any changes using an ophthalmoscope after administration of a mydriatic. At the end of the study, the animals of the control and high dose group were examined.

- Functional observational battery (FOB):
was performed towards the end of the study, starting at about 10.00 a.m.. The FOB started with passive observations without disturbing the animals, followed by removal from the home cage, open field observations in a standard arena and sensorimotor tests as well as reflex tests. The findings were ranked according to the degree of severity, if applicable.
-- Home cage observations:
The animals were observed in their closed home cages; any disturbing activities were avoided during these examinations in order not to influence the behavior of the animals. Attention was paid to posture, tremor, convulsions, abnormal

movements, impairment of gait and general observations.
-- Open field observations:
The animals were transferred to a standard arena (50x37.5 cm with sides of 25 cm high) and observed for at least 2 minutes.

Following parameters were examined: behavior when removed from cage, fur, skin, salivation, nose discharge, lacrimation, eyes / pupil size, posture, palpebral closure, respiration, tremors, convulsions, abnormal movements / stereotypics, impairment of gait, activity/arousal level, feces, urine and number of rearings.
-- Sensorimotor Tests/Reflexes:
The animals were removed from the open field and subjected to following sensorimotor or reflex tests:
approach response, touch response, vision, pupillary reflex, pinna reflex, audition, coordination of movements, behavior during, vocalization, pain perception, grip strength of forelimbs, grip strength of hindlimbs, landing foot-splay test
- Motor activity assessment
was measured on the same day as FOB was performed. The measurement was performed in the dark using the Multi-Varimex-System with 4 infrared beams per cage. During the measurement the animals were kept in Polycarbonate cages with absorbent material. The measurements started between 1.30 p.m. and 2.00 p.m. and the number of beam interrupts were counted over 12 intervals, each lasting 5 minutes. The period of assessment for each animal started when the first beam was interrupted by pushing the cage into the rack. Measurements ended exactly 60 minutes thereafter.

CLINICAL PATHOLOGY
Blood was taken from the retroorbital venous plexus in the morning from fasted animals without anesthesia. At necropsy specimen were sampled from fasted anesthetized male animals in a randomized sequence for sperm analyses. The following examinations were carried out in 10 animals per test group and sex at the end of the application period.

- Hematology
The following parameters were determined in blood with EDTA-K3 as anticoagulant using a particle counter: leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, differential blood count.
Prothrombin time was determined using a ball coagulometer.

- Clinical chemistry
An automatic analyzer was used to examine the following clinicochemical parameters.
alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum gamma-glutamyltransferase, sodium, potassium, chloride, inorganic phosphate, calcium, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, cholesterol, magnesium.

- Urinalysis
With the exception of volume, color, turbidity, sediment examination and the specific gravity, all the uine

constituents were determined semiquantitatively using test strips and a reflection photometer. The specific gravity was determined using a urine refractometer. The sediment was evaluated microscopically.
The following examinations were carried out: volume, color, turbidity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, specific gravity, sediment

- Sperm parameters
Immediately after necropsy and organ weight determination the right testis and cauda epididymis were taken from all male animals. The following parameters were determined: sperm motility, sperm morphology, sperm head count (cauda epididymis), sperm head count (testis)

PATHOLOGY
- Necropsy
The animals were sacrificed by decapitation under CO2 anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology.

- Organ weights
The following weight parameters from all animals sacrificed at scheduled dates were determined: Anesthetized animals, liver, kidneys, adrenal glands, testes, epididymides, ovaries, uterus, spleen, brain, heart, thymus, prostate gland

- Histopathology
Left testis, left epididymis and both ovaries were fixed in Bouin' solution. After fixation, the organs were embedded in paraplast. The following organs were fixed in 4% formaldehyde solution, histopathologically processed and examined by light microscopy:
All gross lesions, salivary glands (Glandula mandibularis and Glandula sublingualis), esophagus, stomach (forestomach and glandular stomach), duodenum, jejunum, ileum, cecum, colon, rectum, liver, pancreas, brain, pituitary gland, sciatic nerve, spinal cord (cervical, thoracic and lumbar cord), eyes, adrenal glands, thyroid glands, parathyroid glands, trachea, lungs, pharynx, larynx, nose (nasal cavities), aorta, heart , bone marrow (femur), lymph nodes (mandibular and mesenteric), spleen, thymus, kidneys, urinary bladder, oviducts/uterus/vagina, prostate gland, seminal vesicles, female mammary gland, skin, skeletal muscle, sternum with marrow, femur with knee joint, extraorbital lacrimal glands

STATISTICAL METHODS
Means and standard deviations of each test group were calculated for several parameters. Further statistical analyses were performed.

- Dunnett test:
Food and water consumption, body weight change, food efficiency

- Kruskall-Wallis test:
Feces, rearing, grip strength length forelimbs, grip strength

length hindlimbs, landing foot-splay test, motor activity, clinical pathology, pathological weight parameters (if p-value < = 0.05 Wilcoxon test was additionally performed)

- Fishers exact test:
Urinalysis, except volume, color, turbidity and specific gravity; abnormal sperm > 4%

- Wilcoxon test
Total spermatids/g testis, total sperm/g cauda epi., % motility

Test substance: 3-Methylbut-2-en-1-ol, purity 99.1 %
Reliability: (1) valid without restriction
1a: GLP guideline study
Well conducted guideline study conducted under GLP conditions. Chosen as key study for SIDS endpoint.
Flag: Critical study for SIDS endpoint
06-JUN-2003 (37) (38) (39)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium; TA1535 TA100 TA1537 TA98
Concentration: 20, 100, 500, 2500 and 5000 µg/plate
Cytotoxic Concentration: only in TA 100 from 100 µg/plate onward
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1983
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 1988
Result: SOLUBILITY
The test substance was completely soluble in aqua dest.

TOXICITY
A bacteriotoxic effect was only observed in the preincubation test using TA 100 with S-9 mix from about 100 µg/plate onward.

MUTAGENICITY
An increase in the number of his+ revertants was not observed both in the standard plate test and in the preincubation test either without S-9 mix or after the administration of a metabolizing system.
The positive control substances showed appropriate responses.

CONCLUSION:
The test substance 3-methylbuten-2-ol-1 was not mutagenic in the Ames test under the conditions chosen.
Test condition: SYSTEM OF TESTING
- Metabolic activation system: S-9 mix from rat liver, induced with Aroclor 1254,
- Standard plate test and preincubation test

ADMINISTRATION

- Number of replicates: 3 experiments (2 x standard plate test +/- S-9 mix; 1 x preincubation test +/- S-9 mix
- Plates per test: 3 per dose or per control
- Positive control groups and treatment: - S-9 mix: 5 µg N-methyl-N'-nitro-N-nitrosoguanidine for TA 100 and TA 1535, 10 µg 4-nitro-o-phenylendiamine for TA 98, 100 µg 9-aminoacridine chloride monohydrate for TA 1537; + S-9 mix: 10 µg: 2-aminoanthracene (4 strains)
- Solvent: aqua dest.

GLP:
Test was conducted under GLP working conditions, but not yet certified

Test substance: 3-Methylbut-2-en-1-ol, purity 99 %

Reliability: (1) valid without restriction
1a: GLP guideline study
Well conducted guideline study conducted under GLP conditions. Chosen as key study for SIDS endpoint.

Flag: Critical study for SIDS endpoint

31-AUG-2004 (40)

Type: other: Liquid Suspension Assay (Modified Salmonella/Mammalian-Microsome Mutagenicity Test)
System of testing: Salmonella typhimurium TA 100 and TA 98
Concentration: 20, 100, 500, 2500 and 5000 µg/plate
Cytotoxic Concentration: no bacteriotoxic effect observed
Metabolic activation: with and without
Result: negative

Method: other: comparable to OECD Guide-line 471
Year: 1983
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 1991
Result: SOLUBILITY
The test substance was completely soluble in aqua dest.

TOXICITY
No bacteriotoxic effect was observed.

MUTAGENICITY
An increase in the number of his+ revertants was not observed either without S-9 mix or after the addition of a metabolizing system.
The positive control substances showed appropriate responses.

CONCLUSION:
The test substance 3-methylbuten-2-ol-1 was not mutagenic in the Ames test under the conditions chosen.

Test condition: SYSTEM OF TESTING
- Metabolic activation system: S-9 mix from rat liver, induced with Aroclor 1254,
- modified Ames preincubation test (experimental procedure is based on the method described by Rannug et al. (1976) and Lutz et al. (1982)

ADMINISTRATION
- Number of replicates: 1 experiment

- Plates per test: 3 per dose or per control
- Positive control groups and treatment: - S-9 mix: 5 µg N-methyl-N'-nitro-N-nitrosoguanidine for TA 100, 10 µg 4-nitro-o-phenylendiamine for TA 98; + S-9 mix: 10 µg: 2-aminoanthracene (2 strains)
- Solvent: aqua dest.

EXPERIMENTAL PROCEDURE
0.1 ml test solution or solvent, 1.5 ml bacterial suspension and 0.5 ml S-9 mix were incubated in closed tubes at 37°C for about 90 min.. Subsequently, the bacterial cultures are centrifuged at 5000 rpm, the supernatant is removed and 0.5 ml phosphate buffer and 2 ml of soft agar is added. After mixing and resuspending, the samples are poured onto agar plates. After incubation at 37°C for 48 hrs, the bacterial colonies are counted.

GLP:
Test was under GLP working conditions, but not yet certified

Test substance: 3-Methylbut-2-en-1-ol, purity 99%

Reliability: (2) valid with restrictions
2c: Comparable to guideline study with acceptable restrictions. Restrictions: only two Salmonella strains used instead of five bacteria strains as recommended in the OECD TG. Chosen as key study for SIDS dossier.

Flag: Critical study for SIDS endpoint

31-AUG-2004 (41)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: NMRI
Route of admin.: i.p.
Exposure period: two administrations with a 24-hour interval
Doses: 125, 250 and 500 mg/kg bw
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 2000
Result: MORTALITY
No mortality occurred in all groups.

CLINICAL SIGNS
The administration of the test substance at 2 x 500 mg/kg bw. led to evident signs of toxicity in all treated animals (poor general state, gasping respiration, staggering, tremor). At the 2 lower doses only minor signs of clincal toxicity were observed in a dose dependent manner (squatting posture).

EFFECT ON PCE/NCE RATIO
A slight inhibition of erythropoiesis, determined from the PCE/NCE ratio was detected at 250 and 500 mg/kg bw. The

vehicle and the the positive control substances, CPP and VCR, caused no evident signs of toxicity.

GENOTOXIC EFFECTS
Mean number of PCEs containing MN per 1000 PCE at 24 hrs:

vehicle: 0.8
125 mg/kg bw: 1.1
250 mg/kg bw: 0.8
500 mg/kg bw: 1.5
CPP (20 mg/kg bw): 16.7 (p < = 0.01)
VCR (0.15 mg/kg bw): 89.9 (p < = 0.01)

STATISTICAL EVALUATION
The administration of the test substance did not lead to any statistical significant increase in the number of polychromatic erythrocytes containing either small or large micronuclei. The rate of micronuclei was nearly the range of the concurrent negative control in all dose groups and within the range of the historical control data.

CONCLUSION
Under the experimental conditions chosen, the test substance did not have a chromsome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells in vivo.

Test condition: TEST ORGANISM
male mice with a mean weight of about 28 g (with an age range of about 5-8 weeks according to the information of the breeder), 5 animals per dose and group

ADMINISTRATION
Vehicle: olive oil
Frequency of dosing: 2 injections at a 24 hrs interval
Dosing volume: 10 ml/kg bw
Control groups:
negative: 2 x vehicle control (10 ml/kg bw olive oil)
positive: 1 x 20 mg/kg bw cyclophosphamide (CPP) for clastogenic effects, 1 x 0.15 mg/kg bw vincristine (VCR) for aneugenic effcts

TEST CONDITIONS
Sampling times: 24 hrs after the last treatment samples of bone marrow of the 2 femora were taken and prepared.
Preparation of the bone marrow: according to the method of Schmidt (1976 and 1977) and Salamone et al. (1980)
Microscopic evaluation: 2000 polychromatic erythrocytes (PCEs) from each animal of every test group were investigated for micronuclei (MN). The normochromatic erythrocytes (NCEs) were also scored. The ratio of polychromatic to normochromatic erythrocytes was determined.
Clinical observations: after administration of the vehicle, test substance and positive controls, the animals were examined for clinical signs of toxicity.
Criteria for selection of M.T.D.:
In a pretest for determination of the acute i.p. toxicity, deaths were observed down to a dose of 750 mg/kg bw. 500 mg/kg bw were survived by all animals but led to signs of

clinical toxicity. No distinct differences between the male and female animals were observed. Therefore, doses of 500, 250 and 125 mg/kg bw were selected.
Statistical method: Wilcoxon test

Test substance: 3-Methylbut-2-en-1-ol, purity 99.1 %
Reliability: (1) valid without restriction
1a: GLP guideline study
Well conducted guideline study conducted under GLP conditions. Chosen as key study for SIDS endpoint.
Flag: Critical study for SIDS endpoint
06-JUN-2003 (42)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

Type: other: sub-chronic
Species: rat
Sex: male/female
Strain: Wistar
Route of administration: drinking water
Exposure Period: 90 days
Frequency of treatment: continuously
Doses: 200, 1000 and 5000 ppm
Control Group: yes, concurrent vehicle
Result: No effects on reproductive organs or sperm parameters observed (NOAEL 5000 ppm)

Method: other: OECD TG 408
Year: 1998
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: Year study performed: 2001
Result: Substance intake
The mean daily test substance intake in mg/kg bw over the entire study period was calculated:

200 ppm group: 14.4 (males) and 21.0 mg/kg bw/d (females)
1000 ppm group: 65.4 (males) and 82.1 mg/kg bw/d (females)
5000 ppm group: 243.8 (males) and 307.2 mg/kg bw/d (females)

The study results concerning CLINICAL OBSERVATIONS, CLINICAL PATHOLOGY and PATHOLOGY are fully described in chapter 5.4 (Repeated Dose Toxicity). In the following only observations relevant for the endpoint reproductive toxicity are included.

CLINICAL PATHOLOGY
- Sperm analysis
No treatment-related changes were observed in sperm parameters.

PATHOLOGY
- Absolute body and reproductive organ weights
In male rats, the mean terminal body weight was significantly decreased in the high dose group (-11.7 %). Also in female rats of the high dose group, the mean terminal body weight was

slightly but significantly decreased (-6.4 %). This was regarded treatment-related. In males, the sex organ weights were not changed compared to the control animals.

In female rats of the high dose group, the mean weight of the ovaries was slightly although significantly decreased (-13.6 %, p < = 0.05). The absolute mean ovary weights are tabulated in the following:

Dose Group	Mean Absolute Ovary Weights (mg +/- SD)
Controls	94.9 +/- 10.5
200 ppm	91.5 +/- 23.2
1000 ppm	100.5 +/- 16.1
5000 ppm	82.0 +/- 9.4 (* p < = 0.05)

- Relative reproductive organ weights (related to terminal body weight)
The mean relative weights of testes (+13.7 %) and epididymides (+12.7%) were significantly increased in males of the high dose group. This was regarded to be the consequence of the decrease of the mean terminal body weight (-11.7 %). The relative ovary weights of the high dose females did not show statistically significant changes compared to the controls:

Dose Group	Mean relative Ovary Weights
Controls	0.045 +/- 0.005
200 ppm	0.043 +/- 0.012
1000 ppm	0.05 +/- 0.009
5000 ppm	0.042 +/- 0.004

- Gross lesions and histopathology
There were no gross lesions noted in the reproductive organs of both sexes. No morphologic correlate was obtained for the significantly increased mean relative weights of the testes and epididymides in male high dose group. No microscopic finding was obtained that might have accounted for the significant decreased mean absolute weight of the ovaries in the high dose females which was most likely caused by the decreased body weight of these animals.

CONCLUSION
No effects on reproductive organs or sperm parameters were observed up to the highest tested concentration of 5000 ppm (243.8 and 307.2 mg/kg bw/d for males and females).

Test condition: TEST ORGANISM
Strain: CRL:WI (GlX/BRL/HAN) IGS BR (Supplier: Charles River, Germany)
Age at study initiation (day 0): 41 - 43 days
Weight at study initiation: males: 148.7 - 171.1 g (mean 159.2 g), females: 111.1 - 136.4 g (mean 123.5 g)
Number of animals per group: 10 per dose and sex

ADMINISTRATION / EXPOSURE
Duration of test/exposure: 90 days
Test substance purity: 99.1% (gas chromatography)
Vehicle: drinking water

Preparation of test formulation: appropriate amount of test substance was weighed, then drinking water was filled up to the desired volume and subsequently mixed using a magnetic stirrer. The test substance preparations were prepared twice a week.
Stability of test substance in vehicle: was determined over a period of 4 days at room temperature at the start of the study. As the preparations were solutions in water, no homogeneity analyses were carried out. Concentration control analyses of the test substance preparations were performed in all concentrations at the start and the end of the administration period.

The study conditions concerning CLINICAL OBSERVATIONS, CLINICAL PATHOLOGY, PATHOLOGY and STATISTICAL METHODS are fully described in chapter 5.4 (Repeated Dose Toxicity). In the following only examinations relevant for the endpoint reproductive toxicity are included.

CLINICAL PATHOLOGY
At necropsy specimen were sampled from fasted anesthetized male animals in a randomized sequence for sperm analyses.
- Sperm parameters
Immediately after necropsy and organ weight determination the right testis and cauda epididymis were taken from all male animals. The following parameters were determined: sperm motility, sperm morphology, sperm head count (cauda epididymis), sperm head count (testis)

PATHOLOGY
- Necropsy
The animals were sacrificed by decapitation under CO2 anesthesia. The exsanguinated animals were necropsied and assessed by gross pathology.

- Reproductive organ weights
The following weight parameters from all animals sacrificed at scheduled dates were determined: Anesthetized animals, testes, epididymides, ovaries, uterus, prostate gland

- Histopathology
Left testis, left epididymis and both ovaries were fixed in Bouin' solution. After fixation, the organs were embedded in paraplast. The following organs were fixed in 4% formaldehyde solution, histopathologically processed and examined by light microscopy:
All gross lesions, oviducts/uterus/vagina, prostate gland, seminal vesicles

STATISTICAL METHODS
Means and standard deviations of each test group were calculated for several parameters. Further statistical analyses were performed.

- Kruskall-Wallis test:
Pathological weight parameters (if p-value < = 0.05 Wilcoxon test was additionally performed)

- Fishers exact test:
Abnormal sperm > 4%

- Wilcoxon test
Total spermatids/g testis, total sperm/g cauda epi., % motility

Test substance: 3-Methylbut-2-en-1-ol, purity 99.1 %
Reliability: (1) valid without restriction
1a: GLP guideline study
Well conducted guideline study conducted under GLP conditions. Chosen as key study for SIDS endpoint.
Flag: Critical study for SIDS endpoint
13-JUN-2003 (43)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: day 6 - 19 post conception
Frequency of treatment: once per day
Duration of test: until day 20 post conception
Doses: 50, 200 and 600 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 200 mg/kg bw
NOAEL Teratogenicity: > 600 mg/kg bw
Result: No signs of prenatal developmental toxicity and no indications for teratogenicity.

Method: OECD Guide-line 414 "Teratogenicity"
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: The historical control data used for interpretation of findings refer to the same test facility, the same rat strain and supplier and cover a period of about 2 years (February 2000 - October 2001).
Year study performed: 2001-2002
Result: ANALYSES
The stability of the test substance suspensions over a period of 7 days at room temperature, the homogeneity of the test substance in the vehicle and the correct concentration of the test substance in the preparation was demonstrated.

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: One high dose dam was found dead on day 19 p.c.; it could not be excluded with certainty, that the intercurrent death of this rat shortly before the scheduled termination of the study had a substance-related background.

- Clinical symptoms: All high dose rats showed transient salivation shortly after treatment from day 6 p.c. onwards. However, the observed salivation persisted in the respective females only for a short time (1 - 2 hours) after the actual gavaging had taken place. After cessation of treatment on day

19 p.c., salivation did not occur any longer in these rats. Furthermore, most of the high dose rats were in an abdominal position (in total 20 out of 25 rats), had lacrimation (in total 24 out of 25 rats) and/or piloerection (in total 17 out of 25 rats) shortly after treatment. These findings were predominantly observable at initiation of dosing (days 6 and 7 p.c.) and occurred thereafter only sporadically. Moreover, one high dose dam died before schedule on day 19 p.c. and another rat of this group showed diarrhea on day 10 p.c.. Thus, all high dose rats showed adverse clinical findings during the administration period, which are considered to be substance-induced. No disturbances of the general behavior, however, occurred in the dams of the other test groups including the controls (0, 50 and 200 mg/kg bw/day).
- Food consumption: The mean food consumption of the high dose dams was statistically significantly reduced (about 9% below the concurrent control value) on the first days of the treatment period (days 6 - 8 p.c.), but was similar to or even exceeded control values on the following days until termination. Food consumption of the mid and low dose rats was not affected by the test substance administration. Food consumption values of these rats were similar to control values on days 0 - 20 p.c. [20.3 +/- 3.00 g, 20.1 +/- 3.13 g, 20.4 +/- 2.87 g, 19.9 +/- 3.31 g for controls, low, mid and high dose groups].

- Body weight data: The mean body weight of the high dose rats was slightly [-3.9%], but statistically significantly lowered on day 8 p.c. and an corresponding, statistically significant impairment in mean body weight gain [about 38% below the concurrent control value] occurred in this group on the first treatment days (6 - 8 p.c.); on the other treatment days, weight gains of the 600 mg/kg bw females were sometimes below and sometimes above those of the corresponding controls without attaining statistical significance. Body weight gains of the dams of test groups 1 and 2 (50 and 200 mg/kg bw) were similar to those of the concurrent controls [weight gains days 0 - 20: 98%, 97% and 96% of controls for low, mid and high dose groups]. All observable differences in these two groups in comparison to the controls during the treatment period are without any biological relevance.

- Corrected body weight gain (net maternal body weight change): The corrected body weight gains of the dams of test groups 1 - 2 revealed no differences of any biological relevance to the corresponding control group [102%, 103% and 86% of controls for low, mid and high dose groups]. The net weight change of the 600 mg/kg bw rats, however, was about 14% below the concurrent control value (without attaining statistical significance) and the mean carcass weight was statistically significantly reduced in this test group [- 5%].

EXAMINATION OF THE DAMS AT TERMINATION
- Uterus weight: The mean gravid uterus weights of the animals of all test groups were not influenced by the administration of the test substance [96%, 89% and 102% of controls for low, high and mid dose groups].
- Necropsy findings: There were no substance-related

observations at necropsy in any of the dams. Only one spontaneous finding, i.e. edema of the lungs occurred in two control females and one low dose dam. Lung edema was also observed in one high dose dam which died intercurrently on day 19 p.c..
- Reproduction data of dams: The conception rate reached 92% at 200 mg/kg bw and 96% at 0, 50 and 600 mg/kg bw. As all rats, which became pregnant had implantation sites at necropsy, a sufficient number of females for the purpose of the study was available. There were no substance-related and/or biologically relevant differences between the different test groups in conception rate, in the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and the postimplantation losses, the number of resorptions and viable fetuses. All differences observed are considered to reflect the normal range of fluctuations for animals of this strain and age.

- Summary of reproduction data
(controls, low, mid and high dose groups)

Conception rate, %: 96, 96, 92, 95
Corpora lutea, mean (SD): 10.6 (1.64), 10.8 (1.67), 10.8 (1.96), 10.9 (1.63)
Implantation sites, mean (SD): 9.6 (1.69), 9.6 (2.22), 8.8 (2.67), 10.0 (1.58)
Preimplanation loss, mean (SD): 9.2 (10.32), 10.2 (17.7), 18.4 (20.36), 8.2 (7.98)
Postimplanation loss, mean (SD): 4.2 (7.85), 10.6 (17.87), 10.1 (16.69), 4.3 (7.32)
Total resorptions, mean (SD): 0.4 (0.71), 0.8 (1.14), 0.7 (0.82), 0.4 (0.66)
Live fetuses, mean (SD): 9.3 (1.89), 8.8 (2.77), 8.2 (2.95), 9.6 (1.88)

EXAMINATION OF FETUSES
- Sex distribution of fetuses: The sex distribution of the fetuses in all test groups was comparable with that of the control fetuses.

- Weight of placentae: The mean placental weights in all test groups were not influenced by the test substance administration and were similar to the control values [109%, 118% and 102% of controls for low, mid and high dose animals].

- Weight of fetuses: The mean fetal body weights in all test groups were not influenced by the test substance administration and were nearly identical with the corresponding control values [100%, 100% and 100% of controls for low, mid and high dose animals].

- Fetal external, soft tissue and skeletal observations: Non of the examined rat fetuses showed external or soft tissue malformations. The scattered occurrence of the few observed skeletal malformations in single fetuses of all test groups including the controls without a consistent pattern, without a clear dose-response relationship and/or at incidences, which are similar to historical control rates did not indicate any substance-induced origin of these findings. The malformations

which occurred affected the vertebral column (misshapen sacral vertebra) and the sternum (cleft sternum or malpositioned and bipartite sternebra).

If all different types of malformations were summarized, in total 6 of the 222 examined control fetuses [= 2.7%] in 6 out of 24 litters [= 25%], 2 of the 211 examined low dose fetuses [= 0.9%] in 2 out of 24 litters [= 8.3%], one out of 155 mid dose fetuses [= 0.6%] in one out of 19 litters [= 5.3%] and 3 out of 220 high dose fetuses [= 1.4%] in 3 out of 23 litters [= 13%] showed malformations. The mean percentages of affected fetuses/litter with total malformations amounted to 2.8, 1.1, 0.4 and 1.2% at 0; 50; 200 or 600 mg/kg bw respectively. These incidences did not suggest any treatment-relationship.

External variations did not occur in any of the fetuses in this study. Soft tissue variations, exclusively in the form of dilated renal pelvis and ureters, and a broad range of skeletal variations occurred in all test groups including the controls. All fetal and litter incidences for these variations and the corresponding mean percentages of affected fetuses/litter did not show a clear relation to dosing, were not considered to be of any toxicological relevance and/or can be found at a comparable frequency in the historical control data. This includes the statistically significantly increased rates of one soft tissue variation (dilated renal pelvis) in the 200 mg/kg bw group, of one skeletal variation (cervical rib) at the high dose and of total skeletal variations at the mid dose.

If all variations were summarized, in total 111 of the 222 examined control fetuses [= 50%] in all 24 litters [= 100%], 106 of the 211 examined low dose fetuses [= 50%] in all 24 litters [= 100%], 92 out of 155 mid dose fetuses [= 59%] in all 19 litters [= 100%] and 122 out of 220 high dose fetuses [= 55%] in all 23 litters [= 100%] showed variations. The mean percentages of affected fetuses/litter with total variations amounted to 50.3, 53.3, 62.2 and 55.6% at 0; 50; 200 or 600 mg/kg bw respectively. These incidences did not suggest a treatment-relationship, but reflected the usual biological variation inherent in the strain of rats used for this experiment. The statistically significantly increased percentage of fetuses/litter with total variations at 200 mg/kg bw [21 +/- 23.76% versus 4.4 +/- 8.98% in controls for total soft tissue variations] is fully included in this assessment as it was predominantly caused by a randomly increased rate of a very common soft tissue variation (dilated renal pelvis) in this test group. This value is fully within the historical control data range for this observation [range: 3.2% - 22.2%, mean: 8.1%].
Thus, the oral administration of 3-methylbut-2-en-1-ol to pregnant Wistar rats had no effects on fetal morphology at any of the dose levels tested and caused in particular no indications for substance-induced teratogenicity.

CONCLUSION
3-Methylbut-2-en-1-ol administered to pregnant Wistar rats daily by stomach tube from implantation to one day prior to the expected day of parturition (days 6 - 19 p.c.) caused

clear, substance-related signs of maternal toxicity at 600 mg/kg bw. No signs of substance-induced maternal toxicity occurred at the low and the mid dose level. The oral administration of the test substance to the dams at all 3 dose levels had no influence on the gestational parameters. Conception rate, mean number of corpora lutea, total implantations, resorptions and live fetuses, fetal sex ratio or in the values calculated for the pre- and the postimplantation losses were unaffected by treatment. No substance-related differences were recorded for placental and fetal body weights.
The external, soft tissue and/or skeletal (including cartilage) examinations of the fetuses revealed no differences between the control and the substance-treated groups, which might be related to the test substance administration. Number and type of fetal external, soft tissue and skeletal findings, which were classified as malformations and/or variations, recorded for the 50, 200 and 600 mg/kg bw fetuses were unaffected by treatment. These findings appeared without a clear relation to dosing and/or were seen at incidences previously found to occur spontaneously in control fetuses of this strain of rats. Additionally, there was not found any specific malformation pattern which could be indicative of a selective teratogenicity. Thus the test substance evoked no signs of prenatal developmental toxicity and in particular no indications for teratogenicity.

Based on the results of this prenatal developmental toxicity study, the no observed adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg bw, while it was > 600 mg/kg bw for prenatal developmental toxicity.

Test condition: RANGE FINDING STUDY (MATERNAL TOXICITY SUDY)

3-Methylbut-2-en-1-ol was administered as an aqueous formulation to 10 mated female Wistar rats/group by stomach tube at doses of 0, 100, 300 and 1000 mg/kg bw on day 6 through day 19 post coitum (p.c.) at a dose volume of 10 ml/kg bw (vehicle 0.5% Carboxymethylcellulose CB 30.000 in doubly distilled water). Food consumption and body weights were recorded regularly throughout the study period. The state of health of the animals was checked each day. On day 20 p.c. all females were sacrificed and assessed by gross pathology.

The following substance-induced findings were obtained:

1000 mg/kg bw:
- intercurrent death of 3 dams, unscheduled sacrifice of the remaining 7 dams due to severe clinical findings
- unsteady gait, abdominal position and salivation in all females
- ataxia, tremor, urine smeared fur and piloerection in 1-3 rats
- significantly reduced food consumption (ca. -35% on days 6-8)
- significant body weight loss on days 6 - 8 p.c.
- fluid-filled stomach in all animals and ulcerations of stomach mucosa in one rat

300 mg/kg bw:

- transient salivation in all rats shortly after treatment
- no substance-induced effects on food consumption and body weight data, and no necropsy findings

100 mg/kg bw:
- no substance-induced effects on the dams

Based on these results (lethality and massive clinical symptoms at 1000 mg/kg bw), doses of 50, 200 and 600 mg/kg bw were selected for the follow-up full-scale prenatal developmental toxicity study in rats.

MAIN STUDY

TEST ORGANISMS
Strain: Sexually mature, virgin Wistar rats (CrlGlxBrlHan:WI) supplied by Charles River Laboratories
Number: 25 female animals per group
Age at study initiation: about 70-84 days
Weight at study initiation: 143.3-182.5 g

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: from implanation to one day prior to the expected day of parturition (day 6 to day 19 post conception). On day 20 p.c., all surviving females were sacrificed.
- Treatment: orally by gavage always at approx. the same time of day (in the morning)
- Control group and treatment: gavage application of 10 ml/kg bw 0.5% Carboxymethylcellulose CB 30,000 in doubly distilled water
- Test substance purity: 99.1% (gas chromatography)
- Vehicle: 0.5% Carboxymethylcellulose CB 30,000 in doubly distilled water
- Test substance preparation: At the beginning of the administration period and thereafter at intervals which took into account the analytical results of the stability verification. For the preparation of the suspensions, an appropriate amount of the test substance was weighed depending on the dose group, in calibrated beakers and subsequently suspended in the vehicle using a high - speed homogenizer. A magnetic stirrer was used to keep the suspensions homogeneous during treatment of the animals.
- Concentration in vehicle: 500, 2000 and 6000 mg/100 ml
- Total volume applied: 10 ml/kg bw
- Doses: 50, 200, 600 mg/kg bw
- Analyses: check of stability of test substance, homogeneity of test formulation and concentration control of test substance was performed by gas chromatography

MATING PROCEDURES:
The animals were mated by the breeder ("time-mated") and supplied on day 0 post coitum (= detection of vaginal plug / sperm). The animals arrived on the same day (i.e. day 0 p.c.) at the experimental laboratory. The following day was designed "day 1" p.c.

PARAMETERS ASSESSED DURING STUDY:
- Mortality: A check was made twice a day on working days or once a day (Saturday, Sunday or on public holidays) (days 0 - 20 p.c.).

- Clinical symptoms: The animals were examined for clinical symptoms at least once a day, or more often when clinical signs of toxicity were elicited (days 0 - 20 p.c.).

- Body weight gain: All animals were weighed on days 0, 1, 3, 6, 8, 10, 13, 15, 17, 19 and 20 p.c.. The body weight change of the animals was calculated from these results.

- Food consumption: With the exception of day 0, the consumption of food was determined on the same days as was body weight.

- Corrected body weight gain (net maternal body weight change). Furthermore, the corrected body weight gain was calculated after terminal sacrifice (terminal body weight on day 20 p.c. minus weight of the unopened uterus minus body weight on day 6 p.c.).

- Examination of uterine content: Gravid uterine weight, number of corpora lutea, number and distribution of implantation sites classified as live fetuses, dead implantations, early resorptions, late resorptions and dead fetuses. Calculations of conception rate and pre- and postimplantation losses were carried out.

- Examination of fetuses after dissection from the uterus: Litter size, fetal weight, sex ratio, grossly visible/external/soft tissue/skeletal abnormalities. The viability of the fetuses and the condition of the placentae, the umbilical cords, the fetal membranes and fluids were examined. Individual placental weights were recorded. After these examinations, approximately one half of the fetuses per dam were eviscerated, skinned and placed in ethyl alcohol, the other half was placed in BOUIN's solution for fixation and further evaluation.

- Soft tissue examination of the fetuses: The fetuses fixed in BOUIN's solution were examined for any visceral findings according to the method of BARROW and TAYLOR (1969).

- Skeletal examination of the fetuses:
The skeletons of the fetuses fixed in ethyl alcohol were stained according to a modified method of KIMMEL and TRAMMELL (1981). Thereafter, the skeletons of these fetuses were examined under a stereomicroscope. After this examination the stained fetal skeletons were retained individually.

STATISTICAL METHODS:
Statistical analyses were performed according to following schedule:
- DUNNETT-test (two-sided): Food consumption, body weight,

body weight change, corrected body weight gain, carcass weight, weight of unopened uterus, number of corpora lutea, number of implantations, number of resorptions, number of live fetuses, proportions of preimplantation loss, proportions of postimplantation loss, proportions of resorptions, proportion of live fetuses in each litter, litter mean fetal body weight, litter mean placental weight
- FISHER'S EXACT test (one-sided): Female mortality, females pregnant at terminal sacrifice, number of litters with fetal findings
- WILCOXON-test (one-sided): Proportions of fetuses with malformations, variations and/or unclassified observations in each litter

Test substance: 3-Methylbut-2-en-1-ol, purity 99.1 %

Reliability: (1) valid without restriction
1a: GLP guideline study
Well conducted guideline study conducted under GLP conditions. Chosen as key study for SIDS endpoint.

Flag: Critical study for SIDS endpoint

13-JUN-2003 (44) (45)

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: see also chapter 5.8.2

Flag: Critical study for SIDS endpoint

31-AUG-2004

5.9 Specific Investigations

-

5.10 Exposure Experience

Remark: Tested at 10 % in pet., it produced no irritation after a 48-hr closed-patch test on human subjects. A maximization test was carried out on 26 volunteers. At a concentration of 10 % in pet. no sensitization reactions were produced. Beside 3-methylbut-2-en-1-ol also butyl undecylenate, tricyclo decenyl acetate , and decanal dimethyl acetal were tested, but showed no reaction. No further data given.

Reliability: (2) valid with restrictions
basic data given, acceptable restrictions

Flag: Critical study for SIDS endpoint

23-SEP-2003 (46)

5.11 Additional Remarks

Type: Metabolism

Remark: Title: The toxic and metabolic effects of 23 aliphatic alcohols in the isolated perfused rat liver.

The authors investigated the acute toxic and metabolic effects of 23 aliphatic alcohols (16 saturated and 7 unsaturated) in the isolated perfused rat liver at a concentration of 65.1 mmol/l (~0.3% ethanol).

Following rat liver perfusion experiments with 65.1 mmole/l 3-methyl-2-buten-1-ol, concentrations of GPT, LDH and GLDH released into the perfusate were significantly elevated when compared to controls. O2 consumption, bile flow and perfusion flow were significantly decreased when compared to controls. GSH was significantly decreased when compared to controls. The lactate/pyruvate ratio within the perfusate was significantly increased when compared to controls. This effect was due to an increase in the lactate and a simultaneous decrease in the pyruvate concentrations.

The capacity of the straight chain primary alcohols (methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol) to release the enzymes glutamate-pyruvate transaminase (GPT), lactate dehydrogenase (LDH) and glutamate dehydrogenase (GLDH) into the perfusate was strongly correlated with their carbon chain length.
In general, the secondary alcohols were less active in this respect whereas branching of the carbon chain did not consistently change alcohol toxicity. Unsaturation in the straight chain but not in the branched chain alcohols was accompanied by an increase in toxicity. An increased enzyme release was in general accompanied by, and correlated to, reductions in oxygen consumption, bile secretion, and perfusion flow of the isolated livers. Statistically significant correlations existed between parameters of alcohol-induced hepatotoxicity and the membrane/buffer partition coefficents of the alcohols. With the exception of methanol, all alcohols tested increased the lactate/pyruvate ratio of the perfusate, although this effect was not correlated to the degree of hepatic injury. Hepatic ATP concentrations decreased in most cases in line with hepatic injury and were particularly correlated with changes in oxygen consumption. Hepatic concentrations of reduced glutathione (GSH) were only diminished by the unsaturated alcohols, whereas an increase in hepatic oxidized glutathione (GSSG) occurred only with some of the saturated alcohols. Hepatic concentrations of malondialdehyde (MDA) increased after two saturated and three unsaturated alcohols but did not correlate with other parameters of hepatotoxicity.
The authors concluded that alcohol-induced hepatotoxicity is primarily due to membrane damage induced by the direct solvent properties of the alcohols.

Test substance: 3-Methyl-2-buten-1-ol; source: Merck-Schuchardt, analytical grade, no further data on purity

12-JUN-2003 (47)

6.1 Methods Handling and Storing

Safe Handling: Ensure thorough ventilation of stores and work areas.
Fire/Exp. Prot.: Prevent electrostatic charge - sources of ignition should be kept well clear - fire extinguishers should be kept handy.
Storage Req.: Segregate from acids and acid forming substances.
Containers should be stored tighly sealed in a dry place.
Protect against heat.

Remark: PERSONAL PROTECTIVE EQUIPMENT

Respiratory protection:
Wear respiratory protection if ventilation is inadequate.

Hand protection:
Chemical resistant protective gloves (EN 374)
Suitable materials also with prolonged, direct contact (Recommended: Protective index 6, corresponding > 480 minutes of permeation time according to EN 374):
butyl rubber (butyl) - 0.7 mm coating thickness
fluoroelastomer (FKM) - 0.7 mm coating thickness
Suitable materials short-term contact and/or splashes (recommended: At least protective index 2, corresponding > 30 minutes of permeation time according to EN 374)
nitrile rubber (NBR) - 0.4 mm coating thickness
chloroprene rubber (CR) - 0.5 mm coating thickness
Supplementary note: The specifications are based on own tests, literature data and information of glove manufacturers or are derived from similar substances by analogy. Due to many conditions (e.g. temperature) it must be considered, that the practical usage of a chemical-protective glove inpractice may be much shorter than the permeation time determined in accordance to EN 374.

Eye protection: safety glasses with side-shields (frame goggles) (EN 166)

TRANSPORT INFORMATION

Land transport

ADR/RID	Class	3
	Packaging group	III
	UN-number	1993
	Designation of goods	FLAMMABLE LIQUID, N.O.S. (contains: 3-METHYL-BUTEN-2-OL-1).

Inland waterway transport

ADNR	Class	3
	Item/Letter	31c)
	Packaging group	III
	UN-number	1993
	Designation of goods	FLAMMABLE LIQUID, N.O.S. (contains: 3-METHYL-BUTEN-2-OL-1).

Sea transport

IMDG/ GGVSee
Class 3
Packaging group III
UN-number 1993
Marine pollutant NO
Exact technical name FLAMMABLE LIQUID, N.O.S. (3-METHYL-BUTEN-2-OL-1).

Air transport

ICAO/ IATA
Class 3
Packaging group III
UN-number 1993
Exact technical name FLAMMABLE LIQUID, N.O.S. (3-METHYL-BUTEN-2-OL-1).

Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

6.2 Fire Guidance

Prot. Equipment: Wear self-contained breathing apparatus and chemical-protective clothing.
Ext. Medium: water, foam, dry extinguishing media, carbon dioxide (CO2)
Add. Information: Collect separately contaminated extinguishing water, do not allow to reach sewage or effluent systems.

Flag: non confidential, Critical study for SIDS endpoint
17-FEB-2003 (3)

6.3 Emergency Measures

Type: other: general advice

Remark: Remove contaminated clothing.
Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2002 (3)

Type: injury to persons (skin)

Remark: Wash thoroughly with soap and water.
Flag: non confidential, Critical study for SIDS endpoint
31-MAR-2003 (3)

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at least 15 minutes under running water with eyelids held open, consult an eye specialist.
Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2002 (3)

Type: injury to persons (oral)

Remark: Immediately rinse mouth and then drink plenty of water, seek medical attention.
Flag: non confidential, Critical study for SIDS endpoint

12-NOV-2002 (3)

Type: injury to persons (inhalation)

Remark: Keep patient calm, remove to fresh air, seek medical attention
Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2002 (3)

Type: accidental spillage

Remark: Personal precautions: Ensure adequate ventilation.

Environmental precautions: Do not let product enter drains.

Methods for cleaning up or taking up:
For large amounts: Pump off product.
For residues: Pick up with suitable absorbent material.
Dispose of absorbent material in accordance with regulations.
Flag: non confidential, Critical study for SIDS endpoint
12-NOV-2002 (3)

6.4 Possib. of Rendering Subst. Harmless

Type of destruction: Incineration

Remark: Incinerate in suitable incineration plant, observing local authority regulations.
Flag: non confidential, Critical study for SIDS endpoint
17-FEB-2003 (3)

6.5 Waste Management

6.6 Side-effects Detection

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(26) BASF AG, Department of ecology; unpublished report 01/296/88, (17.08.1988)

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