FOREWORD INTRODUCTION

1,3-Dimethylurea

CAS N°: 96-31-1

SIDS Initial Assessment Report

For

SIAM 17

11–14 November 2003, Arona, Italy

1.	**Chemical Name:**	1,3-Dimethylurea
2.	**CAS Number:**	96-31-1
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; Air Products and Chemicals, Inc., USA
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 next page
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme ?	by ICCA-Initiative
7.	**Review Process Prior to the SIAM:**	last literature search (update): 26 May 2003 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 30 April 2003 (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:**	August 11, 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)

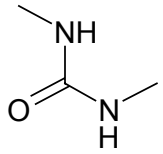
Review of validity of structure-activity relationships

Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)

In case of data gaps, review of testing plan or rationale for not testing

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	**96-31-1**
Chemical Name	**1,3-Dimethylurea**
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

1,3-Dimethylurea was not tested in experimental studies for its toxicokinetics.
The approximate oral LD50 of 1,3-dimethylurea in rats was determined to be 4,000 mg/kg bw. Clinical signs of toxicity were nonspecific and included apathy and narcotic-like state at dose levels near to or exceeding the LD50. No valid test is available on the acute inhalation toxicity. 1,3-Dimethylurea has not been tested for its acute dermal toxicity.
1,3-Dimethylurea (tested as 80 % aqueous solution) was only slightly irritating to the skin of rabbits after 24 hours of occlusive exposure. The undiluted test material induced lacrimation, corneal opacities and redness in the eyes of rabbits with some effects (redness, corneal opacity). The effects were still present in one of the two studies at study termination on day 8 in one animal.

After repeated oral administration for 28 days by gavage to rats in a study following OECD TG 407 (1981), 1,3-dimethylurea caused alterations in the kidneys (tubular necroses, desquamation of tubular epithelial cells and protein casts in the tubuli) in males at 150 and 450 mg/kg bw/day, and nonspecific tubular hyperplasia in females at 450 mg/kg bw/day. The NOAEL was 50 mg/kg bw/day.

1,3-Dimethylurea was not mutagenic in bacterial and mammalian cell culture systems and did not induce chromosomal aberrations in Mouse Lymphoma cells, both in the presence and in the absence of metabolic activation systems. There is no available information from *in vivo* genotoxicity studies in mammals. It is noted that mutagenic nitrosoureas may be produced from 1,3-dimethylurea with nitrite; therefore, a mutagenic potential cannot be totally excluded.

1,3-Dimethylurea had no adverse effects on reproductive performance and fertility of rats in a combined reproduction/developmental toxicity, screening test according to OECD TG 421 (NOAEL, reproductive performance/fertility: 200 mg/kg bw/day (highest tested dose level)). No teratogenic effects, but embryo-/fetotoxicity (reduced placental and fetal body weights) and an increase in the incidence of fetuses with a soft tissue variation (hydroureter) and with delayed ossifications in sternebrae were found at maternally toxic dose levels in a developmental toxicity study in rats in accordance with OECD TG 414 (NOAEL for developmental toxicity and maternal toxicity: 30 mg/kg bw/day).

It is noted that carcinogenic nitrosoureas may be formed with nitrite.

Environment

1,3-Dimethylurea is an organic solid with a melting point of 102 – 107 °C and a density of 1.142 g/cm^3. It has a water solubility of 765 g/l at 21.5 °C, (pH = 9 – 9.5 at 100 g/l), a vapor pressure of 0.00042 hPa (at 20 °C) and a measured log K_{OW} of –0.783 (at 25 °C).

The substance is readily biodegradable as shown in a DOC Die-Away-Test according to OECD TG 301A with non-adapted inoculum. At a test substance concentration of 50 mg/l, a biodegradation of > 93 % within 10-days was found. In unsterilized soil 1,3-dimethylurea is fairly rapidly mineralized.

The log Kow and a calculated BCF of 3 do not indicate a significant potential for bioaccumulation.
Using a fugacity model (Mackay level I), the substance is predicted to appear mainly in the aqueous compartment (> 99.9 %), with 0.0013 % in soil and 0.0013 % in sediment, and negligible amounts in air. The hydrosphere is therefore the target compartment for this substance. 1,3-Dimethylurea is potentially susceptible to hydrolysis because of the amide structure. The calculated half-life for hydrolysis, however, is over one year. The half-life for photo-oxidation in water (reaction with OH radicals) is estimated at 111 days. The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of 1,3-dimethylurea in air is 5.2 days. Adsorption to solid phase is not expected based on a calculated log Koc of 0.946.

Short-term tests with fish, invertebrates and algae are available for 1,3-dimethylurea. The lowest effects values from the short-term tests are: *Leuciscus idus*: 96h-LC_{50} ca. 10,000 mg/l, *Daphnia magna*: 48h-EC_{50} > 500 mg/l, *Scenedesmus subspicatus* 72h-E_rC_{50} > 500 mg/l (72h-E_bC_{50} = 560 mg/l). Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 0.5 mg/l is derived from the 48h EC_{50} for *Daphnia magna*.

Exposure

For 2001, estimated production quantities are less than 10,000 metric tonnes in Europe (Germany), less than 5,000 metric tonnes in the US and less than 15,000 metric tonnes in Asia (the worldwide production volume being less than 25,000 metric tonnes).
The substance is mainly used as an industrial intermediate in the synthesis of caffeine, pharmachemicals, textile aids, herbicides and others. According to Swiss, Danish and Swedish Product Registers 1,3-dimethylurea is contained in a large number of products. Some of them may be available to consumers and contain the substance in concentrations up to 10 %.
Releases into the environment may occur from production of 1,3-dimethylurea and from its use as intermediate as well as from use of products containing the substance.
Occupational exposure may occur during production and processing of 1,3-dimethylurea. No workplace exposure information is available with regard to the manufacturing and processing sites.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:
The chemical is currently of low priority for further work because of its low hazard potential.

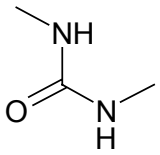
Environment:
The chemical is currently of low priority for further work because of its low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 96-31-1
IUPAC Name: 1,3-Dimethylurea
Molecular Formula: $C_3 H_8 O N_2$
Structural Formula:



Molecular Weight: 88.108 g/mol
Synonyms: N,N'-Dimethylurea
sym-Dimethylurea
Urea, 1,3-dimethyl-
Urea, N,N'-dimethyl-

1.2 Purity/Impurities/Additives

Substance type: organic

Physical status: solid

Purity: > 96.5 % w/w

Main Impurities: methylurea (≤ 1%), trimethylurea (≤ 1%),
trimethylbiuret (≤ 0.6%), water (≤ 0.6%)

1.3 Physico-Chemical properties

1,3-Dimethylurea is a colorless, crystalline powder having the following physical-chemical properties and characteristics:

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Melting point	102-107 °C	BASF AG, 1991; Béguin, C. Gäumann, T., 1958
Boiling point	268-270 °C	Wurtz, 1862
Density	1.142	Mez, 1902
Vapor pressure	0.00042 hPa at 20 °C (extrapolated)	BASF AG, 1990
log K_{OW} (n-octanol/water partition coefficient)	- 0.783 (25 °C) (measured)	BASF AG, 1988a
Water solubility	765 g/l at 21.5 °C	BASF AG, 1988a
Henry Law Constant	1.78 x 10^{-4} Pa *m^3/mol at 25 °C	EPI Suite, 2002
pH	9 – 9.5 (at 100 g/l)	BASF AG, 2002a

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

For 2001, the estimated production quantities are (t refers to metric ton):

Europe (Germany): < 10,000 t

USA: < 5,000 t

Asia: < 15,000 t

World: < 25,000 t

1,3-Dimethylurea is used for synthesis of caffeine, pharmachemicals, textile aids, herbicides and other.

In the textile processing industry 1,3-dimethylurea is used as intermediate for the production of formaldehyde-free easy-care finishing agents for textiles.

In the Danish Product Register 6 products containing up to 2 % of 1,3-dimethylurea are listed; five of these are agricultural pesticides. No use information was provided for the other product. The total amount of 1,3-dimethylurea in the products is < 1 t/a (Danish Product Register, 2002). The Swedish Products Register lists 3 products that contain 1,3-dimethylurea up to 20 %. None of these products is intended for use by consumers (Swedish Product Register, 2003). In the Swiss Product Register there are 38 products containing 1,3-dimethylurea, among them 17 products intended for consumer use. Product types are e.g. paints and cleaning agents. The content of 1,3-dimethylurea in consumer products is up to 10 % (Swiss Product Register, 2003). Use in cosmetics has been proposed (Balingit and Scafidi, 1981), but there is no information available as to its actual use in such applications.

Releases into the environment may occur from production of 1,3-dimethylurea and from its use as intermediate as well as from use of products containing the substance.

During production and internal processing at BASF AG, Ludwigshafen (Germany), < 25 kg were emitted into the air in 2000. No information on the emission into wastewater or surface water is available for this site.

No further exposure information is available. In addition to a possible exposure of surface waters, an exposure of the terrestrial compartment is possible from the use of 1,3-dimethylurea in agricultural pesticides.

2.2 Environmental Exposure and Fate

1,3-Dimethylurea has a water solubility of 765 g/l at 21.5 °C (BASF AG, 1988a), a vapor pressure of 0.00042 hPa at 20 °C (BASF AG, 1990), and a calculated Henry's Law constant of 1.78 x 10^{-4} Pa $*m^3$/mol at 25 °C (EPI Suite, 2002b). 1,3-Dimethylurea is potentially susceptible to hydrolysis because of the amide structure. The hydrolysis rate is extremely slow (> 1 year, calculated with HYDROWIN v 1.67) (BASF AG, 2002). The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of 1,3-dimethylurea in air is 5.2 days (Syracuse AOPWIN 1.90) (BASF AG, 2002b). The half-life for photooxidation in water is estimated to be 111 days (Buxton et al., 1988, Mill, 1999). As 1,3-dimethylurea does not absorb light in wavelength > 300 nm, no significant direct photolysis is to be expected.

2.2.1 Transport between Environmental Compartments

Using a fugacity based model (Mackay Level I), 1,3-dimethylurea is predicted to appear mainly in the aqueous compartment (99.99 %) with 0.0013 % in the soil, and 0.0013 % distributed to sediment, and negligible amounts in air ($1.7x10^{-4}$%) (BASF AG, 2002d). Adsorption to solid phase is not expected (log K_{OC} = 0.946) (BASF AG, 2002b). Since the density of 1,3-dimethylurea (1.14 g/cm^3 at 20 °C) is slightly higher than that of water, sedimentation or stratification in surface waters in case of accidental losses is possible.

2.2.2 Biodegradation

1,3-Dimethylurea was readily biodegradable in a DOC Die-Away-test following OECD 301A (>93 % biodegradation within 10 days; activated sludge from laboratory waste water treatment plants fed with municipal sewage; not adapted, test substance concentration 50 mg/l) (BASF AG; 2002c).

In unsterilized soil, 1,3-dimethylurea is mineralized fairly rapidly (a concentration of 312,5 mg N/kg was degraded within 5 weeks in terms of carbon dioxide evolution), and subsequently nitrified (Praveen-Kumar and Brumme,1995).

2.2.3 Bioaccumulation

Based on its log K_{Ow} and a calculated BCF of 3 (Syracus BCFWIN v2.14), 1,3-dimethylurea is not likely to bioaccumulate (BASF AG, 2002a).

2.3 Human Exposure

2.3.1 Occupational Exposure

Exposure of workers to 1,3-dimethylurea may occur during production and processing, or through the professional use of 1,3-dimethylurea containing products. Potential exposure may occur via inhalation of aerosols, splashes to skin or eyes, or inhalation of dust, or dermal contact with the solid.

The manufacturing process for 1,3-dimethylurea is largely enclosed with breaching for loading/unloading of product and some maintenance activities. Workplace exposure measurements are not available.

2.3.2 Consumer Exposure

6 Products containing up to 2 % of 1,3-dimethylurea are listed in the Danish product register (2002); five of these are agricultural pesticides. There is no information on whether these products are for industrial or consumer use (Danish Product Register, 2002). In the Swiss Product Register there are 38 products containing 1,3-dimethylurea, among them 17 products intended for consumer use. Product types are e.g. paints and cleaning agents. The content of 1,3-dimethylurea in consumer products is up to 10 % (Swiss Product Register, 2003). No information on consumer exposure to 1,3-dimethylurea could be located in product registers from Sweden, and in the open literature.

Use of 1,3-dimethylurea in cosmetics has been proposed (Balingit and Scafidi, 1981), but there is no information available as to its actual use in such applications.

Due to its low bioaccumulation potential a significant exposure of the general public via the environment is not expected.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

1,3-dimethylurea was not tested in experimental studies for its toxicokinetics.

3.1.2 Acute Toxicity

The oral LD_{50} or 1,3-dimethylurea in rats was determined to be approximately 4,000 mg/kg bw (BASF AG, 1959a). The clinical signs were nonspecific and included apathy and narcotic-like state at dose levels near to or exceeding the LD_{50}.

No valid test is available on the acute inhalation toxicity.

1,3-Dimethylurea has not been tested for its acute dermal toxicity.

The pulmonary findings in some acute studies are hardly plausible, since no such effects have been observed in a 28-day guideline study with similar doses.

Conclusion

The approximate oral LD_{50} of 1,3-dimethylurea in rats was determined to be 4,000 mg/kg bw. Clinical signs of toxicity were nonspecific and included apathy and narcotic-like state at dose levels near to or exceeding the LD_{50}.

3.1.3 Irritation

Skin Irritation

In a Draize test 1,3-dimethylurea (0.5 g; tested as a 80% aqueous preparation) caused only very slight erythema in two out of six rabbits when tested under occlusive conditions for 24 hours on

intact skin. The effects were completely reversible within 8 days (mean Draize scores: 24 hr - 0.3; 72 hr - 0.2). Edema was not observed at any time (BASF AG, 1979).

Eye Irritation

In two eye irritation studies according to the Draize method, slight to marked redness (grades 1-2) and lacrimation were present in all animals up to 72 hours after instillation of the undiluted test material. These effects were completely reversible within 8 days in the first study, but erythema (grade 1) persisted in 3 of 6 animals of the second study until the termination of the study (day 8). Edema (grade 1) were observed in 2 of 6 animals in the second study after 24 hours.. In 2 out of 6 animals of the first study, and in 1 animal (out of 6) of the second study corneal opacities (grade 1) were noted at 24, 48 and/or 72 hours. The corneal effect persisted in one animal of the first study until study termination on day 8. Since the reversibility of this effect cannot be judged from the available data, the possibility of persistent eye damage cannot be excluded (BASF AG, 1979).

Conclusion

1,3-Dimethylurea (tested as 80% aqueous solution) was only slightly irritating to the skin of rabbits after 24 hours of occlusive exposure. The undiluted test material induced lacrimation, corneal opacities and redness in the eyes of rabbits with some effects (grade 1 erythema, grade 1 corneal opacity) still present in one of the two studies at study termination on day 8 in one animal.

3.1.4 Sensitisation

There is no experimental data available.

3.1.5 Repeated Dose Toxicity

1,3-Dimethylurea was tested in a 28-day gavage study in Wistar rats (5 male and 5 female animals per dose group) following OECD TG 407(1981) at dose levels of 0, 15, 50, 150 and 450 mg/kg bw/day (BASF AG, 1993a). A decrease in body weights (-11%) and renal alterations in male animals were seen in the high-dose group, including tubular necroses, desquamation of tubular epithelial cells and protein casts in the tubular lumen (no data on incidences and severity available). In high-dose females, nonspecific tubular hyperplasia was found. At 150 mg/kg bw/day, which represents the LOAEL, renal alterations (tubular necrosis, desquamation of tubular epithelial cells and protein casts in tubular lumen) were still seen in male animals (no data on incidences and severity available). The NOAEL was 50 mg/kg bw/day for both genders.

In some older studies, hematuria, changes in the kidneys and - in part - hemorrhages in the urinary bladder were noted after repeated oral administration to rats dosed with approx. 1000 and 2000 mg/kg bw/day, and rabbits, cats and dogs at the only tested dose level of approx. 1000 mg/kg bw/day (BASF AG, 1959a,b,c). These studies are mentioned here since the effects are treatment related and consistent across species. Pneumonia is reported to be found in various species in these older repeated dose studies, presumably due to the poor hygienic conditions and the use of non-standardized animals at that time. These studies are limited due to very poor documentation, and the low number of animals used.

Conclusion

After repeated oral administration for 28 days by gavage to rats in a study following OECD TG 407 (1981), 1,3-dimethylurea caused alterations in the kidneys (tubular necroses, desquamation of tubular epithelial cells and protein casts in the tubuli) in males at 150 and 450 mg/kg bw/day, and nonspecific tubular hyperplasia in females at 450 mg/kg bw/day. The NOAEL was 50 mg/kg bw/day.

3.1.6 Mutagenicity

In vitro Studies

1,3-Dimethylurea was not mutagenic in the Ames test (preincubation assay) at doses of 0.10, 0.33, 1.0, 3.3, and 10 mg/plate in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, and TA100 in the presence and absence of rat or hamster liver S-9 with no cytotoxicity observed at any dose (Mortelmans et al, 1986). Furthermore, the substance did not induce a mutagenic response with and without metabolic activation (S-9 mix) in *Salmonella typhimurium* strainsTA98, TA100, and TA104 when tested at doses of 0, 0.5, 1, 10, 20, 40, 80 mg/plate). In this test, cytotoxicity was observed at 80 mg/plate. (Meshram et al., 1992)

1,3-Dimethylurea did not induce toxicity, gene mutations or chromosomal aberrations in cultured mouse lymphoma cells both with and without metabolic activation in a study performed equivalent to OECD TG 476 (Caspary and Myhr, 1986). The substance was tested up to and including the maximum recommended concentration of 5 mg/mL with no cytotoxicity observed at any concentration tested. A marginal increase in mutant colonies was observed in the first of the two independent experiments with metabolic activation (liver S-9 mix) at 5 mg/mL. This response, however, was not reproduced in the second S9 experiment, nor was there any dose-response relationship.

In vivo Studies

No adequate experimental data on the in vivo mutagenicity of 1,3-dimethylurea is available. It is noted, however, that nitrosation of 1,3-dimethylurea may occur with nitrite with the formation of nitrosoureas. Nitrosoureas have been shown to be mutagenic (Hill, 1988; Koehl and Eisenbrandt, 1999).

Conclusion

1,3-Dimethylurea was not mutagenic in bacterial and mammalian cell culture systems and did not induce chromosomal aberrations in Mouse Lymphoma cells, both in the presence and in the absence of metabolic activation systems. There is no available information from *in vivo* genotoxicity studies in mammals. It is noted that mutagenic nitrosoureas may be produced from 1,3-dimethylurea with nitrite; therefore, a mutagenic potential cannot be totally excluded.

3.1.7 Carcinogenicity

1,3-Dimethylurea has not been tested for its carcinogenic activity. It is noted, however, that nitrosation of 1,3-dimethylurea may occur with nitrite with the formation of nitrosoureas. Nitrosoureas have been shown to be carcinogenic (Hill, 1988; Koehl and Eisenbrandt, 1999).

Conclusion

It is noted, however, that carcinogenic nitrosoureas may be formed with nitrite.

3.1.8 Toxicity for Reproduction

Effects on Fertility

The administration of 1,3-dimethylurea for 4 weeks had no adverse effects on reproductive performance or fertility of the F0 parental animals (10 male and 10 female animals per dose group) in a combined reproduction/developmental toxicity screening test in rats following OECD TG 421 (BASF AG, 2003a). At all tested dose levels (20; 60; 200 mg/kg bw/day), there were no substance-related effects on mating behavior, conception, gestation, parturition and lactation. Sexual organ

weights were not different from controls, and there were no pathological gross and microscopic findings. Signs of general systemic toxicity in the F0 parental animals were confined to the rats of the 200 mg/kg bw/day group, and were characterized by a slightly decreased food consumption (about 10 % in males and females) correspondingly lowered mean body weights and impaired body weight gains (males –36.6%; females –15.9%), and significantly decreased serum glucose levels in the males of the high-dose group. The NOAEL for reproductive performance and fertility was 200 mg/kg bw/day; the NOAEL for general toxicity was 60 mg/kg bw/day in both genders.

Developmental Toxicity

In a rat teratogenicity study according to OECD TG 414(1981) (21-23 female rats per dose group dosed from day 6 - 15 p.c.), 200 mg/kg bw/day produced embryo-/fetotoxicity (markedly reduced mean placental of -13.3% and reduced fetal body weights of -7.7%). The malformations rate was not increased; however, the number of fetuses with a soft tissue variation (hydroureter) and with indications of delayed ossification (sternebrae) was clearly increased. At the intermediate dose (100 mg/kg bw/day), signs of developmental toxicity (substantiated by an increased number of fetuses with hydroureter) were still present. 30 mg/kg bw/day was a NOAEL for developmental toxicity. Clear signs of maternal toxicity were observed at 200 mg/kg bw/day (reduced food consumption of –34%, impaired body weight gain of –37% (net weight change), and piloerection). At the intermediate dose (100 mg/kg bw/day), overt signs of maternal toxicity in the form of reduced food consumption of – 21% and retarded weight gain, were still present. The NOAEL for maternal toxicity was 30 mg/kg bw/day (BASF AG, 1993b).

In a reproductive/developmental toxicity, screening test in Wistar rats according to OECD TG 421 (10 male and 10 female animals per dose group dosed for approx. 4 weeks), no indications of developmental toxicity in the progeny of the F0 parents up to and including the high dose group (200 mg/kg bw/day) were found. Signs of general systemic toxicity in the F0 parental animals were confined to the rats of the 200 mg/kg bw/day group, and were characterized by a slightly decreased food consumption (about 10 % in males and females) correspondingly lowered mean body weights and impaired body weight gains (males –36.6%; females –15.9%), and significantly decreased serum glucose levels in the males of the high-dose group (NOAEL developmental toxicity: 200 mg/kg bw/day; NOAEL general toxicity: 60 mg/kg bw/day) (BASF AG, 2003a).

Conclusion

1,3-Dimethylurea had no adverse effects on reproductive performance and fertility of rats in a combined reproduction/developmental toxicity, screening test according to OECD TG 421 (NOAEL, reproductive performance/fertility: 200 mg/kg bw/day (highest tested dose level)).

No teratogenic effects, but embryo-/fetotoxicity (reduced placental and fetal body weights) an but embryo-/fetotoxicity (reduced placental and fetal body weights) and an increase in the incidence of fetuses with a soft tissue variation (hydroureter) and with delayed ossifications in sternebrae were found at maternally toxic dose levels in a developmental toxicity study in rats in accordance with OECD TG 414 (NOAEL for developmental toxicity and maternal toxicity: 30 mg/kg bw/day).

3.2 Initial Assessment for Human Health

1,3-Dimethylurea was not tested in experimental studies for its toxicokinetics.

The approximate oral LD50 of 1,3-dimethylurea in rats was determined to be 4,000 mg/kg bw. Clinical signs of toxicity were nonspecific and included apathy and narcotic-like state at dose levels near to or exceeding the LD50. No valid test is available on the acute inhalation toxicity. 1,3-Dimethylurea has not been tested for its acute dermal toxicity.

1,3-Dimethylurea (tested as 80 % aqueous solution) was only slightly irritating to the skin of rabbits after 24 hours of occlusive exposure. The undiluted test material induced lacrimation, corneal opacities and redness in the eyes of rabbits with some effects (redness, corneal opacity), still present in one of the two studies at study termination on day 8 in one animal.

After repeated oral administration for 28 days by gavage to rats in a study following OECD TG 407 (1981), 1,3-dimethylurea caused alterations in the kidneys (tubular necroses, desquamation of tubular epithelial cells and protein casts in the tubuli) in males at 150 and 450 mg/kg bw/day, and nonspecific tubular hyperplasia in females at 450 mg/kg bw/day. The NOAEL was 50 mg/kg bw/day.

1,3-Dimethylurea was not mutagenic in bacterial and mammalian cell culture systems and did not induce chromosomal aberrations in Mouse Lymphoma cells, both in the presence and in the absence of metabolic activation systems. There is no available information from *in vivo* genotoxicity studies in mammals. It is noted that mutagenic nitrosoureas may be produced from 1,3-dimethylurea with nitrite; therefore, a mutagenic potential cannot be totally excluded.

1,3-Dimethylurea had no adverse effects on reproductive performance and fertility of rats in a combined reproduction/developmental toxicity, screening test according to OECD TG 421 (NOAEL, reproductive performance/fertility: 200 mg/kg bw/day (highest tested dose level)). No teratogenic effects, but embryo-/fetotoxicity (reduced placental and fetal body weights) and an increase in the incidence of fetuses with a soft tissue variation (hydroureter) and with delayed ossifications in sternebrae were found at maternally toxic dose levels in a developmental toxicity study in rats in accordance with OECD TG 414 (NOAEL for developmental toxicity and maternal toxicity: 30 mg/kg bw/day).

It is noted that carcinogenic nitrosoureas may be formed with nitrite.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Data are available on the acute toxicity of 1,3-dimethylurea to fish, crustacea and algae. 1,3-Dimethylurea has not been assessed in chronic studies.

The following valid test results with aquatic organisms are available:

a) fish

Leuciscus idus LC_{50} (96 hours): ca. 10,000 mg/l

(static test, nominal concentrations) (BASF AG, 1989)

b) invertebrates

Daphnia magna EC_{50} (48 hours): > 500 mg/l

(effect: immobilisation: 0 % immobility at 500 mg/l), nominal concentration) (BASF AG, 1988c)

c) algae

Scenedesmus subspicatus E_bC_{50} (72 hours): = 560 mg/l

E_bC_{10} (72 hours) = 97 mg/l

E_rC_{50} (72 hours): > 500 mg/l

E_rC_{10} (72 hours) = 318 mg/l

(nominal concentrations) (BASF AG, 1988d)

d) microorganisms

Pseudomonas putida EC_{50} (17 hours): > 10,000 mg/l

(effect: growth rate during exponential growth phase, nominal concentration) (BASF AG, 1988b)

activated sludge EC_{20} (30 min): > 1,000 mg/l

(effect: inhibition of Oxygen Consumption, nominal concentration) (BASF AG, 2003b)

Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 0.5 mg/l is derived from the 48h EC_{50} for *Daphnia magna.*

4.2 Terrestrial Effects

There are no data available.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

1,3-Dimethylurea has a water solubility of 765 g/l at 21.5 °C (pH = 9 – 9.5 at 100 g/l), a vapor pressure of 0.00042 hPa (at 20 °C), and a measured log K_{OW} of –0.783.

The substance is readily biodegradable as shown in a DOC-Die-Away-Test according to OECD 301A with non-adapted inoculum. A biodegradation of > 93 % within the 10-day window was found.

In unsterilized soil 1,3-dimethylurea is fairly rapidly mineralized.

The log K_{OW} and a calculated BCF of 3 do not indicate a significant potential for bioaccumulation.

Using a fugacity model (Mackay level I), the substance is predicted to appear mainly in the aqueous compartment (> 99.9 %), with 0.0013 % in soil and 0.0013 % in sediment, and negligible amounts in air. The hydrosphere is therefore the target compartment for this substance. 1,3-Dimethylurea is potentially susceptible to hydrolysis because of the amide structure. The calculated half-life for hydrolysis, however, is over one year. The half-life of photochemical degradation in water is 111 days.

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of 1,3-dimethylurea in air is 5.2 days. Adsorption to solid phase is not expected based on a calculated log Koc of 0.946.

Short-term tests with fish, invertebrates and algae are available for 1,3-dimethylurea. The lowest effects values from the short-term tests are: *Leuciscus idus*: 96h-LC_{50} ca. 10,000 mg/l, *Daphnia magna*: 48h-EC_{50} > 500 mg/l, *Scenedesmus subspicatus* 72h-EbC_{50} = 560 mg/l, 72h-ErC_{50} > 500 mg/l. With an assessment factor of 1000 a $PNEC_{aqua}$ of 0.5 mg/l was derived from the 48h-EC_{50} for *Daphnia magna*.

5 RECOMMENDATIONS

Human Health:

The chemical is currently of low priority for further work because of its low hazard potential.

Environment:

The chemical is currently of low priority for further work because of its low hazard potential.

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I U C L I D

D a t a S e t

Existing Chemical ID: 96-31-1
CAS No. 96-31-1
EINECS Name 1,3-dimethylurea
EC No. 202-498-7
Molecular Formula C3H8N2O

Producer Related Part
Company: BASF AG
Creation date: 23-SEP-1999

Substance Related Part
Company: BASF AG
Creation date: 23-SEP-1999

Memo: master

Printing date: 09-MAR-2004
Revision date:
Date of last Update: **09-MAR-2004**

Number of Pages: **108**

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: Product Safety Regulations, Toxicology, and Ecology c/o Dr. Hubert Lendle GUP/CL - Z570 **Date:**
Street: Carl-Bosch-Strasse
Town: 67056 Ludwigshafen
Country: Germany
Phone: + 49 621 60 44712
Telefax: + 49 621 60 58043
Email: hubert.lendle@basf-ag.de
Homepage: www.basf.com

Flag: Critical study for SIDS endpoint
06-JAN-2003

Type: cooperating company
Name: Air Poducts and Chemicals, Inc.
Contact Person: Dr.Bronek Z. Drozdowicz **Date:**
Street: 7201 Hamilton Boulevard
Town: Allentown, PA 18195-1501
Country: United States
Phone: 610 481-4620
Telefax: 610 706-7029

Flag: Critical study for SIDS endpoint
06-JAN-2003

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: C3H8N2O
Mol. Weight: 88.108 g/mol

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

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: >= 96.5 - % w/w
Colour: colourless to white
Odour: amine-like

Method: HPLC
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,3-Dimethylharnstoff

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

1,3-Dimethylurea

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Dimethylharnstoff

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

N,N'-Dimethylharnstoff

Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002

N,N'-Dimethylurea

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

sym-Dimethylurea

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Symmetric dimethylurea

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Urea, 1,3-dimethyl- (8CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

Urea, N,N'-dimethyl- (9CI)

Flag: non confidential, Critical study for SIDS endpoint
02-DEC-1992

1.3 Impurities

Purity type: typical for marketed substance
CAS-No: 598-50-5

EC-No: 209-935-0
EINECS-Name: methylurea
Mol. Formula: C2 H6 N2 O
Contents: <= 1 - % w/w

Method: HPLC
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (1)

Purity type: typical for marketed substance
CAS-No: 632-14-4
EC-No: 211-169-7
EINECS-Name: trimethylurea
Mol. Formula: C4 H10 N2 O
Contents: <= 1 - % w/w

Method: HPLC
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (1)

Purity type: typical for marketed substance
EINECS-Name: trimethylbiuret
Contents: <= .6 - % w/w

Method: HPLC
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (1)

Purity type: typical for marketed substance
CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Mol. Formula: H2 O
Contents: <= .6 - % w/w

Method: DIN 51777
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (1)

1.4 Additives

1.5 Total Quantity

Remark: production quantities (year 2001):

Germany: < 10.000 t
Europe : < 10.000 t
USA : < 5.000 t
Asia : < 15.000 t

World : < 25.000 t
Flag: Critical study for SIDS endpoint
15-JAN-2004

1.6.1 Labelling

Labelling: no labelling required (no dangerous properties)

Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

1.6.2 Classification

Classified: no classification required (no dangerous properties)

Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
05-JAN-1999

Type: industrial
Category: Agricultural industry

Flag: non confidential, Critical study for SIDS endpoint
05-JAN-1999

Type: industrial
Category: Chemical industry: used in synthesis

Remark: Used for synthesis of caffeine, pharmachemicals, textile aids, herbicides and others.
Flag: non confidential, Critical study for SIDS endpoint
11-AUG-2003

Type: industrial
Category: Textile processing industry

Remark: Symmetric N,N'-dimethylurea is used as intermediate for the production of formaldehyde-free easy-care finishing agents for textiles.
Flag: non confidential, Critical study for SIDS endpoint
15-JAN-2004 (3)

Type: use
Category: Cosmetics

Remark: Preparation for increasing hair body by permanently swelling the hair shaft with less loss of tensile strength then with usual preparations containing solution of synthetic amphoteric detergent, a bisulfite, 1,3-dimethylurea, a cationic conditioner and an alcohol or glycol. There is no information available as to its actual use in such applications.
Flag: non confidential, Critical study for SIDS endpoint

05-AUG-2003 (4)

Type: use
Category: Intermediates

Remark: Symmetric N,N'-dimethylurea is used for the synthesis of caffeine by the Traube method.
Flag: non confidential, Critical study for SIDS endpoint
11-AUG-2003 (3)

Type: use
Category: Intermediates

Remark: Intermediate for the synthesis of pharmaceuticals (e.g. theophylline, caffeine)
Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (5)

Type: use
Category: Pesticides

Remark: 6 products containing 0-2% 1,3-dimethylurea are listed in the Danish Product Register of 2002. 5 of these products are listed under the category of "agricultural pesticides".
Flag: non confidential, Critical study for SIDS endpoint
03-JUL-2003 (6)

Type: use
Category: other: rubber curing

Flag: non confidential, Critical study for SIDS endpoint
08-JUL-2003 (7)

Type: use

Remark: The content of 1,3-dimethylurea in consumer products is up to 10 %.
Flag: non confidential, Critical study for SIDS endpoint
15-JAN-2004 (8)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: Esters of carbonic and carbamic acids (carbonates and carbamates) react with amines at elevated temperatures to give symmetrically disubstituted ureas.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (3)

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

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

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (9)

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: 1142
Flag: non confidential, Critical study for SIDS endpoint
17-JAN-2003 (10)

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. 202-498-7

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: ENCS
Additional Info: ENCS No. 2-1734

Remark: ENCS Classification:
Low Molecular Chain-like Organic Compounds
Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: ECL
Additional Info: ECL Serial No. KE-11903

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: other: SWISS
Additional Info: SWISS No. G-1560

Remark: SWISS Classification:
Giftliste 1 (List of Toxic Substances 1), 31 May 1999
Toxic Category 4: Acute oral lethal dose of 500-2000 mg/kg
Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
26-MAR-2002 (11)

1.9.1 Degradation/Transformation Products

CAS-No: 74-89-5
EC-No: 200-820-0
EINECS-Name: methylamine

Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

1.9.2 Components

1.10 Source of Exposure

1.11 Additional Remarks

Memo: Hazardous reactions: reacts with alkalis and nitrites

Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 3, 4, 5
Date of Search: 06-DEC-2002

Remark: CAS number search in external and internal databases, eg HSDB, Aquire, Biosis, Embase, Toxline etc.
Flag: Critical study for SIDS endpoint
08-DEC-2002

Type of Search: Internal and External
Chapters covered: 1
Date of Search: 17-JAN-2003

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

Type of Search: Internal
Chapters covered: 8
Date of Search: 19-DEC-2002

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

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 06-NOV-2002

06-FEB-2003

Type of Search: External
Chapters covered: 2
Date of Search: 29-APR-2003

Remark: CAS number search in external databases: Beilstein, Biosis, Chemical Abstracts
Flag: non confidential, Critical study for SIDS endpoint
15-JAN-2004

Type of Search: External
Chapters covered: 3, 4
Date of Search: 29-APR-2003

Remark: CAS number search in external databases: Beilstein, Biosis, Chemical Abstracts

Flag: non confidential, Critical study for SIDS endpoint
15-JAN-2004

1.13 Reviews

2.1 Melting Point

Value: = 102 degree C

Method: other: equivalent to OECD TG 102 (1995)
Year: 1991
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Test on the solid and liquid phase of test substance with differential scanning calorimeter DSC-2 and DSC-7 of PERKIN-ELMER
Result: 102.02 +/- 0.800 °C
Reliability: (1) valid without restriction
Guideline study according to OECD 102
Flag: Critical study for SIDS endpoint
29-DEC-2002 (12)

Value: 107 degree C

Remark: Substance purified by recrystallisation and checked by elementary analysis.
Reliability: (2) valid with restrictions
basic data given: comparable to guidelines
Flag: Critical study for SIDS endpoint
08-JUL-2003 (13)

Value: = 108 degree C

Method: other: no data
GLP: no data

Reliability: (2) valid with restrictions
data from handbook or collection of data
11-JUL-2003 (14)

2.2 Boiling Point

Value: = 268 - 270 degree C

Method: other: no data
GLP: no data

Reliability: (2) valid with restrictions
study report which meets basic scientific principles
Flag: Critical study for SIDS endpoint
11-JUL-2003 (15)

Value: = 260 degree C
Decomposition: yes

Remark: at 1,013 bar
Reliability: (4) not assignable
Manufacturer / producer data without proof, only secondary literature
19-MAR-2003 (2)

Value: 269 degree C

Method: other: estimation

Method: Estimation from vapour pressures and enthalpies of liquid and gaseous phases
Result: original value: 542 K
Reliability: (4) not assignable
only secondary literature
08-JUL-2003 (16)

Value: = 270 degree C

Reliability: (4) not assignable
only secondary literature
14-DEC-1999 (17)

2.3 Density

Type: relative density
Value: = 1.142 at 20 degree C

Method: other: no data
GLP: no data

Reliability: (2) valid with restrictions
acceptable, well-documented publication which meets basic scientific principles
Flag: Critical study for SIDS endpoint
08-JUL-2003 (18)

Type: density
Value: = 1.14 g/cm³ at 20 degree C

Method: other: no data

Reliability: (4) not assignable
Manufacturer / producer data without proof, only secondary literature
29-DEC-2002 (2)

Type: bulk density
Value: = 500 kg/m3

Reliability: (4) not assignable
Manufacturer / producer data without proof, only secondary literature
07-DEC-1999 (2)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .00042 hPa at 20 degree C

Method: Directive 84/449/EEC, A.4 "Vapour pressure"
Year: 1990
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: equivalent to OECD Guideline 104 (1995), gas saturation method
Remark: The value at 20 °C is extrapolated.
Result:

temperature °C	pressure mbar
30.3	1.27E-3, 1.47E-3 (measured), 0.0013 (calculated*)
44.6	5.62E-3, 6.41E-3 (measured), 0.0058 (calculated)
55.0	1.45E-2, 1.51E-2 (measured), 0.016 (calculated)
59.2	2.39E-2 (measured), 0.023 (calculated)
60.0	2.30E-2 (measured), 0.025 (calculated)
76.4	9.32E-2 (measured), 0.100 (calculated)
76.5	1.01E-1 (measured), 0.101 (calculated)
90.2	3.03E-1, 3.15E-1 (measured), 0.293 (calculated)

*from regression analysis: ln(p/bar) = A + B / (C + t/Cels), A = 19.1770, B = - 9923.60, C = 273.15;
Mean deviation between measured and calculated values: 5.68% (30.3-90.2 °C)
Test substance: purity: 99.5 %
Reliability: (1) valid without restriction
comparable to guideline study
Flag: Critical study for SIDS endpoint
15-JAN-2004 (19)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -.783 at 25 degree C

Method: other (measured): equivalent to OECD TG 107 (1995), Shake-flask method
Year: 1988
GLP: no

Method: Nitrogen-determination by KJELDAHL (water phase) and DOHRMANN (octanol phase)
Result: mean value, determined from 3 measurements (log Kow: -0.787, -0.779, -0,783)
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
19-MAR-2003 (20)

Partition Coeff.: octanol-water
log Pow: = -.62

Method: other (calculated): KowWIN, Version 1.66
Year: 2002
GLP: no

Reliability: (2) valid with restrictions
accepted calculation method
19-MAR-2003 (21)

Partition Coeff.: octanol-water
log Pow: = -2.04

Method: other (calculated)
Year: 1989
GLP: no

Method: Calculated with pro-logP (CompuDrug Ltd.) with modifications (not specified).
Reliability: (2) valid with restrictions
Calculated value
19-MAR-2003 (22)

Partition Coeff.: octanol-water
log Pow: = -.49

Method: other (measured)

Reliability: (4) not assignable
secondary citation
01-SEP-2002 (23)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 765 g/l at 21.5 degree C
Descr.: very soluble (> 10000 mg/L)

Method: other: measured
Year: 1988
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result:

temperature (°C)	solubility (g/L)
21.5	765
36.1	813
58.5	880

Reliability: (2) valid with restrictions
method is not specified, authorised laboratory
Flag: Critical study for SIDS endpoint
08-JUL-2003 (20)

Solubility in: Water
Descr.: very soluble (> 10000 mg/L)

Reliability: (2) valid with restrictions
data from handbook or collection of data
08-JUL-2003 (14)

2.6.2 Surface Tension

2.7 Flash Point

Value: > 157 degree C

Reliability: (4) not assignable
Manufacturer / producer data without proof
07-DEC-1999 (2)

2.8 Auto Flammability

Value: = 400 degree C

Method: other: DIN 51 794

Remark: Autoignition temperature
Reliability: (4) not assignable
Manufacturer / producer data without proof
07-DEC-1999 (2)

2.9 Flammability

2.10 Explosive Properties

Result: not explosive

Method: other
Year: 1999
GLP: no

Remark: The structure contains no chemical groups indicating explosive or oxidizing properties.
03-DEC-2002 (24)

2.11 Oxidizing Properties

Result: no oxidizing properties

Method: other
Year: 1999
GLP: no

Remark: The structure contains no chemical groups indicating explosive or oxidizing properties.
03-DEC-2002 (24)

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Memo: pH-value

Result: pH value of aqueous solution:
pH = 9 - 9.5 at a concentration of 100 g/l at 20 °C
Reliability: (4) not assignable
only secondary literature
Flag: Critical study for SIDS endpoint
11-JUL-2003

Remark: Conditions to avoid:
Can decompose at above 150 °C.
Substances to avoid:
Dangerous reaction with nitrites.
Hazardous decomposition products: methylamine
Reliability: (4) not assignable
Manufacturer / producer data without proof
07-DEC-1999 (2)

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .000000000003115 cm³/(molecule * sec)
Degradation: = 50 % after 5.2 day(s)

Method: other (calculated): with AOP, V 1.90
Year: 2002
GLP: no

Result: A 24h-day was used with the 24h average OH radical concentration.
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
15-JAN-2004 (21)

Type: water
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 36000 molecule/cm³
Rate constant: = .000000000002 cm³/(molecule * sec)
Degradation: = 50 % after 111 day(s)
Deg. products: not measured

Method: other (calculated)

Remark: Calculated from the reaction rate constant of 1,3-dimethylurea with hydroxyl radicals in fresh water as published by Buxton et al. (1988) and the concentration of OH radicals in fresh water as published by Mill(1999).
Result: As 1,3-dimethylurea does not absorb light in wavelength >300 nm, no significant direct photolysis is to be expected.
Test condition: Reaction rate constant: 1.02*10E+9 l/mol*s; hydroxyl radical concentration in fresh water:
6*10E-17 mol/l = 1.02*10E-12 mg/l = 36000 molecules/cm3.
From this, a reaction rate of 7.2*10E-8 s-1 and average lifetime of 1.4*10E+7 s (equivalent to 161 days) can be calcultated.
Reliability: (2) valid with restrictions
calculated data, generally accepted method
Flag: Critical study for SIDS endpoint
15-JAN-2004 (25) (26)

3.1.2 Stability in Water

Type: abiotic
t1/2 pH : > 1 year

Method: other: calculation with HYDROWIN, V 1.67
Year: 2002
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: hydrolysis rate is extremely slow (t1/2 > 1 year)
Reliability: (2) valid with restrictions

accepted calculation method
Flag: Critical study for SIDS endpoint
19-MAR-2003 (21)

3.1.3 Stability in Soil

Type: laboratory
Soil temperature: 20 degree C
Soil humidity: 20 g water/100g soil dry weight
Organ. carbon: = 1.1 %
pH: = 7.4
Deg. products: yes

Method: other
Year: 1995
GLP: no data
Test substance: other TS: 1,3-dimethylurea from Fluka (CH)

Result: 1,3 dimethylurea mineralized after a delay period of approx. 1 week in unsterilized soil, and subsequently the N was nitrified. 1,3-Dimethylurea mineralized as rapidly as urea after the delay period was over. The mineralization coincided with rapid evolution of CO2 and N2O and an increase in soil pH, and the formation of urea as an intermediate was hypothesized by the authors of this study. The mineralization was completed after 5 weeks in terms of carbon dioxide evolution and nitrate concentration. 1,3-Dimethylurea did not mineralize in sterilized soil.

Test condition: The experiments were carried out using an agricultural soil (Luvisol, pH 7.4, C 1.1%, N 0.1%, bulk density 1.3, total pore volume 49.6%) collected from the agricultural research farm of the University of Göttingen / Germany. The soil was air dried and ground to pass a 2mm sieve. 5 kg of soil was put into a large polyethene bag and water was added to bring the soil moisture content to 20%. The bags were tied and the contents were mixed by slowly turning the polyethene bag. The bags were stored at room temperature (23 °C) for 10 days but were opened every day for a few minutes to aerate the soil.
At the start of experiments the moisture content was gravimetrically determined. Subsequently the soil was divided into half, and one half of the soil was sterilized at 121.6 °C for half an hour.
Ten alkylated ureas, amongst them 1,3-dimethylurea were used in this study. A weight of the test substance equivalent to 312.5 ug N/g soil (oven dry) was mixed into 225 g of sterilized or unsterilized wet soil in triplicate sets. Appropriate controls were also maintained.
The soils were placed in 250 mL beakers which were incubated in 1.6 L jars with lids fitted with rubber septum to facilitate the sampling of the atmosphere in the jars with a needle and syringe. The jars were kept closed except for 10-12 minutes to allow exchange of air every day. The soil moisture level was kept at 20% by weighing the beakers twice weekly. The incubation was carried out for 11 weeks at 20 °C. The incubation was discontinued as and when the test substance nitrified completely and CO2 production became constant. The soils were analyzed weekly for their content of NO3, NH4 and pH. The CO2 and N2O evolution from soil was

measured daily by GC. The amount of NO3, NH4, CO2 and N2O measured in control was subtracted from treatments.
Reliability: (2) valid with restrictions
Acceptable, well-documented publication which meets basic scientific principles.
Flag: Critical study for SIDS endpoint
08-JUL-2003 (27)

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air
Method: other: calculation with HENRYWIN V.3.10
Year: 2002

Method: bond estimation method
Result: Henrys Law Constant (calculated, at 25 °C)
H = 1.76*10E-9 atm-m3/mole = 1.78*10E-4 Pa*m3/mol
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
11-JUL-2003 (21)

3.3.2 Distribution

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

Remark: Calculated with Level 1, v 2.11 Model,
Parameters used:
temperature = 20 °C,
log Kow = - 0.78,
water solubility = 7.65 E+05 g/m³,
Vapour Pressure = 0.00042 hPa (extrapolated at 20°C),
Melting Point = 102 °C,
Amount of chemical: 1.00 E+5 kg,
Volumes (m³):
air = 6.00 E+09,
Water = 7.00 E+06,
Soil = 45000,
Sediment = 21000,
Susp. Sedmt. = 35.0,
Fish = 7.00,
Aerosol = 0.120.
Result: water: 99.99 %,
air: 1.7E-4 %,
soil: 0.0013 %,
sediment: 0.0013 %.
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint

09-MAR-2004 (28)

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 50 mg/l related to Test substance
20 mg/l related to DOC (Dissolved Organic Carbon)
Contact time: 21 day(s)
Degradation: = 90 - 100 % after 21 day(s)
Result: readily biodegradable
Kinetic:

1 day(s)	0 %
3 day(s)	0 %
5 day(s)	= 0 - 6 %
7 day(s)	= 23 - 25 %
10 day(s)	= 93 - 94 %

Control Subst.: Aniline
Kinetic:

1 day(s)	= 9 %
3 day(s)	= 94 %

Deg. product: not measured

Method: OECD Guide-line 301 A (new version) "Ready Biodegradability: DOC Die Away Test"
Year: 2002
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: Duration of the adaptation phase: 6 days.
Duration of the degradation phase: 11 days.
Degradation of the test substance at the end of the 10-day window: 90-100% DOC removal.
Degradation of the test substance at the end of the test: 90-100% DOC removal.
Physico-chemical (abiotic) elimination of the test substance: <10% at the end of the test.
Elimination of the test substance by adsorption: <10% after 5 days.

Degradation of the reference substance after 14 days: 90-100% DOC removal.
Degradation in the inhibition control after 14 days: 90-100% DOC removal.

The validity criteria as laid down in OECD TG 301 were fulfilled.
Test condition: Inoculum: activated sludge from laboratory waste water plants fed with municipal sewage; not adapted.
CONCENTRATION OF ACTIVATED SLUDGE: 30 mg/L (as the concentration of suspended solid).
TEST VOLUME: 1000 mL.
TEST TEMPERATURE: 22 +/- 2 °C.
Conclusion: The test substance is readily biodegradable according to OECD criteria.
Reliability: (1) valid without restriction
Guideline study

Flag: Critical study for SIDS endpoint
15-JAN-2004 (29)

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 100 mg/l related to Test substance
Contact time: 14 day(s)
Degradation: = 27.3 - 53.1 % after 14 day(s)
Result: other: biodegradable
Control Subst.: Aniline

Method: other: see Test Condition
Year: 1984
GLP: no data
Test substance: other TS: 1,3-dimethylurea, purity not stated

Result: sludge I: 53.1 % degradation after 14 days.
sludge II: 27.3 % degradation after 14 days.
Results for reference substance not reported.
Test condition: INOCULUM: activated sludge from domestic waste water treatment plant.
CONCENTRATION OF ACTIVATED SLUDGE: 30 mg/L (as the concentration of suspended solid).
sludge I: cultivated for 2 weeks.
sludge II: cultivated for at least 2 months.
TEST TEMPERATURE: 25 +/- 2 °C.
VALIDITY CRITERIA: degradation of reference substance (aniline) >= 40% after 7 days.
Reliability: (4) not assignable
limited documentation; the validity of these test results is questionable as the difference between results is > 20%
15-JAN-2004 (30)

Type: aerobic
Inoculum: other: effluent from waste water treatment plant
Degradation: > 80 % after 30 day(s)
Result: other: biodegradable

Method: other: DIN 38409-51/DEV H5
Year: 1987
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: BOD of ThOD
Remark: BOD5 < 5 mg/g,
BOD30 = 2270 mg/g,
COD = 1100 mg/g,
BOD30*100/ThOD > 80 %.
(ThOD without nitrification: 1636 mg/g; ThOD with nitrification: 2727 mg/g).
Test condition: INOCULUM: effluent from industrial waste water treatment plant
Reliability: (4) not assignable
documentation insuffcient for assessment
15-JAN-2004 (31)

Inoculum: Pseudomonas sp. (Bacteria)

Method: other: not reported
Year: 1966

GLP: no
Test substance: other TS: 1,3-dimethylurea mineral salts, not further specified

Result: Various species of Pseudomonas isolated from soil enrichments containing 3-(p-chloro-phenyl)-1,1-dimethylurea formed nitrite and nitrate when incubated with 1,3-dimethylurea, urea or certain urea derivatives.
Test condition: not reported.
Reliability: (4) not assignable
documentation insuffcient for assessment
15-JAN-2004 (32) (33)

Inoculum: other: diverse heterotrophic soil microorganisms

Method: other: see Test Conditions
Year: 1966
GLP: no
Test substance: other TS: 1,3-dimethylurea from commercial source, purity not stated

Result: 1,3-dimethylurea can serve as substrate for diverse heterotrophic soil microorganisms (bacteria, Streptomycetes) to form nitrite. None of the cultures produced nitrate, however, and the yield of nitrite-N was no more than 1.88 ppm.
Test condition: In an attempt to isolate microorganisms capable of oxidizing the N in urea or substituted ureas, enrichments were prepared which contained mineral salts, either with or without 0.5% ammonium sulfate, and 0.5% of one of the following carbon sources: urea, methylurea, 1,1-dimethylurea, 1,3-dimethylurea, n-buylurea, or phenylurea.
5 mL aliquots of the nutrient solutions were dispensed in test tubes and inoculated with either 0.1g of Dunkirk silty clay loam or with 0.5 mL of liquid from a 2-month old soil enrichment culture containing 100 ppm of 3-(p-chlorophenyl)-1, 1-dimethylurea in the salts solution. The tubes were incubated on a reciprocal shake and the solutions tested for nitrite production at 48-hour intervals. When a culture was found to contain nitrite, 0.5 mL was inoculated into the appropriate fresh medium. Following four serial transfers, isolations were made and the cultures purified.
The pure cultures thus obtained were inoculated into 250-mL-flasks containing 50 mL of various media. The flasks were incubated on a shaker for 10 days and the contents tested at 48-hour intervals for nitrite and nitrate.
Year of study: not reported.
Reliability: (3) invalid
unsuitable test system
15-JAN-2004 (33)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

BCF: = 3.16

Method: other: calculation with BCFWin v 2.14
Year: 2002
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: equation used to make BCF estimate: log BCF = 0.50 (default value at log Pow < 1)
Result: estimated log BCF = 0.500 (BCF = 3.162)
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
08-JUL-2003 (34)

3.8 Additional Remarks

Memo: Koc (estimated)

Result: Koc = 8.832 (calculated with PCKOCWIN v1.66),
Log Koc = 0.9460
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
19-MAR-2003 (21)

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: 4600
LC50: ca. 10000
Limit Test: no

Method: other: DIN 38 412
Year: 1982
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: RESULTS EXPOSED:

LC50 (96 hr) about 10,000 mg/L

Lethality:
- 1/10 at 10,000 mg/L after 24 hours
- 1/10 at 10,000 mg/L after 48 hours
- 3/10 at 10,000 mg/L after 72 hours
- 6/10 at 10,000 mg/L after 96 hours

Nominal conc. (mg/l)	dead fish	Mortal. (%)
control	0	0
1000	0	0
2150	0	0
4640	0	0
10000	6	60

Maximum Concentration Tested without Mortality: 4640 mg/L.

RESULTS CONTROL:

positive control (chloroacetamide): LC50 (48hr) ca. 32 mg/L. This value was within the range of expected values.

negative control: no mortality, no symptoms

Test condition: photoperiod: 16 hours light and 8 hours darkness

STOCK AND TEST SOLUTION AND THEIR PREPARATION:
- test water: reconstituted freshwater according to DIN 38 412, prepared from fully demineralized tap water. Conductivity max 10 micro mho (total hardness 2.5 mmol/L, acid capacity 0.8 mmol/L, Ca/Mg 4:1, Na/K 10:1, pH 8.0)
- test solution: the test substance was added to the test water without any pretreatment; subsequently the fish were placed into the aquaria

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assumed stable

TEST SYSTEM:
- Test type: static
- Concentrations: 0; 1000; 2150, 4640; 10,000 mg/L (nominal)

- Controls: positive control with chloroacetamide (run approx. 1 week before the test)
- Renewal of test solution: no
- Exposure vessel type: all-glass aquaria (30 cm x 22 cm x 24 cm)
- Number of replicates: 1
- Fish per concentration: 10
- Test temperature: 20 °C
- Dissolved oxygen: 8.1 - 8.6 mg/L
- pH: 7.3 - 7.5
- Adjustment of pH: no
- Adaptation to test water and test temperature: 3 days

TEST PARAMETER: lethality and symptoms
STATISTICAL METHOD: Calculation of the Median Lethal Concentration (LC50) and the LC5 and the LC95 using the Probit analysis (Finney DJ., 1971).

Reliability: (2) valid with restrictions
National Guideline study

Flag: Critical study for SIDS endpoint

10-JUL-2003 (35)

Type: static
Species: Semolitus atromaculatus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC0: ca. 7000
LC100: ca. 15000
Limit Test: no

Method: other: see Test Conditions Field
Year: 1952
GLP: no
Test substance: other TS: 1,3-dimethylurea from commercial source, purity not stated

Remark: This reference reports results for numerous test materials, specific details for each product are not given.

Result: RESULTS EXPOSED:
- critical range: 7,000 - 15,000 ppm (the toxicity of the chemical was expressed as "critical range", defined as the range in concentration in parts per million below which the four fish all lived for 24 hours and above which they all died).

Test condition: TEST ORGANISMS: creek chub (Semotitus a. atromaculatus)
- supplier: commercial bait dealer (no further details given)

TEST SYSTEM:
- Test type: static
- Concentrations: a "range of concentrations" (not specified)
- Controls: stock water
- Dosing rate: not reported
- Renewal of test solution: not reported
- Exposure vessel type: 3000 mL of test solution were placed in a 3,8 L glass jar equipped with a glass aerating tube and a cover with an air release.
- Number of replicates: 1
- Fish per replicate: 4
- Test temperature: between 15 and 21 °C

- Dissolved oxygen: A constanct stream of filtered air was forced through the water in the test jars to maintain the dissoved oxygen content
- pH: 8.3

DURATION OF THE TEST: 24 hours
TEST PARAMETER: At "frequent" (not specified) intervals the condition of the fish was observed and any dead fish were removed to avoid contamination

Reliability: (3) invalid
small number of fish exposed; short exposure period; limited documentation.

15-JAN-2004 (36)

Type: static
Species: Poecilia reticulata (Fish, fresh water)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 2500
Limit Test: no

Method: other: see Test Conditions field
Year: 1994
GLP: no data
Test substance: other TS: 1,3-dimethylurea (Fluka), purity not stated

Remark: It is reported that "the size of fish swelled gradually and they became less active", without providing further details.
Result: RESULTS EXPOSED:no mortality
RESULTS CONTROLS: no mortality
Test condition: TEST ORGANISMS: guppy fish (Poecilia reticulata). No further details reported.

- Concentrations: approx. 0.5 g/L was applied every 24 hours till the concentration of dimethylurea reached up to approx. 2500 mg/L
- Dosing rate: test substance added at 0, 24, 48, 72 and 96 hours
- Renewal of test solution: not reported
- Exposure vessel Type: 10 L aquaria
- Number of replicates: 1
- Fish per replicate: 10
- Test temperature: 26-28 °C.
- Dissolved oxygen: 6.3-11.9 mg/L (average: 8.5 mg/L)
- Chemical Oxygen Demand: 6.7 - 13.4 mg/L (average: 9.7 mg/L)
- pH: 7.2 - 9.1 (average: 8.4)

TEST PARAMETER: observations at 24, 48, 72 and 96 hours
STATISTICAL METHOD: Probit analysis (Finney, 1952)

Reliability: (3) invalid
inconsistencies and severe limitations in reporting; no standard test design

15-JAN-2004 (37)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no

EC0: = 500
EC50: > 500
EC100: > 500
Limit Test: no

Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1988
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: equivalent to OECD 202
Remark: EC values given as nominal concentrations
Result: Results after 24 h:
EC0 = 500 mg/l
EC50 > 500 mg/l
EC100 > 500 mg/l

No immobility (0 %) of Daphnia was observed after 48 h up to the highest concentration of 500 mg/l.
Test condition: TEST ORGANISMS
- Strain: daphnia magna Straus.
- Source/supplier: derived from a culture received from the Institut National de Recherche Chimique Apliquee, France in 1978
- Age: 2-24 hours
- Feeding: yeast and green algae
- Pretreatment: not reported
- Feeding during test: not reported
- Control group: yes, dilution water

STOCK AND TEST SOLUTION AND THEIR PREPARATION: stock solution 500 mg/L.

STABILITY OF THE TEST SUBSTANCE SOLUTIONS: assumed
DILUTION WATER
- source: filtered, unchlorinated tap water
- aeration: yes
- alkalinity: 0.83 mmol/l
- hardness: 2.80 mmol/l
- conductivity: 550 - 650 µS/cm
- Ca:Mg = 4:1
- Na:K = 10:1

TEST SYSTEM
- concentrations: 0; 31.25; 62.5; 125; 250; 500 mg/L
- renewal of test solution: no
- exposure vessel type: reagent tubes with flat bottom
- test volume: 10 mL
- volume/animal: 2 mL
- number of animals/vessel: 5
- total number of animals/concentration: 20
- number of replicates: 4
- test temperature: 292-294 K
- dissolved oxygen: 8.5-8.7 mg/L (at study begin); 8.0 after 48 hours
- pH: 8.0 (at study begin); 7.7 - 7.9 after 48 hours
- adjustment of pH: with H2SO4
- light intensity: 5 µE at a wave lenght of 400 - 750 nm
- photoperiod: day:night = 16:8 hours, artifical light
TEST PARAMETER: mortality/immobility; readings at 0, 3, 6,

24 and 48 h (evaluation of swimming ability)
STATISTICAL METHOD: 95% confidence limits.

Reliability: (2) valid with restrictions
Guideline study

Flag: Critical study for SIDS endpoint

15-JAN-2004 (38)

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
NOEC: = 62.5
EbC10 : = 97
EbC50 : = 560
EC90 : > 500
Limit Test: no

Method: other: DIN 38412, part 9
Year: 1988
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: EC values relate to biomass.
The EC values were calculated (linear regression analysis) from the concentration-response relationship.
The EC- values are given as nominal concentration.

ErC50 > 500 mg/l
At the highest test concentration growth rate was inhibited by about 15 %.

Results - Growth Rate:

ErC10 = 318 mg/l
ErC50 > 500 mg/l
NOEC = 62.5 mg/l

Validity criterion was fulfilled (ca. 50fold increase).

Test condition: TEST ORGANISMS
The test strain of Scenedesmus subspicatus CHODAT SAG 86.81 as obtained at regular intervals from SAG
inoculum density: 10000 cells/mL

STOCK AND TEST SOLUTION AND THEIR PREPARATION: not reported.
STABILITY OF THE TEST SUBSTANCE SOLUTION: assumed to be stable
GROWTH/TEST MEDIUM CHEMISTRY: conforming to OECD medium
TEST SYSTEM
- test type: static
- concentrations: 0; 31.25; 62.5; 125; 250; 500 mg/L
- renewal of test solution: no
- exposure vessel type: Erlenmeyer flasks
- test volume: 10 mL
- number of replicates: 4 inoculated parallels, 2 uninoculated controls
- test temperature: 20 °C
- pH at 0 hours: 8.5-8.6

- Illumination: artificial light - permanent illumination
- light intensity: 50-200 µE at a wave lenght of 400 - 700 nm

TEST PARAMETER: spontaneous chlorophyll-A fluorescence at 685 nm as criterion for biomass (excitation with short light impulse at 435 nm). Measurements at 0, 24, 48, and 72 hours.
STATISTICAL METHOD: linear regression analysis

Reliability: (2) valid with restrictions
National Guideline study

Flag: Critical study for SIDS endpoint

15-JAN-2004 (39)

Species: Chlamydomonas reinhardtii (Algae)
Endpoint: other: mortality, mutagenicity
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:** no
LOEC: ca. 8800
EC50: ca. 35200

Method: other: see Test Conditions
Year: 1975
GLP: no
Test substance: other TS: 1,3-dimethylurea, synthesized in the Research Institute of Agrochemical Technology, Bratislava; purity not stated

Remark: The lethal and mutagenic activity of six urea derivatives was investigated in this study: N-methyl-N-nitroso- and N-ethyl-N-nitrosourea, N-methyl- and N-ethylurea, 1,3-dimethyl- and 1,3 diethylurea.
LOEC and EC50 values relate to toxicity (nominal concentrations).

Result: survival (%) in complete medium: 55.68 at 0.4 M.
survival (%) in minimal medium: 71.71 at 0.4 M.

mutation frequency (%) in complete medium: 3.78 at 0.4 M.
mutation frequency (%) in minimal medium: 1.84 at 0.4 M.

The mutation frequency induced by 1,3-dimethylurea was described as "relatively low" by the study authors. At 0.005 M, N-methyl-N-nitrosourea, and N-ethyl-nitroso-urea induced mutation frequencies of 30.2 and 5.27 and 29.2 and 5.51 %, in complete and minimal medium, respectively. The mutation frequency of untreated controls was not reported, and was presumably below 0.05% (deduced from figure in publication).

An increased survival and a partially reduced mutagenic effect was found with all 4 tested non-nitroso urea derivatives at experimental concentrations on minimal medium as compared to that found with complete medium. The author ascribe this effect to the cellular repair mechanism. The cell division in minimal medium proceeds with a lower rate than in complete one and the repair systems may hence act for a longer period, repairing more damages in the DNA than is possible in a complete medium, where the DNA replication is faster.

Test condition: TEST SYSTEM: Chlamydomonas reinhardtii, no further data.
MEDIA: the composition of both complete and minimal cultivation media has been described in a preceding paper

(Miadoková et al., 1972: Acta F.R.N. Univ. Comen.-Genetica III, 35 (in Slovak)).
TEST FOR MUTAGENICITY: the test substances were applied in the light and under constant shaking to a culture grown for 5-6 days on complete liquid medium (stationary phase). After double centrifugation and washing with sterile distilled water the sedimented cells were resuspended for 30 minutes in aqueous solutions of the test substances at various molarity (0.1, 0.2 and 0.4 M; corresponding to approx. 8.8, 17.6, 35.2 g/L). The treated cells were then inoculated in Petri-dishes with both complete and minimal media, and then placed in a luminostat for cultivation (12 hours at artificial illumination, intensity 1500 lux, 12 hours under daylight at 25-27 °C).
EVALUATION OF CYTOTOXICITY: the survival of cells was evaluated microscopically on solid media after 6-7 days of cultivation. The study was performed on about 800 untreated and treated algal cells.
EVALUATION OF THE MUTAGENIC EFFECT: the mutagenic effect was appraised microscopically on Petri dishes after 10-14 days of cultivation; it was based on phenotypical analysis of changes detected on growing colonies. The examination included pigment, morphological and lethal mutations. The evaluation did not include evaluation of microcolonies.

Reliability: (2) valid with restrictions
short exposure period; study is not appropriate to judge on a potential mutagenic effect (no negative control or historical control data provided, evaluation criteria not given, non-standard test system).

15-JAN-2004 (40)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 30 minute(s)
Unit: mg/l **Analytical monitoring:**
EC50: > 1000
EC80 : > 1000
EC20 : > 1000

Method: Directive 88/302/EEC, C.11
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: corresponds to OECD 209 and ISO Standard 8192
Remark: The quality criteria are fulfilled (the 2 control respiration rates should be withon 15% each other and the EC50 of 3,5-dichlorphenol is in the accepted range of 5 to 30 mg/l).
Test condition: concentration of dry substance: 1 g/l
Reliability: (1) valid without restriction
Guideline study
Flag: Critical study for SIDS endpoint
19-JAN-2004 (41)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)

Unit: mg/l **Analytical monitoring:** no
EC10: > 10000
EC50: > 10000
EC90 : > 10000

Method: other: DIN 38412, part 8
Year: 1988
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Test condition: TEST ORGANISMS: The test strain of Pseudomonas putida DSM 50026 as obtained in regular intervals from DSM.
-stem culture: 10 mL
-pre-culture: 100 mL
-test culture: 10 mL
-growth period: 7 +/- 1 hour

STOCK AND TEST SOLUTION AND THEIR PREPARATION:
stock solution 12,500 mg/L.

TEST MEDIUM: AK-medium according to German national standard DIN 38412/part 8

TEST SYSTEM:
test vessel: Erlenmeyer flasks
test volume: 10 mL (1 mL medium, 1 mL suspension of bacteria, 8 mL test solution)
concentrations (nominal): 0; 156.25; 312.5; 625; 1250; 2500; 5000; 7500; 10,000 mg/L
control: untreated
test period: 17 hours
temperature during the test: 20 °C,
number of replicates: 4 inoculated parallels, 1 uninoculated
pH at study begin: 7.1 - 7.2
pH at study end (17 hrs): 7.1-7.2 (control), 4.9-5.0 (exposed)

PARAMETER: optical density 436 nm

Reliability: (2) valid with restrictions
National Guideline study
Flag: Critical study for SIDS endpoint
15-JAN-2004 (42)

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

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: no data
Sex: male/female
No. of Animals: 29
Vehicle: water
Doses: 20; 79; 316; 1260 mg/kg (1 animal per dose); 3160; 5010; 6310; 7940; 10000 mg/kg (5 animals per dose)
Value: ca. 4000 mg/kg bw

Method: other: BASF-test
GLP: no
Test substance: other TS: 1,3-dimethylurea, technical grade

Remark: Due to the poor documentation of the study details in the original study report, a supplementary document (dated 7 March 2003) was prepared based on the study raw data which gives the study details.

Result: CLINICAL SYMPTOMS: unspecific; apathy and narcotic like state at doses near to or exceeding the LD50. None of the animals had blood in the urine.
MORTALITIES: the approximative LD50 was determined as 4000 mg/kg bw.
Results are given as dead animals/total number of animals at this dose at 24 h, 48 h and 7 days after dosing:

20 mg/kg bw: 0/1, 0/1, 0/1
79 mg/kg bw: 0/1, 0/1, 0/1
316 mg/kg bw: 0/1, 0/1, 0/1
1260 mg/kg bw: 0/1, 0/1, 0/1
3160 mg/kg bw: 0/5, 0/5, 0/5
5010 mg/kg bw: 0/5, 0/5, 4/5
6310 mg/kg bw: 0/5, 4/5, 5/5
6310 mg/kg bw: 1/5, 5/5, 5/5
10000 mg/kg bw: 5/5, 5/5, 5/5

SYMPTOMS PER DOSE GROUP:
20-3160 mg/kg bw: no symptoms
5010 mg/kg bw: piloerection, vocalisation during urination
6310-7940 mg/kg bw: piloerection, narcotic-like state
10000 mg/kg bw: partly lateral position, staggering-unsteady gait, apathy, piloerection, narcotic-like state

Test condition: TEST ORGANISMS
5 rats per dose group, except for the four lowest dose levels (1 rat/dose).
Weight: not stated.

ADMINISTRATION
1,3-dimethylurea was given by gavage as a aqueous preparation. Dosing volume not reported.

EXAMINATIONS
Animals were inspected for signs of pharmacologic or toxicologic effects daily during a 7 d observation period after dosing. At the end of the observation period survivors were sacrificed and necropsied as were animals that had died during the study.

STATISTICAL METHOD: not reported

YEAR OF STUDY: not reported

Reliability: (2) valid with restrictions
limited documentation; short post-exposure observation period.

Flag: Critical study for SIDS endpoint

15-JAN-2004 (43)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 4800

Method: other: no data
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Reliability: (4) not assignable
no experimental details available.

25-JUN-2003 (44)

Type: LDLo
Species: rat
Strain: Wistar
Sex: female
No. of Animals: 7
Vehicle: water
Doses: 1000; 2000 mg/kg bw
Value: > 2000

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea from commercial source (Tokyo Chemical Ind. Co. Ltd.)

Result: No mortality was reported in 1 rat dosed with 1000 mg/kg bw and in 6 rats dosed with 2000 mg/kg bw.
The animals showed no obvious signs of toxicity.
Test condition: The animals were examined for deaths or toxic signs such as depression, diarrhea, etc., for one week. No further experimental details available.
Year of study: not reported.
Reliability: (4) not assignable
very limited documentation; short post-exposure observation period

07-MAR-2003 (45)

Type: LDLo

Species: mouse
Strain: ICR
Sex: female
No. of Animals: 6
Vehicle: water
Doses: 1000; 2000 mg/kg bw
Value: > 2000

Method: other: no data
GLP: no data
Test substance: other TS: 1,3-dimethylurea from commercial source (Tokyo Chemical Ind. Co. Ltd.)

Result: No mortality occurred in each 3 mice dosed with either 1000 mg/kg bw or 2000 mg/kg bw. No further details reported. The animals showed no obvious signs of toxicity.
Test condition: The animals were examined for deaths or toxic signs such as depression, diarrhea, etc., for one week. Year of study: not reported.
Reliability: (4) not assignable very limited documentation, short post-exposure observation period
16-JUN-2003 (45)

Type: other: repellency test
Species: mouse
Strain: other: Peromyscus maniculatus (deer mouse)
Sex: no data
Vehicle: other: not specified
Doses: no data
Value: = 1250 mg/kg bw

Method: other: 3-day feeding test
GLP: no data
Test substance: other TS: 1,3-dimethylurea, not further specified

Remark: The value of 1250 mg/kg bw represents the average amount of chemical that was ingested by each animal over a 3-day test period without killing more than 50 % of the test animals.
Test condition: TEST ORGANISMS: wild-trapped deer mice
NUMBER OF ANIMALS PER DOSE LEVEL: 5
STATISTICAL METHOD: Thompson (1948) and Thompson and Weil (1952).
YEAR OF STUDY: not reported.
Reliability: (4) not assignable only tabulated summary available.
17-JUL-2003 (46)

5.1.2 Acute Inhalation Toxicity

Type: other: IRT (Inhalation risk test)
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 12
Exposure time: 7 hour(s)

Method: other: as described by Smyth et al., Am. Ind. Hyg. Ass. J. 23,

95-107, 1962
GLP: no
Test substance: other TS: 1,3-dimethylurea, purity 97.5%

Remark: this test provides toxicity information at or near vapor saturation concentration, i.e. at a fixed concentration that usually is not analyzed. This test system is suitable to estimate inhalation toxicity risks of volatile substances after spills in confined spaces with low ventilation.
Result: No lethality, and no clinical symptoms observed during the exposure and post-observation period.
No changes performed at the end of the post-observation period at necropsy noted.
Test condition: TEST ORGANISMS: 12 Sprague-Dawley rats
SUPPLIER: Wiga, Sulzfeld/Germany
BODY WEIGHT: 197 gram (mean)
FEED: Altromin-R standard diet, water ad lib.
ADMINISTRATION OF TEST SUBSTANCE:
Animals were placed in an exposure chamber and exposed to an atmosphere at near vapor saturation, generated by bubbling air through a 5 cm - layer of the test substance at a rate of 200 L/hour at 20°C.
EXPOSURE PERIOD: 7 hours
EXAMINATIONS:
Animals were observed for mortality and signs of toxicity.
POST-EXPOSURE OBSERVATION PERIOD: 14 days.
NECROPSY: all animals after the post-exposure observation period and all animals that had died during the exposure.
YEAR OF STUDY: 1977.
Reliability: (3) invalid
Test system not applicable and not valid for solid test substances.
07-JAN-2004 (47)

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: water
Doses: no data
Route of admin.: i.p.
Value: ca. 4000 mg/kg bw

Method: other: BASF-test
GLP: no
Test substance: other TS: 1,3-dimethylurea, technical grade

Result: Animals showed unspecific symptoms of toxicity. At high doses depression was observed. In urine, no blood could be detected. (No further details given.)
Test condition: TEST ORGANISMS
mouse, number/strain/weight: not reported.

ADMINISTRATION

1,3-dimethylurea was given intraperitoneally as an aqueous preparation. Dosing volume not reported.

EXAMINATIONS
Animals were inspected for signs of pharmacologic or toxicologic effects daily during the 7 day observation period after dosing. At the end of the observation period survivors were sacrificed and necropsied as were animals that had died during the study.

YEAR OF STUDY: not reported.

Reliability: (4) not assignable
no experimental details

25-JUN-2003 (44)

Type: LD50
Species: rat
Strain: CD-1
Sex: no data
Vehicle: no data
Doses: no data
Route of admin.: s.c.
Value: > 2000 mg/kg bw

Method: other: not reported
GLP: no
Test substance: other TS: 1,3-dimethylurea, recyrstallized/ redistilled, purity was checked by melting point

Result: No mortality, and no clinical signs reported.
Reliability: (4) not assignable
insufficient experimental details reported to judge validity of results

17-JUL-2003 (48)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Route of admin.: s.c.
Value: = 2000 mg/kg bw

Method: other: no data
GLP: no
Test substance: other TS: 1,3-dimethylurea, not further specified

Reliability: (4) not assignable
no experimental details available

17-JUN-2003 (44)

Type: other: biochemical and haematology parameters
Species: rabbit
Strain: other: New Zealand
Sex: female
No. of Animals: 6
Vehicle: water
Doses: 194 mg/kg bw

Route of admin.: s.c.

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea from Sigma (USA)

Remark: The aim of the study was to investigate whether the hydrolysis products of methylisocyanate, i.e. methylamine and 1,3-dimethylurea play any role in the methylisocyanate induced toxicity.

Result: Animals treated with 1,3-dimethylurea appeared normal without any noticeable respiratory distress.
The administration of the test substance caused a marginal 20-30% increase in the plasma urea level at 1 and 4 hours after treatment that returned to normal by 24 hours.
According to the authors, the obseved marginal increase in the plasma urea level could be attributed either to the possible presence of 1,3-dimethylurea in the plasma of the animals and its interference in the urea estimation method, or to the possible N-demethylation of 1,3-dimethylurea.
None of the other haematological or biochemical parameters studied were changed.
From the results the authors concluded that the haematological and biochemical changes induced by methyl isocyanate intoxication are mainly caused by methylisocyanate per se and not by its hydrolysis products methylamine or 1,3-dimethylurea.

Test condition: TEST ANIMALS: female New Zealand rabbits, bred in the Defence R&D Establishment, Gwalior/India, weighing between 1.5 and 2 kg, maintained on a standard diet. All animals were fasted overnight prior to the experiment while water was allowed ad libitum.
TEST PROCEDURE: 4 groups of 6 animals were injected subcutaneously with 2.2 mmol 1,3-dimethylurea/kg bw (approx. 194 mg/kg bw; in distilled water), or with olive oil, methylisocyanate (2.2 mmol/kg bw = 126 mg/kg bw), or methylamine (2.2 mmol/kg bw).
0.6 mL blood was drawn through a fine incision on the ear marginal vein into tubes containing heparin before treatment, and at 1h, 4h and 24 hours after treatment.
STUDIED BLOOD PARAMETERS:
haemoglobin, erythrocyte volume, leucocyte number, plasma albumin level, plasma total protein level, blood pyruvate, blood lactate, plasma urea level.
STATISTICAL ANALYSIS: Student`s t-test. Significance level $p < 0.05$.

YEAR OF STUDY: not reported.

Reliability: (2) valid with restrictions
limited documentation; small number of animals; only one dose level tested.

25-JUN-2003 (49)

Type: other: clinical parameters
Species: rat
Strain: Wistar
Sex: male
No. of Animals: 8
Vehicle: other: not stated, presumably water
Doses: 507 mg/kg bw

Route of admin.: s.c.

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea from Sigma (USA)

Remark: The aim of the study was to investigate whether the hydrolysis products of methylisocyanate, i.e. methylamine and 1,3-dimethylurea play any role in the methylisocyanate induced toxicity.
Result: The administration of the test substance had no influence on hemoglobin, plasma glucose or lactate levels. There were also no effects on total proteins, and albumin. A marginal 10-15% transient increase in plasma urea level was found at 1 and 4 hours after treatment, and returned to almost normal by 24 hours. A small decrease in plasma cholinesterase activity (-12%) was observed, that was significant only at 24 hours after treatment.
From the results the authors concluded that the haematological and biochemical changes induced by methyl isocyanate intoxication are mainly caused by methylisocyanate per se and not by its hydrolysis products methylamine or 1,3-dimethylurea.
Test condition: TEST ANIMALS: male Wistar rats, bred in the Defence R&D Establishment, Gwalior, weighing 140 +/-20 g, maintained on a standard diet. All animals were fasted overnight prior to the experiment while water was allowed ad libitum.
TEST PROCEDURE: groups of 8 rats were injected subcutaneously with 5.75 mmol 1,3-dimethylurea/kg bw (507 mg/kg bw), or with olive oil, methyl isocyanate (dose equivalent to the LD50), distilled water, or 5.75 mmol methylamine/kg bw.
Blood (0.5 mL) was drawn from the retro-orbital plexuses under light ether anaesthesia into heparinized tubes before treatment, and at 1 h, 4 h, and 24 h after treatment.
The following parameters were assessed: hemoglobin (Hb), plasma total proteins, plasma albumin, blood glucose, blood pyruvate and lactate, plasma urea, and plasma cholinesterase by standard methods as described in the publication.
STATISTICAL ANALYSIS: Student`s t-test for paired data. Level of significance at $p<0.05$.
YEAR OF STUDY: not reported
Reliability: (2) valid with restrictions
only one dose level investigated; limited documentation
07-JAN-2004 (50)

Type: other: lung toxicity
Species: rat
Strain: Wistar
Sex: male
No. of Animals: 4
Vehicle: water
Doses: 507 mg/kg bw
Route of admin.: s.c.

GLP: no data
Test substance: other TS: 1,3-dimethylurea from Sigma (USA)

Remark: The aim of the study was to investigate whether the hydrolysis products of methylisocyanate, i.e. methylamine

and 1,3-dimethylurea play any role in the methylisocyanate induced toxicity.

Result: No mortalities were observed at 24 hours after administration of a single subcutaneous dose of 1,3-dimethylurea. The animals did not exhibit any visible sign of respiratory distress.
At necropsy, the animals showed apparently normal viscera. The lung parenchyma showed some changes, which were lesser in magnitude as compared to the changes observed with equimolar doses of methyl isocyanate or methyl amine. The bronchial epithelium was very much preserved, blood vessels showed varying degrees of eosinophilic changes, and prominent interstitial pneumonitis with mononuclears and histiocytes was found.

Test condition: TEST ANIMALS: male Wistar rats, bred in the Defence R&D Establishment, Gwalior, weighing 140 +/-20 g, maintained on a standard diet. All animals were fasted overnight prior to the experiment while water was allowed ad libitum.
TEST PROCEDURE: groups of 4 rats were injected subcutaneously with 5.75 mmol/kg bw (507 mg/kg bw) of 1,3 dimethylurea (in water) or 5.75 mmol/kg bw of methyl amine (in water) or with 164, 329 or 657 mg/kg bw of methyl isocyanate (in olive oil).
All rats that survived to the study end were necropsied and investigated for macroscopic and microscopic lesions.
CONTROL: olive oil.
YEAR OF STUDY: not reported.

Reliability: (2) valid with restrictions
small number of animals, only one dose level tested

07-MAR-2003 (51)

Type: other: lung toxicity
Species: rat
Strain: Wistar
Sex: male
Vehicle: water
Doses: 507 mg/kg bw
Route of admin.: s.c.

GLP: no data
Test substance: other TS: 1,3-dimethylurea from Sigma (USA)

Remark: The aim of the study was to investigate whether the hydrolysis products of methylisocyanate, i.e. methylamine and 1,3-dimethylurea play any role in the methylisocyanate induced toxicity.

Result: There was a mild consolidation of the lungs only up to 1 week while no apparent changes were observed at subsequent periods. At none of the time intervals were there any noteworthy changes in the bronchi and bronchioles. There was also no evidence of edema at any period. However, at the end of 1 week there was fairly prominent interstitial pneumonitis with widening of interalveolar septa and a moderate cellular infiltration of mononuclear cells. Neither at this period nor later was there any evidence of transformation to macrophages, fibroblasts, argentophilic reticulin fiber formation. From 4 weeks onwards, there was a decrease in the interstitial pneumonitis. At the end of 10 weeks the lungs were practically normal.

Test condition: TEST ANIMALS: male Wistar rats, bred in the Defence R&D

Establishment, Gwalior, weighing 140 +/-20 g, maintained on a standard diet. All animals were fasted overnight prior to the experiment while water was allowed ad libitum.
TEST PROCEDURE: groups of 4 rats were injected subcutaneously with 5.75 mmol/kg bw (507 mg/kg bw in water) and were sacrificed after 1, 4 or 10 weeks.
All rats that survived to the study end were necropsied and investigated for macroscopic and microscopic lesions.
The tissues were processed through paraffin and stained by H&E, PAS, reticulin (silver) and collagen (trichrome) using standard procedures.
CONTROLS: olive oil
YEAR OF STUDY: not reported

Reliability: (2) valid with restrictions
small number of animals; limited documentation; only one dose level tested

28-DEC-2002 (52)

Type: other: cardiovascular depression
Species: rat
Strain: Wistar
Sex: male
Vehicle: no data
Doses: 5; 10; 20; 40 mg/kg bw
Route of admin.: i.v.

Method: other: see Test Conditons
GLP: no data
Test substance: other TS: 1,3-dimethylurea from Fluka AG

Result: At doses of 5, 10, and 20 mg/kg bw 1,3-dimethylurea was found to be devoid of any effect on the blood pressure and heart rate. However, a dose of 40 mg/kg bw produced gradual and sustained fall in blood pressure which could be temporarily reversed by infusion of normal saline. Decrement in heart rate occurred after 45 min and coincided with death of the animals. Lung body weight index and tracheobronchial resistance were not affected.

Test condition: TEST ANIMALS: Wistar rats, weighing 170-210 g, obtained from the animal house of the establishment. A total number of 40 male animals were used for the study (no information, however, on how many animals were treated with 1,3-dimethyluea is provided). Animals were fed standard Hind Lever diet.
TEST SUBSTANCE ADMINISTRATION: groups of rats (number of animals not reported) were administered either with 1,3-dimethylurea i.v. (5; 10; 20; 40 mg/kg bw), methylamine hydrochloride i.v. (3,10,26 mg/kg bw), or methylisocyanate i.v. (5,10,28 mg/kg bw), s.c. (1300, 1500 mg/kg bw) or by the inhalation route (5,10 mg/L).
TEST PROCEDURE: Animals were prepared under pentobarbital sodium anaesthesia for recording various physiological parameters on a Grass Polygraph model 7. All animals were maintained on positive pressure ventilation using rodent ventilator. A bronchospasm transducer was used to measure tracheobronchial resistance. The mean carotid blood pressure was recorded using a P23Dc Statham Transducer. The signals from DC Driver amplfier recording blood pressure were fed into the Tachograph preamplifier to record heart rate. Continous monitoring of EKG was done, and tidal volume and

minute volume were recorded.
ASSESSMENT OF LUNG DAMAGE: lungs were dissected out and were freed from adhering blood and extraneous tissues and weighed. The lung body weight indes (LBI) was calculated by the formula: LBI = (Lung Weight (wet) / Body Weight) x 100.
YEAR OF STUDY: not reported.

Reliability: (4) not assignable
limited documentation; no information on number of animals treated with the test substance. No negative controls used.

28-DEC-2002 (53)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 80 % active substance
Exposure: Occlusive
Exposure Time: 24 hour(s)
No. of Animals: 6
Vehicle: water
PDII: 1.25
Result: slightly irritating

Method: other: Fed. Reg., 38, 187, § 1500.41, (1973)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: On intact skin, 2/6 animals showed very slight erythema, which was completely reversible within 8 days (mean Draize scores: 24 hr - 0.3; 72 hr - 0.2). Edema was not observed at any time.

On scarified skin, erythema and edema was observed in 2/6 animals (mean Draize scores: 24 hr - 2.0 (erythema), 0.7 (edema); 72 hr - 1.5 (erythema), 0.3 (edema)). With the exception of 1 single animal which had still erythema (grade 2) on day 8, these effects were completely reversible within 8 days, and only scaling was present in 4/6 animals at the end of the study.

Test condition: TEST ORGANISMS: rabbits of the Vienna strain, 3 males and 3 females; breeder: Gaukler, Offenbach/Germany. Average weight: 2.87 kg; standard rabbit feed (Ssniff K), water ad lib.

EXPOSURE: the test substance (approx. 0.5 g) was applied as 80% aqueous preparation on intact and scarified skin.

EXPOSURE PERIOD: 24 hours, occluded.

SCORING: according to the Draize scoring system, at 24 and 72 hours and on day 8.

YEAR OF STUDY: 1979

Reliability: (2) valid with restrictions
in deviation of today`s guidelines, occlusive exposure for 24 hours was used, and the effects were also studied on scarified skin. This might be seen as worst-case conditions.

Flag: Critical study for SIDS endpoint
17-JUN-2003 (54)

Species: rabbit
Concentration: 80 % active substance
Exposure: Occlusive
No. of Animals: 2
Vehicle: water
Result: slightly irritating

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

Remark: Due to the poor documentation of the study design in the original study report, a supplementary memo (dated 28 July 2003) was prepared based on the study raw data which gives the details of the study design.
Result: 5 min exposure: one of the two animals showed slight erythema at 24 hours after exposure. Completely reversible within 72 hours.

15 min exposure: both animals showed slight erythema at 24 hours after exposure. Completely reversible within 72 hours.

2 hours exposure: both animals showed slight erythema at 24 hours after exposure. Scabbing at 72 hours and at 8 days.

20 hours exposure: 24 hours after exposure, 1 animal showed slight erythema, the other marked erythema and marked edema. Edema and erythema were completely reversible within 72 hours. Scaling persisted through day 8.
Test condition: TEST ORGANISMS: 2 rabbits, no further data reported.

EXPOSURE PERIOD: 5 min, 15 min, 2 hours, and 20 hours.

APPLICATION SITE: skin of the back (about 2.5 x 2.5 cm application area).

DOSE: Exact dose not reported. An unknown amount of an 8 % aqueous preparation was applied.

YEAR OF STUDY: 1977
Reliability: (2) valid with restrictions
small number of animals; occlusive conditions; limited documentation; exposure dose not reported.
17-JUL-2003 (55)

Species: rabbit
Concentration: 80 % active substance
Exposure Time: 20 hour(s)
No. of Animals: 2
Vehicle: water
Result: slightly irritating

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

Result: both animals showed marked erythema at 24 hours after

exposure. Effects were completely reversible within 72 hours.
Test condition: TEST ORGANISMS: 2 rabbits

EXPOSURE PERIOD: 20 hours

APPLICATION SITE: ear

YEAR OF STUDY: 1977
Reliability: (3) invalid
application site and exposure period are not appropriate for the evaluation of skin irritancy
17-JUN-2003 (55)

Species: rabbit
Concentration: 80 % active substance
Vehicle: water
Result: not irritating

Method: other: no data
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Test condition: TEST SUBSTANCE: 80- and 50% aqueous preparations
Application site: skin of the back and ear
Reliability: (4) not assignable
no experimental details available
17-JUN-2003 (44)

5.2.2 Eye Irritation

Species: rabbit
Concentration: 50 mg
Comment: not rinsed
No. of Animals: 6
Vehicle: none

Method: other: Fed. Reg., 38, § 1500.42, (1973)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: 2 independent studies were performed:

Results of the first study:
24 hours after instillation a slight redness (grade 1) in 6/6 animals, and slight lacrimation in 4/6 animals were observed. Erythema (grade 1) persisted until 72 hours after instillation, but was completely reversible within 8 days. Slight lacrimation was observed in 3/6 animals at 48 hours, and had completely resolved at 72 hours. In 2 out of 6 animals corneal opacity (grade 1, covering between 50 and 75% of area) was noted at 24, 48 and 72 hours. The corneal effect was still present (in same degree) in one of these animals at the end of the study on day 8.

Results of the second study:
24 hours after instillation slight to marked redness (grades 1 and 2) in 6/6 animals, slight edema (grade 1) in 2, and slight lacrimation in 6/6 animals was observed. Erythema persisted (with decreasing severity) until 72 hours after

instillation in all animals, and was still present in three animals on day 8 (grade 1). Lacrimation was observed in 6/6 animals at 48 hours, and in 3/6 at 72 hours, and had completely subsided on day 8. Corneal opacity (grade 1, patchy, iris clearly visible) was noted only in one single animal at 72 hours after instillation; no opacities were found at the end of the study (day 8).

primary irritation score in the first experiment: 7.8 (max. score: 100)
primary irritation score in the second experiment: 4.9 (max score: 110)

Test condition: 2 independent studies were performed, with 6 animals used in each study.

TEST ORGANISMS: rabbits of the Vienna strain (3 males and 3 females in the first study; 5 males and 1 female in the second study). Breeder: Gaukler, Offenbach/Germany. Average weight: 2.9 kg (1st study), 3.1 kg (2nd study).

TEST SUBSTANCE APPLICATION: undiluted, approx. 0.1 mL (50 mg) were instilled in the conjunctival sac of the right eye.

The other eye served as control. After instillation, the lids were gently squeezed together for 1 second.

OBSERVATIONS: visual inspection at 24, 48, 72 hours and 8 days after instillation.

SCORING: according to the DRAIZE score.

YEAR OF STUDY: 1978/1979

Reliability: (2) valid with restrictions
post-observation period too short to judge reversibility of effects

Flag: Critical study for SIDS endpoint

07-JUL-2003 (54)

Species: rabbit
Concentration: 50 mg
No. of Animals: 2
Vehicle: none
Result: slightly irritating

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

Remark: Due to the poor documentation of the study design in the original study report, a supplementary memo (dated 28 July 2003) was prepared based on the study raw data which gives the details of the study design.

Result: No effects on cornea or iris. Slight erythema, lacrimation and edema 1 hour after instillation. Edema completely reversible within 24 hours, lacrimation and erythema within 3 days.

Test condition: 2 Animals used
TEST SUBSTANCE APPLICATION: undiluted, about 50 mg were instilled in the conjunctival sac of the right eye.
The other eye served as control.

OBSERVATIONS: visual inspection at 1, 24, 48, 72 hours and 8 days after instillation.

SCORING: according to the DRAIZE score.

YEAR OF STUDY: 1978/1979

Reliability: (2) valid with restrictions
limited reporting

17-JUL-2003 (55)

Species: rabbit
Concentration: 50 % active substance
Vehicle: water
Result: slightly irritating

Method: other: no data
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: Erythema, conjunctivits and slight corneal opacity were observed for 1-2 days after instillation of a 50% aqueous preparation. All effects were completely reversible within 3 days. Only minimal irritation was observed after instillation of the 10% preparation.

Reliability: (4) not assignable
no experimental details available

19-MAR-2003 (44)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat **Sex:** no data
Strain: no data
Route of administration: drinking water
Exposure period: to 61 exposures
Frequency of treatment: continuously
Post exposure period: no
Doses: 52-90 mg/animal/day corresponding to approx. 750 - 1500 mg/kg bw/day
Control Group: yes, concurrent vehicle
LOAEL: = 750 mg/kg bw

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: 53/60 animals died within 5 days to 7 weeks after begin of the study.
The animals lost weight (- 20 to 36%) during the first 6-10 study weeks. No significant changes were found in urinary parameters. Erythrocytes were found in urinary sediment of 4 rats.
At necropsy, pneumonia was found in 11 rats. The observed inflammation of the gastrointestinal tracts in 12 animals was attributed to an infection with Salmonella. These intestinal changes were also found in 3 control animals. 3

rats had gastric hemorrhages, and kidney changes were found in another 3 animals.

Test condition: TEST ORGANISMS:
- rats. Strain, age, weights, sex: males and females
- Number of animals: 60 (30 males / 30 females) animals in dose group, 40 controls.

ADMINISTRATION/EXPOSURE:
- the test substance was dosed with tea ad libitum (1% test substance in tea; corresponding to dose levels of 52-90 mg/animal/day or 750 - 1500 mg/kg bw/day; no further details)
- Duration of test/exposure: between 5 days and 10 weeks

CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs, mortality, body weights, urine. Frequency not reported.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
not reported.

STATISTICAL METHOD: none reported.

YEAR OF STUDY: presumably before 1959.

Reliability: (3) invalid
Salmonella infection of test and control animals probable
07-JAN-2004 (56) (57) (58)

Type: Sub-acute
Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: gavage
Exposure period: 28 days
Frequency of treatment: 5 days/week
Post exposure period: none
Doses: 0; 15; 50; 150; 450 mg/kg
Control Group: yes, concurrent vehicle
NOAEL: 50 mg/kg
LOAEL: 150 mg/kg

Method: other: OECD TG 407(1981)
GLP: yes
Test substance: other TS: 1,3-dimethylurea, purity >= 96%

Result: 450 mg/kg bw group:
- Transient, statistically significant decrease in food consumption in both sexes during the first week of the study when compared with the control group (-26% in males; -15% in females).
- Statistically significant decrease in body weight/body weight change in male rats (-11%/-29% at the end of the study).
- Increase in renal tubular and transitional epithelial cells in the urine sediment of 3 males.
- Renal alterations in male animals including tubular necrosis, desquamations of tubular epithelial cells and the presence of protein casts in tubular lumen (incidences and severity not reported).
- Non-specific tubular hyperplasia, representing a

regeneration process of the affected renal epithelium cells in females (incidences and severity not reported).

150 mg/kg bw group:
- Renal alterations in male animals including tubular necrosis, desquamation of tubular epithelial cells and the presence of protein casts in tubular lumen (incidences and severity not reported).

50 mg/kg bw group and 15 mg/kg bw group:
No substance related changes.

The analytical results confirmed the target concentrations of the mid and the high dose groups (101-103% of the target concentrations). Higher values (153% of the target concentration) were obtained in the lowest dose. This was assessed as having no influence on the outcome of the study by the study authors.

Test condition: TEST ORGANISMS:
- Age: 32 days at arrival, 42 days at study begin
- Weight at study initiation: males 191-212 g, females 137-157 g
- Number of animals: 5 male and 5 female animals per group

ANALYSES OF THE TEST SUBSTANCE:
purity (before start and at the end of the study), stability in test solution over 10 days, concentrations in test solutions.

ADMINISTRATION/EXPOSURE:
- Duration of test/exposure: 28 days
- Vehicle: doubly distilled water (aqua bidest)
- Concentration in vehicle: 0, 1.5, 5, 15, 45 mg/mL
- Total volume applied: 10 mL/kg
- Doses: 0; 15; 50; 150; 450 mg/kg bw/day

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: twice daily (daily on holidays). In addition, the animals were examined in detail before and after each test substance administration
- Mortality: twice daily
- Body weight: before dosing on day 0 and thereafter in weekly inervals
- Food consumption: weekly

OTHER PARAMETERS EXAMINED:
- urinalyis on day 26 (colour, turbidity, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, sediment)
- hematology on day 27 (leukocytes, erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, differential count and thromboplastin time)
- clinical chemistry on day 27 (GOT, GPT, alkaline phosphatase, serum glutamyltransferase, Na, K, Cl, inorganic phosphate, Ca, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, cholesterol, Mg)

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: full necropsy

- Microscopic: in accordance with OECD TG 407 (1981)

STATISTICAL METHOD:
- clinical examinations: means and standard deviations were calculated for food consumption, body weight and body weight change for the animals in each test group. A statistical one-way analysis of variance was performed with the Kruskal-Wallis-h-test. If the resulting p-value was equal or less than 0.05 a pairwise comparison of each dose group with the control group was carried out. This comparison was done using the Mann-Whitney-U-test for the hypotheses of equal median with significance levels of 0.05, 0.02 and 0.002.
- clinical chemistry and hematology: means and standard deviations were calculated for each test group. Except for the differential blood count a statistical one-way analysis of variance was performed with the Kruskal-Wallis-h-test. If the resulting p-value was equal or les than 0.05 a pairwise comparison of each dose group with the control group was carried out. This comparison was done using the Mann-Whitney-U-test for the hypotheses of equal median with significance levels of 0.05, 0.02 and 0.002.
- urinalysis: a pairwise comparison of each dose group with the control was carried out using Fisher´s exact test for the hypothesis of equal proportions with significance levels of 0.05 and 0.01.

YEAR OF STUDY: The experimental part of the study was carried out from October 29, 1990 to December 7, 1990.

Reliability: (2) valid with restrictions
study in accordance with the OECD guideline 407(1981).

Flag: Critical study for SIDS endpoint

07-JAN-2004 (59)

Type: Sub-acute
Species: rat **Sex:** female
Strain: no data
Route of administration: gavage
Exposure period: 4 to 22 exposures
Frequency of treatment: no data, presumably daily
Post exposure period: no
Doses: 1000; 2000 mg/kg bw as 10% aqueous solutions
Control Group: no
LOAEL: = 1000 mg/kg bw

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: 2000 mg/kg bw/d: all 10 animals died after 6-7 administrations of the test substance.

1000 mg/kg bw/d: 9/10 animals died after 4-22 administrations (2 animals died only after additonal gavage of 1x or 5x 2000 mg/kg bw/d). Some of the animals showed reduced body weights during the study (no quantitative data available). In 7 rats blood stained urine was observed intermittently. At necropsy, pneumonia was found in 10 animals, 1 animal showed cystitis. 3 animals had gastrointestinal hemorrhages, and changes in the kidney were

found in 2 rats.

Test condition: TEST ORGANISMS:
rats. Strain, age, weights
Number of animals: 10 female animals per group.

ADMINISTRATION/EXPOSURE:
- Duration of test/exposure: 4-22 exposures
- Vehicle: water
- Concentration in vehicle: 10%
- Total volume applied: not reported
- Doses: 1000; 2000 mg/kg bw/day

CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs, mortality, body weights, urine. Frequency not reported.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
not reported.

STATISTICAL METHOD: none reported.

YEAR OF STUDY: presumably before 1959.

Reliability: (2) valid with restrictions
Limited documentation, limited examination, only female rats, no control animals, no data on purity

17-JUL-2003 (56) (60)

Type: Sub-chronic
Species: rat **Sex:** female
Strain: no data
Route of administration: gavage
Exposure period: 500 mg/kg bw/day: up to 137 applications (ca. 20 weeks); 1000 mg/kg bw/day: up to 84 applications
Frequency of treatment: presumably daily
Post exposure period: no
Doses: 500; 1000 mg/kg bw/day as 10% aqueous preparation
Control Group: no
LOAEL: = 500 mg/kg bw

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: 500 mg/kg bw/day: 5/10 rats died after 10-66 administrations. The surviving rats were sacrificed after 137 administrations. All animals showed weight loss (-15%) during the first weeks of the study. 1 animal had blood stained urine at day 8 and during the second month of the study. At necropsy, 2 animals had pneumonia, 5 animals had gastric hemorrhages, and 2 animals showed kidney changes. No changes were found in kidneys and urinary bladders of the other animals.

1000 mg/kg bw/day: 9/10 animals died after 6-84 administrations. Body weight loss (-10 to 30%) was noted during the first 8 days of the study. At necropsy, 3 animals had pneumonia. No other pathological changes were noted.

Test condition: TEST ORGANISMS:
rats. Strain, age, weights
Number of animals: 10 female animals per group.

ADMINISTRATION/EXPOSURE:
- Duration of test/exposure: up to 137 exposures (500 mg/kg bw/day), and 84 exposures (1000 mg/kg bw/day).
- Vehicle: water
- Concentration in vehicle: 10%
- Total volume applied: not reported
- Doses: 500; 1000 mg/kg bw/day

CLINICAL OBSERVATIONS AND FREQUENCY:
Clinical signs, mortality, body weights, urine. Frequency not reported.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
not reported.

STATISTICAL METHOD: none reported.

YEAR OF STUDY: presumably before 1959.

Reliability: (2) valid with restrictions

Limited documentation, limited examinations, only female rats, no control animals, no data on purity

17-JUL-2003 (56) (57) (60)

Type: Sub-acute
Species: rabbit **Sex:**
Strain: no data
Route of administration: gavage
Exposure period: see test conditions field
Frequency of treatment: daily
Post exposure period: see test conditions field
Doses: 1000 mg/kg bw/day
Control Group: no
LOAEL: = 1000 mg/kg bw

Method: other: see test conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, technical grade

Result: Blood stained urine was observed in 2 out of 3 animals after the second administration of the test substance, and in the third animal after 4 administrations. Blood was spectroscopically, microscopically and chemically detected in urine for a total of 3-4 days. No clinical symptoms were noted, but one animal died two days after the 4th administration. In this animal a 10% body weight reduction was noted. At necropsy, this animal showed changes in liver and kidneys, that were confirmed histopathologically (fatty infiltrations of liver and kidneys).
After a recovery period of 20 days, the surviving 2 animals were again dosed with 1000 mg/kg bw/day. Again, blood was observed in the urine after 2 applications of the test substance. Blood was detected in the urine for 4-5 days.
After a recovery period of 11 weeks, one of the two animals was dosed with 1000 mg/kg bw/day for 3 days; the other animal served as control. At necropsy, cystitis and fatty infiltrations of liver and kidneys were found in the dosed animal, whereas the untreated control showed no macroscopic or microscopic changes.
In a similar study, 2 animals died after 3 applications.

Another animal died after 41 applications from pneumonia. Intermittently, haematuria was observed, but no changes were found in the urogenital tract at necropsy.

Test condition: TEST ORGANISMS: 3 rabbits

PARAMETERS: clinical observation; body weights were recorded 5 days/week; daily urine analysis; necropsy and histopathology of liver and kidneys.

EXPOSURE TO TEST SUBSTANCE: Application as 20 % aqueous preparation until blood in urine was detected. Repeated after 20 days and 11 weeks recovery period in 2 and 1 animal, respectively.

YEAR OF STUDY: not reported.

Reliability: (2) valid with restrictions
only one concentration, no control group, no data on purity, small number of animals; limited documentation

17-JUL-2003 (43) (56) (61) (60)

Species: cat **Sex:**
Route of administration: oral unspecified
Exposure period: other: see TC
Frequency of treatment: other: see TC
Post exposure period: no
Doses: 100-1000 mg/kg bw/day; total doses 11,000 and 13,500 mg/kg bw

GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: 2/2 cats died after 25 and 40 days. Haematuria was noted in both animals on day 12 or 15. Clinically, the animals showed vomiting, weakness, and muscular cramps. One cat lost weight (- 30%). At necropsy, pneumonia was found in both cats. No other changes were found.

Test condition: TEST ORGANISMS: 1 male and 1 female cat

PARAMETERS: Clinical observation, urine analysis, necropsy and histopathology of lung

EXPOSURE TO TEST SUBSTANCE: Application as 20 % aqueous preparation, either 3 x 500 mg/kg bw followed by 12 x 1000 mg /kg bw in the male cat or 5 x 100 mg/gk bw followed by 21 x 500 mg/kg bw in the female cat

YEAR OF STUDY: not reported

Reliability: (2) valid with restrictions
poor documentation; only one concentration, no control group, no data on purity

17-JUL-2003 (62) (56) (60)

Type: Sub-acute
Species: dog **Sex:**
Strain: no data
Route of administration: oral unspecified
Exposure period: 2.5 weeks
Frequency of treatment: 5 times per week; 12 administrations in total
Post exposure period: no
Doses: 1000 mg/kg bw/d

Control Group: no
LOAEL: = 1000 mg/kg

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, technical grade

Result: No clinical symptoms were noted after the first two test substance administrations. The dog vomited after the 3rd, 4th and 8th application, and was sedated. Blood stained urine was first noted after the 4th administration. Plasma urea levels increased from 19 and 11 mg% at study begin to 35 and 46 mg%. No further details reported. Liver function was not impaired as measured by bromosulphothaleine excretion.
Blood parameters were unchanged.
At necropsy, kidney necroses and cystitis were found, and were confirmed at microscopic evaluations.

Test condition: TEST ORGANISMS: 1 dog.

PARAMETERS: clinical observation; body weights were recorded 5 days/week; daily urine analysis; blood urea; liver function (bromosuphothaleine test), blood parameters (not specified), necropsy and histopathology of liver and kidneys.

YEAR OF STUDY: not reported.

Reliability: (2) valid with restrictions
only single animal; limited documentation, only one concentration, no control group, no data on purity

17-JUL-2003 (43) (60)

Type: Chronic
Species: dog **Sex:**
Route of administration: other: oral
Exposure period: 50-984 days
Frequency of treatment: 20-232 administrations
Post exposure period: no
Doses: 1000 mg/kg bw/day
Control Group: no
LOAEL: = 1000 mg/kg bw

Method: other: see test conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: 2 dogs died after the 3rd or 9th administration from intercurrent diseases that were not considered related to the test substance (hepatitis, intestinal invagination).

Haematuria was the most prominent clinical symptom, and was present in all animals. Haematuria was first noted after 3-4 administrations of the test substance. From the 6th study week onwards, bladder epithelia were found in urinary sediments.

Some animals showed leucocytosis. 7 animals vomited after application of the test substance, all animals showed loss of appetite. 6 animals lost weight (up to 30%).

All animals showed weakness of hinglegs, and 4 animals showed stiffness
of hind legs, wich turned into complete paralysis in one animal after 8 months.

At necropsy, 3 animals had intestinal inflammation, 3 had interstitial nephritis, and 3 had pneumonia. 8 of 9 animals had pathological changes in the urinary bladder. The histopathological examination revealed thickening of urinary bladder wall, hemorrhages, hypertrophic mucosa, partial loss of epithelia and signs of secondary bacterial infection. Urethrae and ureters were without changes.

Histopathologically, no changes were found in brain, spinal cord or peripheral nerves.

Test condition: TEST ORGANISMS: 10 male and 1 female dog

PARAMETERS: Clinical observation; body weights were recorded 5 days/week; daily urine analysis, necropsy, macroscopic and microscopic examination of various organs

EXPOSURE TO TEST SUBSTANCE: Application either as 20 % aqueous preparation by gavage or via feed

YEAR OF STUDY: not reported

Reliability: (2) valid with restrictions
limited documentation; no control group, only one concentration

07-JAN-2004 (62) (56) (57) (61) (60)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA1535, TA1537, TA98, TA100, TA97
Concentration: 0; 0.10; 0.33; 1.0; 3.3; 10 mg/plate
Cytotoxic Concentration: no cytotoxicity found
Metabolic activation: with and without
Result: negative

Method: other: Preincubation test according to Haworth et al., Environ. Mutagen. 5 (Suppl.1), 3-142, (1983) and Zeiger E. and Drake J.W., IARC Scientific Publ. No. 27, 303-313, (1980)
GLP: no data
Test substance: other TS: 1,3-dimethylurea, purity 98%

Result: 1,3-dimethylurea was negative in these tests and the highest ineffective dose tested in any S. typhimurium strain was 10 mg/plate. Positive controls were functional.

Test condition: 1,3-dimethylurea was tested in the Salmonella / microsome preincubation assay using the standard protocol approved by the National Toxicology Program (NTP).
METABOLIC ACTIVATION SYSTEM: rat and hamster liver S-9 mix from Aroclor 1254 induced animals.
VEHICLE: distilled water.
CYTOTOXICITY: was determined in a preliminary dose-setting experiment with strain TA100. Nontoxic chemicals were tested in the main experiment up to the 10 mg/plate dose level.

POSITIVE CONTROLS: sodium azide for TA1535 and TA100, 4-nitro-o-phenylenediamine for TA98, and 9-aminoacridine for TA1537; 2-aminoanthracene was used with all strains with hamster and rat liver metabolic activation systems. The dose level used were reported in Haworth et al. (1983), Environ Mutagen 5 (Suppl. 1), 3-142.
DATA EVALUATION: a dose-related, reproducible increase in the number of revertants over background, even if the increase was less than twofold, was evaluated as a "mutagenic response". When no increase in the number of revertants was elicited by the chemical, this was evaluated a "negative response" and when there was an absence of a clear-cut dose-related increase in revertants, when the dose-related increase in the number of revertants were not reproducible or when the response was of insufficient magnitude to support a determination of mutagenicity, this was evaluated a "questionable response".
STATISTICAL METHOD: none reported.
YEAR OF STUDY: not reported.

Reliability: (2) valid with restrictions
equivalent to OECD TG 471, except that test was not performed in E. coli or TA102, limited documentation
Flag: Critical study for SIDS endpoint
07-JAN-2004 (63) (64)

Type: Mouse lymphoma assay
System of testing: L5178Y mouse lymphoma cells
Concentration: 0; 500; 1000; 2000; 3000; 4000 or 5000 ug/mL
Cytotoxic Concentration: no cytotoxicity
Metabolic activation: with and without
Result: negative

Method: other: equivalent to OECD TG 476, according to Myhr B. et al. see test conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea, purity 98%

Remark: colony sizing not required, since no positive response
Result: 1,3-dimethylurea induced no toxicity and no increase in mutations at the tk locus, though a marginal increase was observed in the first experiment with induced S9 at 5000 ug/mL (57 mM). This response was not reproduced in the second S9 experiment.

Test 1 (without metabolic activation), Mutation Frequencies (mean of 3 replicates) *=stat. sign., p<0.05:
neg control: 36; 500 ug/mL: 35; 1000 ug/mL: 31, 2000 ug/mL: not determined; 3000 ug/mL: 40, 4000 ug/mL: 40, 5000 ug/mL: 39, pos. control: 224*.

Test 2 (without metabolic activation), Mutation Frequencies (mean of 3 replicates) *=stat. sign., p<0.05:
neg control: 23; 500 ug/mL: 25; 1000 ug/mL: 27, 2000 ug/mL: 18; 3000 ug/mL: 22, 4000 ug/mL: 25, 5000 ug/mL: 27, pos. control: 97*.

Test 1 (with metabolic activation), Mutation Frequencies (mean of 3 replicates) *=stat. sign., p<0.05:

neg control: 29; 500 ug/mL: 34; 1000 ug/mL: 29, 2000 ug/mL: 33; 3000 ug/mL: 30, 4000 ug/mL: 31, 5000 ug/mL: 52*, pos. control: 183*.

Test 2 (with metabolic activation), Mutation Frequencies (mean of 3 replicates) *=stat. sign., p<0.05:
neg control: 43; 500 ug/mL: 38; 1000 ug/mL: 46, 2000 ug/mL: 48; 3000 ug/mL: 55, 4000 ug/mL: 51, 5000 ug/mL: 56, pos. control: 213*.
MMS and MCA (used as positive controls) were functional.

Test condition: TEST SYSTEM: Mouse Lymphoma
STRAIN INDICATOR: L5178Y (TK+/TK-)

TEST PROCEDURE: according to Myhr B et al.: Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. In: Ashby J et al. (eds.): Progress in Mutation Research, Vol. 5, 555-568 (1985).

METHOD: Suspension Assay

TEST MATERIAL SOLVENT: distilled water

CONTROLS:
- solvent and positive controls were run concurrently.
- positive controls: methyl methanesulfonate (MMS; 5 nL/mL) for nonactivation experiments, and 3-methylcholanthrene (MCA; 2.5 ug/mL) in S9 activation experiments.

METABOLIC ACTIVATION: Aroclor 1254 induced rat-liver S9.

NUMBER OF REPLICATES: 3. Two independent experiments were peformed, both for the activated and the non-activated trials.

ADMINISTRATION OF TEST SUBSTANCE AND EXPRESSION PERIOD:
Six million cells were treated with the test chemical for 4 hours, washed, resuspended in media, and allowed to multiply in suspension culture for 2 days to express the trifluorothymidine (TFT)-resistance phenotype. The cells were then plated for both cloning efficiency (600 cells) and mutant selection (3x10e6 cells, 3 ug/mL TFT). All plates were incubated at 37 °C in 5% CO2 and colonies counted after 11-12 days. The mutant count was divided by the product of the cloning efficiency and the number of cells at risk (3x10e6 cells) to yield the mutant fraction.

STATISTICAL METHOD: all data were evaluated statistically for both trend and peak response. The statistical analysis consisted of a trend test and a pairwise comparison of the variance of the mutation frequency of the treated samples against the solvent control. The variance of the mutation frequency was determined by using a series of statistical assumptions associated with a mathematical model of the assay that was described by Lee and Caspary, 1983 (Mutation Research, 113, 417-430).

EVALUATION CRITERIA: An experiment was considered positive if the p value was less than 0.05 for at least 1 of the 3 highest dose sets (peak response) and if there was a

significant trend ($p<0.05$). If there was only a trend response or a single dose increase without a trend, the evaluation was "questionable"; a "negative" evaluation was made when there was no trend or peak response. A chemical was considered "positive" only if the positive response was confirmed in a repeat test.

QUALITY CONTROL CRITERIA: as published by Myhr et al., 1985 (in Ashby J et al. (eds): Progress in Mutation Research. Vol. 5, Elsevier, Amsterdam, pp. 555-568).

YEAR OF STUDY: not reported.

Conclusion: 1,3-dimethylurea did not induce gene mutations or chromosomal aberrations in cultured mouse lymphoma cells at dose levels up to and including 5000 ug/mL in the presence or absence of a rat liver metabolising system.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

07-JAN-2004 (65) (64) (66)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA104
Concentration: 0; 0.5; 1; 10; 20; 40; 80 mg/plate
Cytotoxic Concentration: 80 mg/plate
Metabolic activation: with and without
Result: negative

Method: other: liquid preincubation test, as described by Maron and Ames (1983), equivalent to OECD TG 471

GLP: no data

Test substance: other TS: 1,3-dimethylurea, purity 98%

Result: 1,3-dimethylurea did not induce a mutagenic response in any of the tester strains, both in the presence and in the absence of S9 mix.
Positive controls were functional. The substance was toxic at a dose of 80 mg/plate, reducing the number of the surviving cells in the background lawn. The addition of S9 mixture resulted in a reduction of the toxic effect.

Chemical	Dose (mg/plate)	Tester strain	-S9	+5% S9	+15% S9	+30% S9
DMU	0 (NC)	TA98	34	43	40	38
	0.5		29	37	42	38
	1.0		28	39	41	40
	10.0		27	45	44	47
	20.0		31	43	45	37
	40.0		28	40	43	45
	80.0		18	41	37	38
	0 (NC)	TA100	198	203	202	222
	0.5		201	204	209	201
	1.0		202	201	201	206
	10.0		189	212	212	176
	20.0		197	209	186	208
	40.0		197	192	201	211
	80.0		185	182	179	184
	0 (NC)	TA104	400	484	536	512

0.5	411	474	511	507
1.0	431	442	514	505
10.0	428	481	507	526
20.0	403	496	494	512
40.0	362	467	469	518
80.0	322	458	427	481

Test condition: METHOD: liquid preincubation protocol
(30 min preincubation)

METABOLIC ACTIVATION: 0, 5, 15, and 30% Aroclor 1254-induced rat liver S9 mix.

SOLVENT: Dimethylsulfoxid (DMSO)
Positive controls: 2,4,7-trinitrofluorene for TA98, 4-nitroquinoline-N-oxide for TA100, methylglyoxal for TA104 and 2-aminofluorene was used for all strains with metabolic activation system. Number of replicates: 2; data evolution: the mutagenic response was considered to be positive if the mean number of revertant colonies obtained was double the solvent control at any dose, either in the presence or in the absence of S9-mix.

YEAR OF STUDY: not reported

Reliability: (2) valid with restrictions
Equivalent to OECD TG 471, except that was not performed in TA 1535, TA 1537, TA 97 and that only mean number and standard deviation of duplicate plating is presented.

Flag: Critical study for SIDS endpoint

07-JAN-2004 (67)

5.6 Genetic Toxicity 'in Vivo'

Type: other: lethal effects, sex ratio, wing shape modifications
Species: Drosophila melanogaster **Sex:** male/female
Strain: other: 4 different strains, see Test Conditions
Route of admin.: other: through nutrition medium
Exposure period: 6 days
Doses: 0; 1M; 0.5M; 0.4M; 0.2M

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, purity not stated

Remark: The study was designed to investigate the effects of 1,3-dimethylurea and 1,3-diethylurea on four wild lines of Drosophila melanogaster.

Result: Parental generation (F0)/TOXICITY:
1M: 100% lethality of males of the Novosibirsk, Hikone and N72 line. Only 60% lethality was observed in the Suchumi line. In females, 100% lethality was found in the Hikone line, only. Lethality of females of the other lines varied between 60% (Suchumi) and 81% (Novosibirsk).
0.5M: The most sensitive line was Hikone (80% lethality (m); 60% lethality (f)), then N72 (50% lethality (m); 80% lethality (f)). In Suchumi 40% lethality (m) and 60% lethality (f) was found, in Novosibirsk 30% lethality (m) and 40% lethality (f).
0.4M: Toxic effects were only observed in lines Novosibirsk (16.6% lethality (m)) and Hikone (16.6% lethality (m); 33.3%

lethality (f)).
0.2M: no observed toxic effect.

Progeny/SEX RATIO:
At 0.2 and 0.4M, the sex ratio in the F1 generation was found to be different from that of controls (significance levels between 5 and 90%). In F2, and F3 the differences in the sex ratio became smaller.

Progeny/WING SHAPE:
0.2M, F1 (% modified): all below or same as controls, except for Suchumi (m): 1.17 (control 0).
0.2M, F2 (% modified): Suchumi, N72, Novosibirsk (m): below or same as control values; Hikone m: 0.59 (control 0.27), f: 0.53 (control 0.28), Novosibirsk (f): 2.06 (control 0).
0.2M, F3 (% modified): Suchumi (f), N72 (f), Hikone (m) and Novosibirsk: below or same as control; Hikone f: 1.58 (control 0.45), Suchumi m: 0.58 (control 0.39), N72 m: 0.47 (control 0.35).

0.4M, F1 (% modified), only Suchumi and Hikone evaluated: Suchumi and Hikone (m) same as control, Hikone (f) 0.62 (control 0).
0.4M, F2 (% modified), only Hikone evaluated: m 0.58 (control 0.29), f 1.37 (control 0.28).
0.4M, F3 (% modified), only Hikone evaluated: m 0.75 (control 0.86), f 0.77 (control 0.45).

Test condition: TEST ORGANISMS:
Four wild lines of Drosophila melanogaster:
- standard type 72(N72) without signal genes originating from Bratislava,
- line Suchumi and Hikone without signal genes originating from Prague,
- line Novosibirsk without signal genes originating from Leningrad.

TEST SOLUTION:
50 mL of the test solution was thoroughly mixed with 250 mL nutrition medium, and then distributed to 20 test tubes (no further details reported).

TEST PROCEDURE:
The parents were cultivated on a "soil" with the test substance for 6 days. In parallel, a control was cultivated on soil without test substance. On the sixth day following application lethality was evaluated. Progeny was kept up to the F3 generation. The sex ratio and the frequency of Drosophila with various changes on wings was investigated (no further details reported).

STATISTICAL METHOD:
chi-square test, analysis of variance.

YEAR OF STUDY: not reported.

Conclusion: The toxicity was related to the exposure levels with some differences between the different lines. Individual developmental stages reacted differently.

Reliability: (3) invalid
poor documentation; non-standard test system; inhomogeneous experimental groups; no information on mating procedure,

numbers/group, sampling, scoring criteria etc.; study is not appropriate for assessing potential mutagenic effects.
24-DEC-2002 (68)

5.7 Carcinogenicity

Species: rat **Sex:** female
Strain: no data
Route of administration: drinking water
Exposure period: 56 days
Frequency of treatment: daily
Doses: other: see test conditions
Control Group: no

Method: other: see test conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, no further data

Result: No clinical symptoms were observed in groups 1 & 2. Animals in groups 3 & 4 showed reduced drinking water and feed intake. All animals of group 5 died within 4 weeks.
In the group treated with 1,3-dimethylurea or sodium nitrite alone, none of the animals developed tumors. In groups 3 & 4, all animals died between 117 and 432 days after end of treatment. All animals of the respective groups showed tumors which were considered to be malign and were located in the central nervous system, heart, thymus, kidneys and thyroid. No tumors were observed in animals of group 5. No further details are given.
Test condition: Groups of 5 female rats (120 g) were treated for 56 days with 1,3-dimethylurea and/or sodium nitrite under the following conditions:
Group 1: 0.3 % 1,3-dimethylurea in drinking water
Group 2: 0.3 % sodium nitrite in feed
Group 3: 0.1 % 1,3-dimethylurea in drinking water + 0.3 % sodium nitrite in feed
Group 4: 0.3 % 1,3-dimethylurea in drinking water + 0.3 % sodium nitrite in feed
Group 5: 0.9 % 1,3-dimethylurea in drinking water + 0.3 % sodium nitrite in feed
Reliability: (3) invalid
very limited documentation, small group size, limited exposure period, no untreated control group, study is not appropriate to assess carcinogenic potential.
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Species: Syrian hamster **Sex:** female
Route of administration: other: cheek pouches
Exposure period: 3 times per week, 6 weeks (after a 4-week-application of 0.2 % DMBA as initiator)
Doses: 0.1 M

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea from Sigma (USA), purity not stated

Result: Dimethylurea, dimethylacetamide and tetramethylurea uniformly lowered the yield and/or incidences of total tumors, benign plaques, benign hyperkeratotic lesions and

advanced tumors as compared with the yields for the retinyl acetate and croton oil groups, although differences between the effects of the agents were not detectable. The percentage of plaques was increased by dimethylurea, dimethylacetamide and tetramethylurea, suggesting that they inhibited progression of plaques to more advanced tumors.

Test condition: Effect on tomour promotion by retinyl acetate and croton oil
Cheek pouches of female Syrian hamsters were painted three times a week with 7,12-dimethylbenz(a)anthracene (DMBA, 0.2% in dimethylsulfoxide (DMSO)) for 4 weeks, followed by painting with retinyl acetate (0.05M) or croton oil (0.5% in DMSO) alone or each in combination with dimethylacetamide, dimethylurea or tetramethylurea at a concentration of 0.1M for another 6 weeks. Controls were painted with vehicle (DMSO) only. At necropsy all visible tumors were counted and classified according to size and gross morphology, and histopathological examinations were carried out.
10 animals about 1 month old were used per treatment group.

Year of study: not reported.

Conclusion: 1,3-dimethylurea had no effect on the promoting activity of retinyl acetate and croton oil in this model.

Reliability: (3) invalid
Application only in combination with other substances.

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Result: Urea compounds such as 1,3-Dimethylurea may form carcinogenic nitrosoureas with nitrite.

Reliability: (2) valid with restrictions
accepted scientific experience published in many textbooks

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5.8.1 Toxicity to Fertility

Type: other: Reproduction/Developmental Toxicity Screening Test
Species: rat
Sex: male/female
Strain: Wistar
Route of administration: gavage
Exposure Period: approx. 4 weeks
Frequency of treatment: daily
Premating Exposure Period
male: 14 days
female: 14 days
Duration of test: males: 4 weeks; females: until at least 4 days after giving birth
No. of generation studies: 2
Doses: 0; 20; 60; 200 mg/kg bw/day in aqueous solution
Control Group: yes, concurrent vehicle
NOAEL Parental: = 60 mg/kg bw
NOAEL F1 Offspring: = 200 mg/kg bw
other: NOAEL parental for reproductive performance and fertility : = 200 mg/kg bw

Method: other: OECD TG 421(1995)
GLP: yes
Test substance: other TS: 1,3-dimethylurea, purity 99.2 %

Result: F0 (parental) animals:

CLINICAL OBSERVATIONS
- All dose groups: no substance-related clinical signs were observed in male or female parental animals (including the lactation period), and no change in the general behavior was noted.
- Signs of systemic toxicity in the F0 parental animals were confined to the rats of the 200 mg/kg bw/day group and were characterized by a slightly decreased food consumption (both genders), correspondingly lowered mean body weights and impaired body weight gains (both genders). In males, significantly decreased serum glucose levels were found in the high dose group.
- One sperm positive female of the 60 mg/kg bw/day group did not deliver any pups. This was considered to be unrelated to treatment by the study authors due to the isolated occurrence of this finding without a dose-response relationship.

CLINICAL EXAMINATIONS
- 200 mg/kg bw/day: slightly reduced food consumption (with or without attaining statistical significance) in the F0 males during study weeks 0-4 (about 10% below the corresponding control value if calculated for the entire treatment period) and in the F0 females during premating (about 8% below controls) and gestation (about 7% below controls)
- 200 mg/kg bw/day: impaired body weights (BW)/body weight gains (BWC) in the F0 males (BW about 9% below controls; BWC about 37% below controls) during the entire treatment period (weeks 0-4) and in the F0 females during premating (BW about 6% below controls; BWC about 53% below controls), gestation (BW about 6-9% below controls; BWC about 16% below controls) and lactation (BW about 7% below controls; BWC about 6% below controls), achieving statistical significance on some, but not all intervals
- 20; 60 mg/kg bw/day: no substance-related effects on body weights/body weight gains. A statistically significant decrease in food consumption of the 20 mg/kg/day males during premating weeks 1-2 and week 3-4, and the decreased mean body weight gain of this group during weeks 1-2 were not considered as of biological significance since not dose-related.

MALE COHABITATION DATA:
- all dose groups: for all F0 parental males which were placed with females to generate F1 pups, mating was confirmed. The male mating index for all groups was 100%
- Except for one single animal of the 60 mg/kg group, fertility could be confirmed in the scheduled mating interval for all dose groups. The fertility indices therefore varied between 90-100% with no relation to exposure level. The fact that one mid dose male did not generate F1 pups was regarded to be spontaneous in nature and not associated with the treatment of the animals. The macroscopic and microscopic examination of this animal and its mating partner did not reveal any pathological changes.

FEMALE REPRODUCTION AND DELIVERY DATA:
- all dose groups: the female mating index was 100% in all groups
- the mean cohabitation time (duration until sperm was detected) was 3.0 / 3.1 / 2.5 / 2.0 days for the 0; 20; 60 and 200 mg/kg groups, respectively. These values reflected the normal range of biological variation inherent in the strain used
- with the exception of one F0 parental female of the 60 mg/kg/day group, all mated females became pregnant. The fertility indices therefore varied between 90 and 100%. The fact that this female did not become pregnant was regarded to be spontaneous in nature and not substance-related by the authors of the study. The macroscopic and microscopic examination of this animal and its mating partner did not reveal any pathological changes
- the mean duration of gestation was very similar in all groups (between 21.8 and 21.9 days)
- the gestation index was 100% for all groups, indicating that all pregnant females had live F1 pups in their litters.
- implantation was not affected by treatment since the mean number of implantation sites was comparable between all test groups. There were no indications of substance-induced intrauterine embryo-/fetolethality since the postimplantation loss values were not affected.
- the mean number of F1 pups delivered per dam was not affected by the treatment with the substance. The number of liveborn and stillborn pups was comparable between the groups and the live birth index varied between 97 and 99%.

F1 generation pups
- the mean number of delivered F1 pups/dam and the percentage of liveborn pups were not affected by the administration of the test substance. The differences observed are without any biological relevance and do not show a dose-response relationship (10.1 / 11.4 / 11.6 / 9.2 pups per dam for 0; 20; 60; 200 mg/kg groups, respectively).

- there were no substance-related differences concerning pup viability and mortality (viability indices for days 0-4 p.p.: 84% / 98% / 99% / 98% at 0, 20, 60, 200 mg/kg bw).
- the sex ratio of live F1 pups on the day of birth and on day 4 p.p. did not show any substantail differences between controls and treated groups

CLINICAL PATHOLOGY
- all dose groups: no changes were observed in serum enzyme parameters
- dose-dependent, statistically significantly decreased glucose level were found in the serum of the males of all dose groups. The decreases in the mid- and low-dose group were, however, within the range of the normal values of the strain used.

GROSS AND HISTOPATHOLOGICAL FINDINGS/ CLINICAL PATHOLOGY
- no substance-related effects in F0 males and F0 females. One female of the low dose group had an ovarian cyst, two females (one of the control group, one of the high dose group) showed paraovarian cysts. Histopathology of kidneys, testes, epididymides and ovaries did not reveal any

treatment related pathological changes. In all treated males the stages VII or VIII of the spermatogenic cycle could be identified easily. There were no aberrations in the morphological appearances of the testicular architecture between the control and the treatment groups. In particular, there was no retention of step 19 spermatids.
- no substance-related adverse effects in the F1 pups.

ANALYSES:
The concentrations of the test solutions were verified analytically (90.5% - 99.8% of target concentrations).

Test condition: TEST ANIMALS: 10 male and 10 female healthy Wistar (CrlGlxBrlHan:W) rats per group; supplier: Charles River Wiga GmbH, Sulzfeld, Germany.
Acclimatization period: 6 days.
Age (at beginning of treatment): 76-83 days.
Weights (at beginning of treatment): males 238.7g (214.9-262.2g), females: 173.0g (160.1-187.5g).
Females were nulliparous and non-pregnant at the beginning of the study. According to a written statement from the breeder, male and female animals were derived from different litters. During the study the rats were housed individually in wire mesh DKIII cages with the exception for the overnight mating when the females were put into the cages of the males. From day 18 p.c. until sacrifice, the pregnant animals and their litters were housed in makrolon type MIII cages. Pregnant females were provided with nesting material (cellulose wadding) toward the end of pregnancy.

The animals were fed standard Kliba laboratory diet ad libitum. Drinking water was supplied from water bottles ad libitum.

TEST SUBSTANCE ANALYSES:
purity, stability, and concentrations in the test solution.

ADMINISTRATION / EXPOSURE: The test substance was administered as an aqueous solution at a standard dose volume of 10 mL/kg body weight. The control groups were dosed with the vehicle only (doubly distilled water). The test substance was administered to the parental animals once daily by oral gavage at approximately the same time of each day. The calculation of the volume administered was based on the most recent individual body weight. The F0 adult males were sacrificed about 4 weeks after the first test substance administration. Females were allowed to litter and rear their pups until day 4 after parturition (p.p.). Thereafter, the pups and the F0 generation female parental animals were sacrificed. The treatment lasted up to one day prior to sacrifice.

MATING PROCEDURES: Fourteen days after the beginning of treatment, F0 male and female animals were mated 1:1 for a maximum of two weeks to produce a litter. Mating pairs were from the same dose group.

PARAMETERS ASSESSED DURING STUDY: The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances; this included determinations of the number of

implantations and the calculation of the postimplantation loss.
Food consumption of the F0 parents was determined regularly during premating, after the mating period and - in dams - during gestation and lactation periods.
In general, body weights of F0 parents were determined once weekly. However, during gestation and lactation F0 females were weighed on days 0, 7, 14 and 20 of gestation, on the day of parturition, and on days 4 and, if still alive, on day 7 after birth.
The pups were sexed and were weighed on the day after birth and on day 4 post partum. Their viability was recorded.
Clinicochemical examinations were carried out in the adult males and females at the end of the administration period.
Clinical chemistry parameters were determined in 10 animals/group and sex at the end of the application period and included 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, and magnesium.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
All F0 parental animals were assessed by full gross pathology. All F0 parental were subjected to a histopathological examination, special attention being paid to the organs of the reproductive system. The following organs or tisues were fixed in 4% formaldehyde solution for microscopic evaluation: vagina, cervix uteri, ovaries, uterus, oviducts, seminal vesicles, coagulating glands, prostate gland, pituitary gland, liver, kidneys, all gross lesions, target organs. Testes and Epididymides were fixed in Bouins`s solution.
Uteri and ovaries were removed (including the uteri of apparently non-pregnant animals) to determine the number of implantation sites according to the method of Salewski (1964).
All surviving pups were sacrificed by CO2 on day 4 p.p. and were examined macroscopically at necropsy for external and visceral findings. In addition, all stillborn pups and those that died before schedule, were examined externally, eviscerated and their organs were assessed macroscopically. If there were notable findings or if abnormalities were found in the daily clinical observation of the animals after their delivery, the affected animals were examined additionally using appropriate methods (eg skeletal staining according to modified Dawsons`s method (1926)).

ORGAN WEIGHTS:
The following weights were determined from all animals sacrificed at schedule:
- (anesthetized) animal weights
- testes weights
- epididymides weights
- kidneys weights

STATISTICAL METHODS:
Food consumption* (parental animals), body weight and body

weight change (parental animals and pups; for the pup weights, the litter means were used), number of mating days, duration of gestation, number of pups delivered per litter: Simultaneous comparison of all dose groups with the control group using the DUNNETT-test (two-sided) for the hypothesis of equal means ($p < 0.05$, $p < 0.01$)(DUNNETT, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121; DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482 - 491

Male and female mating index, male and female fertility index, gestation index, females with liveborn pups, females with stillborn pups, females with all stillborn pups, live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, viability index, number of litters with affected pups at necropsy: Pairwise comparison of each dose group with the control group using FISHER'S EXACT test for the hypothesis of equal proportions ($p < 0.05$; $p < 0.01$) Siegel S. (1956): Non-parametric statistics for behavioural sciences. McGraw-Hill New York

Proportions of affected pups per litter with necropsy observations: Pairwise comparison of each dose group with the control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians ($p < 0.05$; $p < 0.01$) Nijenhuis, A.; Wilf, H.S. (1978): Combinatorial Algorithms. Academic Press New York, 32-33; Hettmansperger, T.P. (1984); Statistical Inference based on Ranks. John Wiley & Sons New York, 132-142

* Note: For the parameter food consumption the "mean of means" was calculated. The "mean of means" values allow a rough estimation of the total food consumption during the different time intervals (premating, gestation and/or lactation); they are not exactly precise values, because the size of the intervals taken for calculation may differ (especially during gestation and lactation periods). For the "mean of means" values no statistical analysis was performed.

YEAR OF STUDY CONDUCT: 2002

Conclusion: The administration of the test substance had no adverse effects on reproductive performance or fertility of the F0 parental animals. Mating behaviour, conception, gestation, parturition and lactation as well as the determined sexual organ weights, and gross and histopathological findings of these organs were similar between the substance-treated rats and the corresponding controls.

Reliability: (1) valid without restriction
reproduction/developmental toxicity screening test

Flag: Critical study for SIDS endpoint

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5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: gestation day 6 to 15
Frequency of treatment: daily
Duration of test: until day 20 post coitum
Doses: 0; 30; 100; 200 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 30 mg/kg bw
NOAEL Teratogenicity: = 200 mg/kg bw
NOAEL Fetotoxicity : = 30 mg/kg bw
NOAEL Embryotoxicity : = 100 mg/kg bw

Method: other: OECD Guideline 414(1981)
GLP: yes
Test substance: other TS: 1,3-dimethylurea, purity >= 96%

Result: MATERNAL EFFECTS:
200 mg/kg bw/day: clear signs of maternal toxicity were observed as distinctly reduced food consumption of the dams during the treatment period (days 6-15 p.c.; -34%), markedly lower mean body weights of the dams in comparison to the controls, negative mean weight gains on day 6-10 p.c., and diminished corrected mean body weight gains (-37%). Piloerection on 11 dams during the treatment period about 2-7 hours after the test substance administration.
100 mg/kg bw/day: overt signs of maternal toxicity in form of reduced food consumption during the whole treatment period (days 6-15 p.c.; -21%), lower mean body weights, distinctly impaired mean weight gains on day 6-10 p.c. (-66%), as well as diminished corrected mean body weight gains (-26%). There were no clincal signs of toxicity.
30 mg/kg bw/day: no substance-induced findings on dams.

REPRODUCTIVE DATA:
There were no differences between the groups in conception rate (92; 92; 84; 92% in the 0; 30; 100 and 200 mg/kg bw/day groups, respectively), 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 or sex ratio of fetuses.

EMBRYO/FETAL DATA:
200 mg/kg bw/day: embryo-/fetotoxicity was observed in this group in form of reduced mean placental weights (-13%) and fetal body weights (-8%). The malformations rate was not increased. However, the numbers of fetuses with one soft tissue variation (hydroureter) and with indications of delayed ossification (incomplete ossification or reduced size of sterneba(e)) were increased.
100 mg/kg bw/day: Increased incidence of one fetal soft tissue variation (hydroureter). No teratogenic effects were recorded.
30 mg/kg bw/day: no substance-induced findings on fetuses.

External malformations were recorded for 1 control fetus (cleft palate) and for one high dose fetus (brachygnathia, cleft palate and aglossia). These or very similar

malformations were also present in the historical laboratory control data at a low frequency and were therefore assessed as being of spontaneous origin. Soft tissue examinations revealed malformations of the heart (dilatation of both or one ventricle(s), dextrocardia, septal defects) in all groups except the low dose without dose relationship. Furthermore, hydrocephaly was found in one low dose fetus, while a unilobular lung occurred in one intermediate and one high dose fetus each. Due to the fact that no statistically significant differences were found between the groups, and no dose-relationship existed, and/or because several of the aforementioned effects (i.e. dextrocardia, hydrocephaly and dilatation of heart ventricles) were also present in the historical laboratory control data at a low incidence, these malformations were regarded as being of spontaneous nature by the authors.
In all groups two soft tissue variations occurred (dilated renal pelvis and hydroureter), attaining statistical significance in the 100 and 200 mg/kg bw/day groups. If compared with the historical control data it is obvious that the increased occurrence of dilated renal pelvis was a sponstaneous effect and not related to treatment with the substance. All relevant values (fetal incidence 27 and 35% in 100 and 200 mg/kg bw/day groups, respectively; litter incidence 80% or 91%) were within the range of biological variation (fetal incidence 7.1 - 66.9%, litter incidence 36.4 - 100%) and the concurrent control values were rather low (fetal incidence 16%, litter incidence 52%). The increase in hydroureters, however, was induced by the test substance with incidences clearly outside the historical control ranges (8.2; 9.4; 19; 27% in control; 30; 100; 200 mg/kg bw/day groups, respectively).

ANALYSES confirmed stability and target concentrations of the test solutions.

Test condition: TEST ORGANISMS: sexually mature, virgin Wistar rats (Chbb:THOM(SPF)), supplied by Karl Thomae, Biberach/Germany, which were free from clinical signs of disease.
Acclimatization period: at least 5 days, age at study begin (day 0): 75-84 days, weight at study begin (day 0): 232 g.
During the study the rats were housed singly in type DKIII stainless steel wire mesh cages and fed standard Kliba 343 diet and water ad libitum.

MATING PROCEDURE: 25 females/group were mated from about 16:00 hours to about 7:30 hours on the following day. If sperm were detected microscopically in the vaginal smear in the morning, the animals were considered to be fertilized. This day was designated "day 0".

ANALYSES: purity, homogeneity and stabilty of test substance, concentrations and stability of test solutions. Food and drinking water.

ADMINISTRATION / EXPOSURE:
The test substance was administered as aqueous solution to 21-23 pregnant rats per group by gavage in the morning; a control group was dosed with doubly distilled water.
A standard dose volume of 10 mL/kg bw was used. The calculation of the volume adminsitered was based on the

individual body weight determined at the beginning of the administration period (day 6 p.c.). Each day, the test substance solutions were freshly prepared shortly before the administration.

PARAMETERS ASSESSED DURING STUDY:
The animals were examined for clinical symptoms at least once a day.
Food consumption and body weights were recorded regularly throughout the study period. All animals were weighed on days 0,1,3,6,8,10,13,15,17,and 20 p.c. The state of health of the animals was checked at least once each day.

ORGANS/PARAMETERS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
on day 20 p.c., all surviving females were sacrificed and assessed by gross pathology. In additon, the following was recorded:
- weight of unopened uterus
- number of corpora lutea
- number and distribution of implantation sites, classified as live fetuses, dead implantations (early resorptions, late resorptions, dead fetuses).
The corrected body weight gain was calculated (terminal body weight on day 20 p.c. minus weight of the unopened uterus minus body weight on day 6 p.c.), as were conception rate, and pre- and postimplantation losses.
The fetuses were dissected from the uterus, sexed, weighed and further investigated for any external, soft tissue and/or skeletal findings. Furthermore, the viability of the fetuses and the condition of the placentae, the umbiical cords, the fetal membranes and fluids were examined.
Individual placental weights were recorded. Half of the fetuses per dam were placed in ethyl alcohol and the others were placed in Bouin`s solution for fixation and further evaluation. Soft tissue examination was performed according to the method described by Barrow and Taylor (J. Morph. 127, 291-306, 1969), skeletal examinations were made under a stereo-microscope after staining according to Dawson's method (Stain Technol 1, 123, 1926).

STATISTICAL EVALUATION: Dunnett`s t-test for body weight, body weight change, corrected body weight gain, weight of the uterus, weight of fetuses, weight of placentae, corpora lutea, implantations, pre-and postimplantation losses, resorptions, live fetuses.
Fisher`s Exact Test for conception rate, mortality of dams, all fetal findings.
Significance levels set at $p < 0.05$ and $p < 0.01$.

YEAR OF STUDY: 1991

Conclusion: 1,3-Dimethylurea induced clear signs of maternal toxicity at 100 and 200 mg/kg bw/day in a dose related manner. At these dose levels some signs of embryo-/fetotoxicity occurred, but no indications of any teratogenic effect were noted.

Reliability: (1) valid without restriction
Full guideline and GLP-compliant study

Flag: Critical study for SIDS endpoint

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Species: rat **Sex:** male/female
Strain: Wistar
Route of administration: gavage
Exposure period: approx. 4 weeks
Frequency of treatment: daily
Duration of test: males: 4 weeks; females: until at least 4 days after giving birth
Doses: 0; 20; 60; 200 mg/kg bw/day in aqueous solution
Control Group: yes, concurrent vehicle
NOAEL Teratogenicity: = 200 mg/kg bw
other: NOAEL developmental toxicity : = 200 mg/kg bw
other: NOAEL parental toxicity : = 60 mg/kg bw

Method: other: OECD TG 421(1995)
GLP: yes
Test substance: other TS: 1,3-dimethylurea, purity 99.2%

Result: F0 (parental) animals:
CLINICAL EXAMINATIONS
- 200 mg/kg bw/day: slightly reduced food consumption (with or without attaining statistical significance) in the F0 males during study weeks 0-4 (about 10% below the corresponding control value if calculated for the entire treatment period) and in the F0 females during premating (about 8% below controls) and gestation (about 7% below controls)
- impaired body weights (BW)/body weight gains (BWC) in the F0 males (BW about 9% below controls; BWC about 37% below controls) during the entire treatment period (weeks 0-4) and in the F0 females during premating (BW about 6% below controls; BWC about 53% below controls), gestation (BWC about 16% below controls) and lactation (BWC about 6% below controls), achieving statistical significance on some, but not all intervals

ORGAN WEIGHTS/ GROSS AND HISTOPATHOLOGICAL FINDINGS
- no substance-related effects in F0 males and F0 females

CLINICAL PATHOLOGY
- statistically significantly decreased glucose level in the serum of the males
- no substance related effects in FO males and FO females

F1 pups:

CLINICAL EXAMINATIONS
- no substance-related adverse effects in the pups

GROSS FINDINGS:
The macroscopic examination of all pups at necropsy revealed only spontaneous findings. These findings were restricted to single pups of the low- and high-dose groups. Macroglosia in combination with cleft palate occurred in three low dose pups from one litter and in three high dose pups from one litter. As these findings were not dose-related, and as they occur occasionally in controls of the strain of rats used and since they were restricted to only one litter each, they were considered to be spontaneous in nature by the study authors.

One pup of the high-dose group showed an infarct of the liver, and one pup of the low-dose group showed hemorrhagic testis. These two findings were also considered as spontaneous in nature by the study authors.

ANALYTICS:
The concentrations of the test solutions were verified analytically (90.5% - 99.8% of target concentrations).

Test condition: TEST ANIMALS: 10 male and 10 female healthy Wistar (CrlGlxBrlHan:W) rats per group; supplier: Charles River Wiga GmbH, Sulzfeld, Germany.
Acclimatization period: 6 days.
Age (at beginning of treatment): 76-83 days.
Weights (at beginning of treatment): males 238.7g (214.9-262.2g), females: 173.0g (160.1-187.5g).
Females were nulliparous and non-pregnant at the beginning of the study. According to a written statement from the breeder, male and female animals were derived from different litters. During the study the rats were housed individually in wire mesh DKIII cages with the exception for the overnight mating when the females were put into the cages of the males. From day 18 p.c. until sacrifice, the pregnant animals and their litters were housed in makrolon type MIII cages. Pregnant females were provided with nesting material (cellulose wadding) toward the end of pregnancy.

The animals were fed standard Kliba laboratory diet ad libitum. Drinking water was supplied from water bottles ad libitum.

TEST SUBSTANCE ANALYSES:
purity, stability, and concentrations in the test solution.

ADMINISTRATION / EXPOSURE: The test substance was administered as an aqueous solution at a standard dose volume of 10 mL/kg body weight. The control groups were dosed with the vehicle only (doubly distilled water). The test substance was administered to the parental animals once daily by oral gavage at approximately the same time of each day. The calculation of the volume administered was based on the most recent individual body weight. The F0 adult males were sacrificed about 4 weeks after the first test substance administration. Females were allowed to litter and rear their pups until day 4 after parturition (p.p.). Thereafter, the pups and the F0 generation female parental animals were sacrificed. The treatment lasted up to one day prior to sacrifice.

MATING PROCEDURES: Fourteen days after the beginning of treatment, F0 male and female animals were mated 1:1 to produce a litter. Mating pairs were from the same dose group.

PARAMETERS ASSESSED DURING STUDY: The parents' and the pups' state of health was checked each day, and parental animals were examined for their mating and reproductive performances; this included determinations of the number of implantations and the calculation of the postimplantation loss.
Food consumption of the F0 parents was determined regularly

during premating, after the mating period and - in dams - during gestation and lactation periods.
In general, body weights of F0 parents were determined once weekly. However, during gestation and lactation F0 females were weighed on days 0, 7, 14 and 20 of gestation, on the day of parturition, and on days 4 and, if still alive, on day 7 after birth.
The pups were sexed and were weighed on the day after birth and on day 4 post partum. Their viability was recorded.
Clinicochemical examinations were carried out in the adult males and females at the end of the administration period.
Clinical chemistry parameters were determined in 10 animals/group and sex at the end of the application period and included 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, and magnesium.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
All F0 parental animals were assessed by full gross pathology. All F0 parental were subjected to a histopathological examination, special attention being paid to the organs of the reproductive system. The following organs or tisues were fixed in 4% formaldehyde solution for microscopic evaluation: vagina, cervix uteri, ovaries, uterus, oviducts, seminal vesicles, coagulating glands, prostate gland, pituitary gland, liver, kidneys, all gross lesions, target organs. Testes and Epididymides were fixed in Bouins`s solution.
Uteri and ovaries were removed (including the uteri of apparently non-pregnant animals) to determine the number of implantation sites according to the method of Salewski (1964).
All surviving pups were sacrificed by CO2 on day 4 p.p. and were examined macroscopically at necropsy for external and visceral findings. In addition, all stillborn pups and those that died before schedule, were examined externally, eviscerated and their organs were assessed macroscopically. If there were notable findings or if abnormalities were found in the daily clinical observation of the animals after their delivery, the affected animals were examined additionally using appropriate methods (eg skeletal staining according to modified Dawsons`s method (1926)).

ORGAN WEIGHTS:
The following weights were determined from all animals sacrificed at schedule:
- (anesthetized) animal weights
- testes weights
- epididymides weights
- kidneys weights

STATISTICAL METHODS:
Food consumption* (parental animals), body weight and body weight change (parental animals and pups; for the pup weights, the litter means were used), number of mating days, duration of gestation, number of pups delivered

per litter: Simultaneous comparison of all dose groups with the control group using the DUNNETT-test (two-sided) for the hypothesis of equal means ($p < 0.05$, $p < 0.01$)(DUNNETT, C.W. (1955): A multiple comparison procedure for comparing several treatments with a control. JASA, Vol. 50, 1096-1121; DUNNETT, C.W. (1964). New tables for multiple comparisons with a control. Biometrics, Vol. 20, 482 - 491

Male and female mating index, male and female fertility index, gestation index, females with liveborn pups, females with stillborn pups, females with all stillborn pups, live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, viability index, number of litters with affected pups at necropsy: Pairwise comparison of each dose group with the control group using FISHER'S EXACT test for the hypothesis of equal proportions ($p < 0.05$; $p < 0.01$) Siegel S. (1956): Non-parametric statistics for behavioural sciences. McGraw-Hill New York

Proportions of affected pups per litter with necropsy observations: Pairwise comparison of each dose group with the
control group using the WILCOXON-test (one-sided) for the hypothesis of equal medians ($p < 0.05$; $p < 0.01$) Nijenhuis, A.; Wilf, H.S. (1978): Combinatorial Algorithms. Academic Press New York, 32-33; Hettmansperger, T.P. (1984); Statistical Inference based on Ranks. John Wiley & Sons New York, 132-142

* Note: For the parameter food consumption the "mean of means" was calculated. The "mean of means" values allow a rough estimation of the total food consumption during the different time intervals (premating, gestation and/or lactation); they are not exactly precise values, because the size of the intervals taken for calculation may differ (especially
during gestation and lactation periods). For the "mean of means" values no statistical analysis was performed.

YEAR OF STUDY CONDUCT: 2002

Conclusion: The administration of 1,3-dimethylurea had no adverse effects on the development in the progeny of the F0 parents up to and including the highest exposure group. The observable, marginal differences between the pups of the control group and the progeny of the substance-treated groups reflected the usual fluctuations inherent in the strain of rats used for the present study.

Signs of general, systemic toxicity in the F0 parental animals were confined to the rats of the 200 mg/kg bw/day group. Toxicity was characterized by a slightly decreased food consumption (both genders), correspondingly lowered mean body weights and impaired body weight gains (both genders) and significantly decreased serum glucose levels in the males.

Reliability: (2) valid with restrictions
reproduction/developmental toxicity screening test

Flag: Critical study for SIDS endpoint

07-JAN-2004 (75)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: on day 12 or 14 of gestation
Frequency of treatment: single treatment
Duration of test: until day 20 of pregnancy
Doses: 2000 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Teratogenicity: = 2000 mg/kg bw
LOAEL Fetotoxicity : = 2000 mg/kg bw

Method: other: see Test Conditons
GLP: no data
Test substance: other TS: 1,3-dimethylurea from commercial source (Tokyo Chemical Ind. Co. Ltd.); no further details given

Remark: 11 compounds related to urea were used in this study; dose corresponded to about half the LD50 in this species

Result: 1,3-dimethylurea caused a decrease in the weight of fetuses:
Mean number of Implants: 13.7 +/- 4.1 (n.s.)*
Mean number of live fetuses: 12.7 +/- 4.2 (n.s.)
% fetal resorptions: 7.3 (n.s.)
Mean fetal weight: 3354 +/- 218 mg (significantly different from control at $p < 0.05$)

% fetuses malformed: 5.3% (n.s.)

*(n.s.) = not significantly different from control

MATERNAL TOXICITY: No toxic signs such as depression, diarrhea etc. were observed in female, non-pregnant rats gavaged with 2000 mg/kg bw in a pre-study. No further details available.

Test condition: TEST ORGANISMS: Wistar rats, 15 weeks of age, purchased from CLEA, Japan. Housed in a controlled environment at 24 +/- 1 °C and 55 +/- 5% humidity, maintained on laboratory chow (Oriental Yeast MF) and given tap water ad libitum.
Females were paired overnight with a male. The follwoing morning they were examined for the presence of vaginal plug and designated as being in day 0 of pregnancy when the plug was found.
TEST SUBSTANCE ADMINISTRATION: orally as aqueous solution at a dosing volume of 10 mL/kg.
NUMBER OF DAMS EXPOSED TO TEST SUBSTANCE: 6
CONTROLS: vehicle control (distilled water, 6 dams), urea (2000 mg/kg bw; 4 dans) and thiourea (1000; 2000 mg/kg bw; 3 dams/group) were used as negative controls, and ethylenethiourea (250 mg/kg bw; 6 dams treated on day 12 p.c, 5 dams treated on day 14 p.c.) was used as a positive control.
NECROPSY: Animals were killed on day 20 of pregnancy, and the number of implants and live and dead fetuses were counted. Living fetuses from each litter were divided into two groups after they were weihged individually and examined for gross abnormalieties. One group which was derived from the right uterine horn was processed for skeletal examinations according to the staining method of Inouye (Cong. Anom 16, 171-173, 1976). The other group of fetuses was fixed in Bouin's solution and examined for visceral anomalies according to the method described by Barrow and

Taylor (J. Morphol 127, 291-306, 1969).
STATISTICAL METHOD: Differences in numbers of implants and live fetuses and fetal body weights between treated and control groups were analyzed by the Student's t test. The litter was considered to be the experimental unit for these analyses. Differences in resorption and malformation incidences, assessed on the basis of number o affected fetuses, were analyzed by the Chi-square test.
YEAR OF STUDY: not reported.

Reliability: (3) invalid
small group size, only single treatment, limited documentation

17-JUN-2003 (78) (79) (45)

Species: rat **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: day 6 to 15 p.c.
Frequency of treatment: daily
Duration of test: until day 16 of gestation
Doses: 0; 150; 300; 450 mg/kg bw/day
Control Group: yes, concurrent vehicle
LOAEL Maternal Toxicity : = 150 mg/kg bw
LOAEL Fetotoxicity : = 450 mg/kg bw
LOAEL Embryotoxicity : = 300 mg/kg bw

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea, no further data

Remark: The aim of this study was to determine the maternal toxicity and to find a dose that could be used as the highest dosage for a full-scale prenatal toxicity study. Therefore, the dams were sacrificed on the day following the last substance application, i.e. day 16 p.c.

Result: All dose groups exhibited clear signs of maternal toxicity in the form of impaired food consumption and reduced body weight change.
FOOD INTAKE: In the 450 and 300 mg/kg bw/day groups, Food intake was approx. 37% and 31% lower throughout the treatment period. In the 150 mg/kg bw/day gorup, food intake was still statistically signifcantly lower than that of controls on days 6-13 p.c. (no quantitative data available)

BODY WEIGHTS/BODY WEIGHT GAINS: Mean body weights were statistically significantly reduced at 450 mg/kg bw/day (-11%) and 300 mg/kg bw/day (no quantitative data reported). In the 150 mg/kg bw/day group, body weights were still lower than in controls on days 10 and 13 p.c. At 450 mg/kg bw/day dams lost body weight on days 6-10 p.c. At 300 mg/kg bw/day the animals gained markedly less body weight, and the corrected body weight gain was statistically significantly lower than that of the control group. At 150 mg/kg bw/day impaired weight gain and reduced corrected body weight gain were still found during the treatment period.

Clinical signs (squatting posture, piloerection) were found in nearly all animals of the 450 mg/kg bw/day group. At 300 mg/kg bw/day, 5 dams showed squatting position and all dams had piloerection during the treatment period. No clinical signs were reported for the 150 mg/kg bw/day group.

The clinical chemistry and hematology parameters were not reported.

From the organ weights determined, only the absolute liver weights were found to be reduced in the 450 and 300 mg/kg bw groups.

At 450 mg/kg bw/day statistically significantly reduced mean placental and fetal body weights were found. At 300 mg/kg bw/day the mean placental weights were reduced.
Taking into account the limited possibilities of fetal examination, in none of the doses chosen any adverse effects were noted on the reproduction-specific parameters or the fetuses.

Test condition: Pregnant Wistar rats (max. 10/group) were treated with the test substance daily from day 6 to day 15 p.c. by gavage and were sacrificed on day 16 p.c. A group of sham treated animals served as control.
Shortly before sacrifice, blood and urine samples were taken for hematological and clinico-chemical examinations. At necropsy liver, kidneys and uterus (unopened) were weighed and the dams assessed by gross pathology. The fetuses were dissected from the uterus and weighed. Due to the study design, only a rough and very limited external examination of the fetuses was possible at necropsy.

Reliability: (4) not assignable
secondary citation; preliminary study (range-finder)

07-JAN-2004 (80)

Species: mouse **Sex:** female
Strain: ICR
Route of administration: gavage
Exposure period: on day 10 of gestation
Frequency of treatment: single treatment
Duration of test: until day 18 of pregnancy
Doses: 2000 mg/kg bw
Control Group: yes, concurrent vehicle
LOAEL Fetotoxicity : = 2000 mg/kg bw
LOAEL Teratogenicity : = 2000 mg/kg bw

Method: other: see Test Conditions
GLP: no data
Test substance: other TS: 1,3-dimethylurea from commercial source (Tokyo Chemical Ind. Co. Ltd.); no further details given

Remark: 11 compounds related to urea were used in this study
Historical spontaneous malformation rates among ICR mice is reported as 5.4 - 6.8 % (Harris et al., 1980, J. Toxicol. Environ. Health 6, 155-165).

Result: Dose corresponded to half the LD50 in rats. 1,3-Dimethylurea induced an increase in fetal resorptions and a decrease in the fetal weights. It also induced cleft palate and fusion of caudal vertebrae in eight fetuses from five dams and in 12 fetuses from eight dams, respectively:
Mean number of Implants: 13.0 +/- 2.3 (n.s.)*
Mean number of live fetuses: 11.2 +/- 2.3 (n.s.)
% fetal resorptions: 14.0 (significantly different from controls at $p < 0.05$)

Mean fetal weight: 1286 +/- 81 mg (significantly different

from
control at p < 0.05)
% fetuses malformed: 6.5% (significantly different from control at p < 0.01)
*(n.s.) = not significantly different from control.

The malformation rate in the vehicle control was reported as 0.9%.

Toxicity of the test compound was determined in a pre-test with non-pregnant females. In this test, no clinical signs of toxicity were noted after a single oral dose of 2000 mg/kg bw. No further details available.

Test condition: TEST ORGANISMS: ICR mice, 8 weeks of age, purchased from CLEA, Japan. Housed in a controlled environment at 24 +/- 1 °C and 55 +/- 5% humidity, maintained on laboratory chow (Oriental Yeast MF) and given tap water ad libitum.
Females were paired overnight with a male. The follwoing morning they were examined for the presence of vaginal plug and designated as being in day 0 of pregnancy when the plug was found.
TEST SUBSTANCE ADMINISTRATION: orally as aqueous sulution at a dose volume of 10 mL/kg.
NUMBER OF DAMS EXPOSED TO TEST SUBSTANCE: 11
CONTROLS: vehicle control (distilled water, 17 dams)
NECROPSY: Animals were killed on day 18 of pregnancy, and the number of implants and live and dead fetuses were counted. Living fetuses from each litter were divided into two groups after they were weihged individually and examined for gross abnormalieties. One group which was derived from the right uterine horn was processed for skeletal examinations according to the staining method of Inouye (Cong. Anom 16, 171-173, 1976). The other group of fetuses was fixed in Bouin's solution and examined for visceral anomalies according to the method described by Barrow and Taylor (J. Morphol 127, 291-306, 1969).
STATISTICAL METHOD: Differences in numbers of implants and live fetuses and fetal body weights between treated and control groups were analyzed by the Student's t test. The litter was considered to be the experimental unit for these analyses. Differences in resorption and malformation incidences, assessed on the basis of number o affected fetuses, were analyzed by the Chi-square test.
YEAR OF STUDY: not reported.

Reliability: (3) invalid
small group size, only single treatment

17-JUN-2003 (78) (79) (45)

Species: rat **Sex:**
Strain: no data
Route of administration: i.p.
Exposure period: single injection on day 13 p.c.
Doses: 1000 mg/kg bw
Control Group: no data specified
LOAEL Teratogenicity : = 1000 mg/kg bw
Result: normal development in 2/3, malformation of posterior extremities in 1/3; no further details provided

Method: other: no data
GLP: no

Test substance: other TS: 1,3-dimethylurea (Merck-Schuchardt), no further data

Reliability: (4) not assignable
secondary citation
17-JUL-2003 (81)

Species: mouse **Sex:**
Strain: no data
Route of administration: i.p.
Exposure period: single injection on day 11 p.c.
Doses: 1000 mg/kg bw
Control Group: no data specified
Result: no adverse effect on development

Method: other: no data
GLP: no data
Test substance: other TS: 1,3-dimethylurea (Merck-Schuchardt), no further data

Reliability: (4) not assignable
secondary citation; insufficient detail to judge on validity
17-JUL-2003 (81)

Species: rat **Sex:** female
Route of administration: s.c.
Exposure period: on day 13 or 14 p.c.
Frequency of treatment: single treatment
Doses: 1000 mg/kg bw
Control Group: no
LOAEL Teratogenicity : = 1000 mg/kg bw
LOAEL Fetotoxicity : = 1000 mg/kg bw

Method: other: see Test Conditions
GLP: no
Test substance: other TS: 1,3-dimethylurea, purified (melting poing 106-107 °C)

Result: 1,3-dimethylurea was reported to produce teratogenic and toxic effects in the rat fetus after a single subcutaneous dose of 1000 mg/kg:
- Treatment of 4 dams on day 13 p.c. resulted in a total of 39 implantations. 25 fetuses had normal development, 3 showed "toxic lesions" (not specified), and 7 had "malformations" (not specified). 2 post-implantation losses occurred after the administration of the test substance.
- Treatment of 3 dams on day 14 p.c. resulted in a total of 33 implantations. Only 4 fetuses showed "normal development", 2 had "toxic lesions" (not specified), and 24 had "malformations" (not specified). Deaths of one embryo and one fetus occurred after the administration of the test substance.

The authors describe skeletal accessories of hind limbs and kinked tail as typical manifestations of teratogenicity for the investigated class of substances (1,3-dimethylurea, trimethylurea, tetramethylurea). "Toxic effects" observed after the administration of 1,3-dimethylurea, trimethylurea or tetramethylurea included umbilical hernia, hydrops, and growth retardations.
SIGNS OF MATERNAL TOXICITY: not reported.

Test condition: TEST ANIMALS: CD-1 or BDIX rats from own breeding station, fed with commercial standard diet Altromin M6 and water ad

libitum.
NUMBER OF ANIMALS: 4 dams were treated on day 13 p.c, 3 dams were treated on day 14 p.c.
EXPOSURE TO TEST SUBSTANCE:
single administration at midday on gestation days 13 or 14. Vehicle not reported. Route of exposure not specifically mentioned, presumably subcutaneous.
PARAMETERS ASSESSED: Fetal malformations, fetal variations, and fetotoxic effects.
Fetuses underwent necropsy, and were microscopically examined according to the method described by Dawson.
YEAR OF STUDY: not reported.

Reliability: (3) invalid
limited documentation; small number of animals, only one dose level, unphysiological route of exposure; no negative control

07-MAR-2003 (82) (48)

Species: other: interaction with nitrite **Sex:**

Result: Simultaneous treatment of pregnant rats and mice with sodium nitrite (0.5-0.75% in drinking water on days 11-15 of gestation) and 1,3-dimethylurea (1000 mg/kg bw intraperitoneally on day 11 or 13 of gestation) produced the same teratogenic effects as treatment with the nitrosylated homologs of these methylureas.

Reliability: (4) not assignable
insufficient details reported to judge on validity

29-DEC-2002 (81)

Species: other: rat brain cells in vitro **Sex:**

Test substance: other TS: 1,3-dimethylurea from Aldrich Chemical, no details on purity given

Result: no effect on neuronal or non-neuronal fetal rat-brain cells growing together in monocell layers was observed.

Test condition: Primary monolayer cultures of neuronal and non-neuronal cells were prepared from dissociated foetal rat brains. After the cells had been cultured for 3 days, the supernatant medium was discarded and replaced by fresh medium containing or not containing the test substances.
Chemicals were tested at concentrations of 0.5, 1 and 2 mM in the medium. The cells cultures were examined daily for cell death and for inhibited outgrowth of neurites and fascicles for 3 days and the test was then terminated.
In this study 109 chemicals were used. The agreement between the neuroteratogenic potential in vivo, as reported in the literature, and the cytotoxicity data obtained in this study was very good for 82 chemicals, reasonable for 10, poor for 4 and undetermined for another 4.

Reliability: (3) invalid
non-standard and non-validated test system.

25-JUN-2003 (83)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: No data available.
Flag: Critical study for SIDS endpoint
10-OCT-2000

5.11 Additional Remarks

Type: other: oxygen radical scavenger function

Result: The oxygen radical scavengers catalase, superoxide dismutase and N, N'-dimethylurea modulated the photoclastogenic and phototoxic effects of three fluoroquinolones (lomefloxacin, fleroxacin, ciprofloxacin).

29-DEC-2002 (84)

Type: other: scavenger function

Result: 1,3-dimethylurea may act as radical scavenger.

03-NOV-2002 (85)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Safe Handling: No special measures necessary provided product is used correctly. Avoid dust formation.
Storage Req.: Segregate from nitrites.
Protect against moisture.
Storage duration: 24 months
Container: Containers should be stored tightly sealed in a dry place.
Transport Code: Not classified as hazardous under transport regulations.

Remark: Personal protective equipment

Respiratory protection:
Breathing protection if breathable aerosols/dust are formed.
Particle filter EN 143 type P1, low
efficiency, (solid particles of inert substances).

Hand protection:
Chemical resistant protective gloves (EN 374)
e.g. nitrile rubber (0.4 mm), chloroprene rubber (0.5 mm), polyvinylchloride (0.7 mm) and other.

Manufacturer's directions for use must be observed because of great diversity of types.

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

Body protection:
light protective clothing

General safety and hygiene measures:
Handle in accordance with good industrial hygiene and safety practice.
Flag: non confidential, Critical study for SIDS endpoint
12-AUG-2003 (2)

8.2 Fire Guidance

Prot. Equipment: In case of fire, wear a self contained breathing apparatus.
Ext. Medium: water, foam, carbon dioxide, dry extinguishing media
Add. Information: Dispose of fire debris and contaminated extinguishing water in accordance with official regulations.
Products arising: Methylamine, nitrous gases can be released in case of fire.

Flag: non confidential, Critical study for SIDS endpoint
11-AUG-2003 (2)

8.3 Emergency Measures

Type: other: general advice

Remark: Remove contaminated clothing.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

Type: injury to persons (skin)

Remark: Wash thoroughly with soap and water.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

Type: injury to persons (eye)

Remark: Wash affected eyes for at least 15 minutes under running water with eyelids held open.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

Type: injury to persons (oral)

Remark: Rinse mouth and then drink plenty of water.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

Type: injury to persons (inhalation)

Remark: If difficulties occur after dust has been inhaled, remove to fresh air and seek medical attention.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

Type: accidental spillage

Remark: Personal precautions:
Handle in accordance with good industrial hygiene and safety practice.

Environmental precautions:
Discharge into the environment must be avoided.

Methods for cleaning up or taking up:
Contain large amounts with dust binding material and dispose.
Flag: non confidential, Critical study for SIDS endpoint
19-DEC-2002 (2)

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

Memo: other: Must be dumped or incinerated in accordance with local regulations.

Flag: non confidential, Critical study for SIDS endpoint
11-AUG-2003 (2)

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

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