FOREWORD **INTRODUCTION**

UREA,N,N''-(2-METHYLPROPYLIDENE)BIS

CAS N°: 6104-30-9

SIDS Initial Assessment Report

For

SIAM 19

Berlin, Germany, 19–22 October 2004

1. Chemical Name:	Urea, N,N"-(2-methylpropylidene)bis- (IBDU)
2. CAS Number:	6104-30-9
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
4. Shared Partnership with:	BASF AG, Germany Mitsubishi Chem. Corp., Japan The Nu-Gro Corp., Canada
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	BASF AG, Germany Contact Person: Dr. Rolf Sarafin GUP/CL – Z570 D-67056 Ludwigshafen
• Process used	The BUA Peer Review Process : 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:	11 May 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 23 April 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search termsOECD/ICCA
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9. Date of Submission:	Deadline for circulation: 23 July 2004
10. Date of last Update:	-

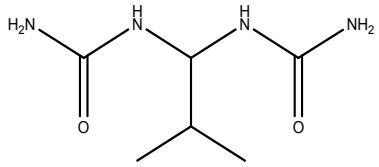
11. Comments:

OECD/ICCA - THE BUA* PEER REVIEW PROCESS

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6104-30-9
Chemical Name	Urea, N,N''-(2-methylpropylidene)bis- (IBDU)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Urea, N,N''-(2-methylpropylidene)bis- (IBDU) had a low acute toxicity by the oral route. The only clinical signs noted after oral exposure to rats were tachypnoea and piloerection (LD50, rat, oral: > 10 000 mg/kg bw, IBDU purity. 90 - 96 %). There are no valid acute studies available using the inhalation or dermal routes of exposure.

No eye or skin irritation studies of IBDU according to the current standard are available. Nevertheless the available studies with rabbits are considered of sufficient and good quality to allow the evaluation of these endpoints. IBDU (0.5 g) as a 50 % aqueous suspension was not irritating to the skin of rabbits under semi-occlusive conditions for 20 hours and 0.05 ml IBDU was slightly irritating to the eyes of rabbits.

After repeated oral administration over 4 weeks by gavage to rats in a screening study following OECD TG 422 (1996), the "No Observed Effect Levels" (NOAELs) were 300 mg/kg bw/day for females (reduced body weight gain during pregnancy and lactation at 1000 mg/kg bw/day), and 1000 mg/kg bw/day for males (highest tested dose level).

IBDU was tested negative in a standard and pre-incubation Ames test performed with *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 according OECD TG 471 (1983) both with and without metabolic activation (rat liver S-9 mix) up to 5000 µg/plate. In vivo, IBDU did not induce micronuclei in male mice treated up to the highest guideline recommended dose (2000 mg/kg bw) in a study performed in accordance with OECD TG 474. Although the ratio between polychromatic and normochromatic erythrocytes was not changed thus lacking to show that the test substance has reached the bone marrow, there is evidence for systemic availability from the above mentioned repeated dose toxicity study in rats where kidney effects were observed in males at 300 mg/kg bw/day.

In a reproductive/developmental toxicity screening test (OECD TG 422), and in a modern one-generation study, IBDU had no effects on the reproductive function of rats (NOAEL: 1200 mg/kg bw/day; highest dose tested). The NOAEL for general toxicity was 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day). No developmental effects were seen in a study performed in accordance with OECD TG 414 on Wistar rats (NOAEL developmental toxicity: 1000 mg/kg bw/day; NOAEL maternal toxicity: 300 mg/kg bw/day), and in the above mentioned screening test in rats according to OECD TG 422 (NOAEL developmental toxicity: 1000 mg/kg bw/day and NOAEL maternal toxicity: 300 mg/kg bw/day).

Environment

IBDU is a solid substance which melts at 205 °C under decomposition. The water solubility is in the range between 0.3 and 3.0 g/l at 20 °C. Henry's law constant was calculated as $4.11*10^{-13}$ Pa*m^3/mol from which a vapour pressure of $4.7*10^{-12}$ can be derived. According to a fugacity model (Mackay level I), the main target compartment for IBDU

is water (almost 100 %), with negligible amounts in the other compartments. The Henry Constant indicates a negligible volatility from water. In air the substance is indirectly photodegraded by hydroxyl radicals (0.5×10^6 OH/cm^3 as a 24 h average) with a calculated half-life for photo-oxidation of 8.2 hours.

IBDU is potentially susceptible to hydrolysis because of its structure. The calculated half-life for hydrolysis, however, is more than one year. Adsorption to solid phase is not expected based on a calculated log K_{oc} of 1.4.

The substance is readily biodegradable as shown in a test according to OECD TG 301C with non-adapted inoculum. At a test substance concentration of 100 mg/l, a biodegradation of 78 % was found within 28 days (72 % within 7 days, and 78 % within 14 days). In soil, IBDU is hydrolyzed to urea and isobutyraldehyde. These two substances are at least inherently biodegradable and have a low acute toxicity (urea: > 100 and isobutyraldehyde: > 10 mg/l). Urea is decomposed by urease into NH_3 and CO_2 (ammonification) and NH_3 then protonated into the ammonium ion. The latter volatilizes or is oxidized via nitrite into nitrate (nitrification). The measured log K_{ow} of - 0.903 for IBDU (at room temperature) does not indicate a significant potential for bioaccumulation.

Short-term tests with fish, invertebrates and algae were available for IBDU. The effect values from the short term tests are: *Salmo gairdneri*: 96h-LC_{50} > 1000 mg/l, *Daphnia magna*: 48h-EC_{50} = 500 mg/l, *Scenedesmus subspicatus*: 72h-E_rC_{50} > 500 mg/l. Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 500 µg/l is derived from the 48h-EC_{50} for *Daphnia magna*.
The 14d-LC_{50} for *Eisenia fetida* was 648 mg/kg soil.

Exposure

In 2003, the worldwide production volume for IBDU was between 30 000 and 50 000 metric tons. Since there is only one producer in each region (Germany, Canada, Japan), no production volumes can be provided for the regions for confidentiality reasons.

The main use of IBDU is as a slow nitrogen release fertilizer for horticulture and turfgrasses. It is marketed worldwide, mainly in the form of granules for professional and consumer use (wide dispersive use). The main route for occupational and consumer exposure is skin contact.

Emissions of IBDU to the environment may occur during manufacture, processing and use of products containing the substance. In the sponsor country, emissions from a production plant amount to about 2 tons/year (as TOC) and 8 tons/year (as NH_4-N). Approximately 488 kg/year are emitted into the air. From the use as fertilizer, an exposure of the terrestrial compartment takes place.

Occupational exposure may occur during production, processing and use of IBDU containing products. No workplace exposure information is available with regard to the manufacturing and processing sites. Exposure of the general public through the environment is not considered as significant as the substance is biodegradable and has no bioaccumulation potential.

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

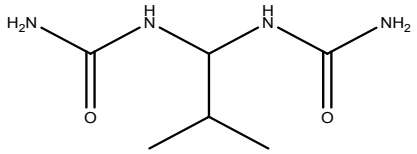
The chemical is currently of low priority for further work because of its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 6104-30-9
IUPAC Name: Urea, N,N''-(2-methylpropylidene)bis-
Molecular Formula: $C_6 H_{14} N_4 O_2$
Structural Formula:



Molecular Weight: 174.20 g/mol
Synonyms: IBDU
1,1-Diureidoisobutane
1,1'-Isobutylidenebisurea
Diureidoisobutane
Isobutylenediurea
Isobutylidenebisurea
Isobutylidenediurea
Isodur
N,N''-(Isobutylidene)diurea
N,N''-(Isobutylidene)bisurea
N,N''-(2-methylpropyliden)-bisurea
Urea, 1,1'-isobutylidenedi- (7CI, 8CI)
Urea, N,N''-(2-methylpropylidene)bis- (9CI)

1.2 Purity/Impurities/Additives

Purity: ca. 92 % (technical product)

Main impurities: urea (ca. 5 %), water (ca. 2 %), magnesium sulfate (ca. 0.5 %), ammonium sulfate (ca. 0.5 %)
(BASF AG 2003c).

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Solid	BASF AG (2003c)
Melting point	205 °C (decomposition)	Hamamoto (1966)
Boiling point	not determined	
Density	0.55 g/cm^3	IPCS (1999)
Vapor pressure	not applicable for solid substance*	
Water solubility	0.3 - 3 g/l at 20 °C	Hamamoto (1966); Ullmann (2001)
pH	5 - 8 (10 wt. % suspension)	Ullmann (2001)
Partition coefficient n-octanol/water (log K_{OW} value)	-0.903 (room temperature)	BASF AG (1988b)
Henry's law constant	4.11 x 10^{-13} Pa-m^3/mole (25 °C; calculated)	BASF AG (1998)
Particle size	between 0.06 and 1.65 mm (technical product)	Hamamoto (1966)
Flammability	At temperatures above 157 °C flammable gases may build up	BASF AG (1987a)
Explosive Properties	Dust explosible	BASF AG (1987a)

*from Henry's law constant a vapor pressure of 4.7 x 10^{-12} Pa (at 25 °C) can be derived

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

IBDU is a high production volume chemical with a worldwide production volume between 30 000 and 50 000 metric tons in 2003. Since there is only one producer in each region (Germany, Canada, Japan), no production volumes can be provided for the regions for confidentiality reasons (BASF AG, 2003d).

Its main use is as slow nitrogen release fertilizer for horticulture and turfgrasses. It is marketed worldwide, mainly in the form of granules for professional and consumer use. In 1989, about 9700, 15 000, and 25 000 metric tons were produced in Germany, USA, and Japan, respectively (BUA, 1995).

IBDU is not listed in the Danish product registers (Arbejdstilsynet, 2002). It is listed in the Swedish registers in 4 products with a total consumption of 6.0 tons in 2001, one of these products, a fertilizer with a concentration of 2 - 100 %, is available to consumers (Swedish product register, 2003). In the Swiss product register (2001) there are 37 consumer products containing IBDU. It is registered for a fertilizer in agriculture with an IBDU concentration of up to 10 % (8 products) or up to 50 % (9 products). Furthermore a fertilizer for horticulture ("Zierpflanzendünger") is registered with an IBDU concentration of up to 1 % (1 product), up to 10 % (9 products) or up to 50 % (10 products) (Swiss product register, 2001).

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Emissions of IBDU to the environment may occur during manufacture, processing and use of the substance in products. From the use as fertilizer, an exposure of the terrestrial compartment takes place.

Emissions from one German production plant into waste water amount to approximately 2 tons/year (as TOC) and 8 tons/year (as NH_4-N), respectively, not taking into account elimination in sewage treatment plants (BASF AG, 1995). Approximately 488 kg/year are emitted into air from the same production plant (BASF AG, 2001). A maximum emission of 5 tons/year is reported for European production and formulation sites, not taking into account the elimination in sewage treatment plants (BUA, 1995).

2.2.2 Photodegradation

In the atmosphere, IBDU will be photodegraded by reaction with hydroxyl radicals (0.5×10^6 OH/ cm^3 as a 24 h average) in the atmosphere with an estimated half-life of approximately 8.2 hours (calculated with AOPWIN v1.87 by BASF AG, 1998).

2.2.3 Stability in Water

Because of its structure, IBDU is potentially susceptible to hydrolysis. The calculated half-life for hydrolysis is, however, over one year (BASF AG, 1998). After dissolving in water IBDU gradually undergoes hydrolysis. One mole of IBDU gives two moles of urea and one mole of isobutyl-aldehyde. Hydrolysis of IBDU will be influenced by pH. Measurements gave an increase of total nitrogen and urea nitrogen in the solution as pH decreased. In two insufficient documented studies it was assumed that dissolved IBDU will be decomposed by hydrogen ion attack (Komatsu and Sakaki, 1971; Hamamoto 1966).

2.2.4 Transport between Environmental Compartments

Using a fugacity based model (Mackay Level I), IBDU is predicted to appear practically only in the aqueous compartment up to almost 100 % with negligible amounts in the other compartments (BASF AG, 2004a).

The Henry's law constant was estimated with the Bond method to 4.11×10^{-13} Pa x m^3/mole (at 25 °C) (BASF AG, 1998), indicating that IBDU is not expected to partition significantly into the atmosphere.

Through its use as slow-release fertilizer, IBDU granules are directly applied on soil. In soil, dissolved IBDU is hydrolyzed to urea and isobutyraldehyde (Hamamoto, 1966). Both substances are at least inherently biodegradable (ECB, 2000a, b). Urea is decomposed by urease into NH_3 and CO_2 (ammonification) and NH_3 then protonated into the ammonium ion. The latter volatilizes or is oxidized via nitrite into nitrate (nitrification). Low pH (pH < 6), high temperatures, high soil moisture and small granular size increase solubilisation of IBDU and, hence, mineralization (Hamamoto, 1966; Hughes, 1976; Markova, 1978). Within 24 weeks, the total amount of mineralized nitrogen in 4 different soil types with pH values of 4.8 to 8.3 was between 88 and 99 % of the introduced IBDU (Markova, 1978).

Adsorption to solid phase is not expected based on a calculated log K_{OC} of 1.4 (BASF AG, 1998).

Results from leaching experiments indicate that no relevant concentrations of IBDU will be leached into ground water. Depending on soil quality between 0.1 and 0.9 % of the applied nitrogen from IBDU were lost as nitrate and 0.1 to 0.6 % as ammonium in leachate after application rates of up to 220 kg IBDU/ha, 5 times per year (Brown, Thomas and Duble, 1982; BASF AG, 1991).

2.2.5 Biodegradation

The substance is readily biodegradable as shown in a test according to OECD TG 301 C with non-adapted inoculum. At a test substance concentration of 100 mg/l, a biodegradation of 78 % was found within 28 days (72 % within 7 days, and 78 % within 14 days) (CERI 2004).

At a concentration of 47 mg/l, IBDU was biodegradable, but not "readily biodegradable" (according to OECD criteria, failure of 10 d-window) in an insufficiently documented test with non-adapted domestic sludge performed in accordance with OECD TG 301 E (11 % was degraded within 7 days; 27 % within 14 days, 62 % within 21 days and 85 % within 28 days (mean values)) (BASF AG, 1988a).

2.2.6 Bioaccumulation

No experimental data on bioaccumulation is available. However, the log K_{OW} of –0.903 indicates no significant potential for bioaccumulation (expert judgement).

2.2.7 Other Information on Environmental Fate

No other information available.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure may occur during manufacture, transportation and industrial use. Results from workplace measurements at the production site of BASF AG (Ludwigshafen, Germany) or other production and processing sites are not available. However, worker exposure is limited by industrial hygiene controls and personal protective measures.

Exposure could also occur during loading, unloading, and transportation of tank trucks, railroad tankers, barges, and drums. Dedicated systems are typically used for loading and unloading purposes and procedures should be in place to prevent spills or leaks during transportation.

Through its application as fertilizer, professional users may be exposed to IBDU, mainly in the form of granules. The likely primary route of exposure is therefore skin contact.

2.3.2 Consumer Exposure

Through its application as fertilizer in horticulture, private users may be exposed to IBDU, mainly in the form of granules. The likely primary route of exposure is therefore skin contact.

Consumer products are listed in the Swedish and Swiss product register; see chapter 2.1.

Assuming a low potential for bioaccumulation (log K_{OW} of –0.903) and due to its degradation in soil, the atmosphere and surface waters, exposure of the general public through the environment is not considered as significant

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

In three out of four sheep, IBDU was not detectable in blood plasma samples taken at 2.5, 7.25 and 24 hours after oral intake of a ^{15}N-IBDU containing diet (ca 1260 mg/kg bw and day). In the other animal, sacrificed at 12 hours after oral intake, 173 mg IBDU/l (ca. 2.2 % of the IBDU intake) was detected in plasma). The blood plasma of another sheep with a ligature at the abomasus entry was found to contain up to 180 mg IBDU/l. This finding is regarded as evidence of the possibility of IBDU to be absorbed through the rumen wall. At 7.25 h, 40 % of the ^{15}N in the rumen was in the form of IBDU, after 12 hours it was 10 % indicating that IBDU undergoes partial decomposition in the rumen.
Only low amounts of unchanged IBDU (max. 1 % of intake) were detected in the urine within 24 hours. The passing of nitrogen from IBDU into the body pool was assumed from recovery experiments, which demonstrated the presence of ^{15}N in plasma proteins and liver. (Bergner, Görsch and Adam, 1978; Bergner and Görsch, 1979; Görsch, 1980).

Two sheep received 30 g IBDU with 1259 mg ^{15}N-IBDU and 680 µCi 14C-IBDU(C1-labelled) via the rumen fistula. The animals were placed in respiration cages.
The peak of specific ^{14}C-CO_2 activity in the expired air (including ruminal gas) was observed 2 h after beginning of the experiment with, about 50 % of the ^{14}C applied being found in the expired air until sacrifice at day 7. Incorporation of ^{15}N into the protein fraction of blood was demonstrated. 3.5 % of the ^{14}C and 23 % of the ^{15}N were excreted in the urine within 6 days. 20 % of the ^{15}N in urine could be detected as ^{14}C-isobutyl residues. An average of 22 % of the ^{15}N applied was excreted in faeces (3.8 % of the applied ^{14}C) (Bergner and Görsch, 1979; Görsch, 1980).

Studies in Humans

No information available.

Conclusion

There are limited studies on the toxicokinetics, metabolism and distribution of IBDU in sheep. However, since sheep are ruminants, the results of these studies are not relevant for man.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

There is no valid acute inhalation study available.

Dermal

No information available.

Oral

There is no study available, which is performed according to the current guideline. Nevertheless the study with rats (no data on strain, only 7 days post observation) is considered of sufficient and good quality to allow the evaluation of this endpoint. Furthermore the low acute toxicity of IBDU does not indicate the necessity of further studies. The LD_{50} in rats (5 animals/sex/dose) was > 10 000 mg/kg bw (IBDU, purity 90 – 96 %). The only clinical symptom noted was tachypnoea and piloerection at concentrations of 3200 mg/kg bw and higher (BASF AG, 1967).

In literature, there is also information on the acute oral toxicity of IBDU in ruminants: In a very limited study with cattle, 3000 mg/kg bw induced a transient increase in NH_3 in blood, 5000 mg/kg bw caused defecation, increased breathing frequency and muscular fibrillations which were reversible within 3 hours. In sheep, 7500 mg/kg bw were lethal for one out of two animals, 10 000 mg/kg bw were lethal for the two animals studied. Clinical symptoms observed were similar to cattle (Gladenko, Zajceva and Sevocova., 1980).

Studies in Humans

No data available.

Conclusion

IBDU had a low acute toxicity by the oral route. The only clinical signs noted after oral exposure to rats were tachypnoea and piloerection (LD_{50}, rat, oral: > 10 000 mg/kg bw, IBDU purity. 90 - 96 %). There are no valid acute studies available using the inhalation or dermal routes of exposure.

3.1.3 Irritation

Skin Irritation

Studies in Animals

In an older skin irritation study with 2 rabbits performed with ca. 0.5 g of a 50 % aqueous suspension of IBDU (purity ca. 90 - 96 %) under semi-occlusive conditions for 20 hours, no local effects or other clinical signs were observed (reading time points: 24 hours and 8 days after application) (BASF AG, 1967).

Studies in Humans

No data available.

Eye Irritation

Studies in Animals

In an older eye irritation study with rabbits performed with 0.05 ml undiluted IBDU (purity ca. 90 - 96 %), redness was observed one hour after application (redness was also observed in the control eye to which talcum was applied). The effect was only slight at 24 hours and subsided within 8 days (BASF AG, 1967).

Studies in Humans

No data available.

Respiratory Tract Irritation

No data available.

Conclusion

No eye or skin irritation studies of IBDU according to the current standard are available. Nevertheless the available studies with rabbits are considered of sufficient and good quality to allow the evaluation of these endpoints. IBDU (0.5 g) as a 50 % aqueous suspension was not irritating to the skin of rabbits under semi-occlusive conditions for 20 hours and 0.05 ml IBDU was slightly irritating to the eyes of rabbits.

3.1.4 Sensitisation

No data available.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Oral

The repeated dose toxicity of IBDU (purity 90.1 %) was assessed in a study on rats according to OECD TG 422 (combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test) (BASF AG, 2003a; *cf* also chapter 3.1.8). 10 male and 10 female Sprague-Dawley rats per group were treated by gavage with 0, 100, 300 or 1000 mg IBDU/kg bw/day. Males were treated during pre-mating (15 days), mating (max. 14 days) and post-mating for a total of 34 days, and females during pre-mating (15 days), mating (max. 14 days), and pregnancy and lactation until day 4 post partum.

There were no substance related deaths, nor were there any substance related clinical signs observed. The high-dose females showed lower body weight gain during gestation (minus 10 % on days 0 - 20 of pregnancy as compared to the controls), and during lactation (minus 38 % on days 1 to 4 post-partum). They also had slightly lower food consumption during gestation. No effects on body weight gain or food consumption were seen in males up to and including the highest tested dose.

The treatment with IBDU had no effects on hematology, blood biochemistry and urine parameters. There were no substance related pathological changes found at necropsy. In males, the histo-pathological examination revealed a dose-related higher severity of acidophilic globules in the cortical tubular epithelium of the kidneys of the 300 and 1000 mg/kg bw/day groups. As no tubular degeneration/necrosis was observed in the kidneys the presence of acidophilic globules was considered as due to the accumulation of the sex-linked alpha-2-u-globulin. This was confirmed by Mallory-Heidenhain and specific immunostaining (BASF, 2004b). As a sex- and species-specific effect of male rats, this finding has no relevance for humans. It was therefore considered of minor toxicological importance and not considered as an adverse effect. No treatment-related abnormalities were found in testes, epididymides, prostate, seminal/vesicles, ovaries, and uterus, and in all other investigated organs.

The "No Observed Effect Levels" (NOAELs) were 300 mg/kg bw/day for females (reduced body weight gain during pregnancy and lactation at 1000 mg/kg bw/day), and 1000 mg/kg bw/day for males.

Studies in Humans

No data available.

Conclusion

After repeated oral administration over 4 weeks by gavage to rats in a screening study following OECD TG 422 (1996), the "No Observed Effect Levels" (NOAELs) were 300 mg/kg bw/day for females (reduced body weight gain during pregnancy and lactation at 1000 mg/kg bw/day), and 1000 mg/kg bw/day for males (highest tested dose level).

3.1.6 Mutagenicity

In vitro Studies

IBDU (purity 92 %) was not mutagenic in the standard and pre-incubation Ames test (OECD TG 471, 1983) with and without metabolic activation (tested up to 5000 µg/plate in *Salmonella typhimurium* TA1535, 1537, 98, 100; metabolic activation: liver S-9 mix from Aroclor 1254-induced rats). Cytotoxicity was not observed, positive controls were functional (BASF, 1988d). As this test was performed according to the older guideline version of 1983, TA 102 and *E. coli* were not used for testing. These strains were introduced later to cover oxidizing mutagens, cross-linking agents and hydrazines. However, since IBDU does not have these properties, the study is comparable to a current guideline study.

In vivo Studies

IBDU (purity 90.1 %) did not induce micronuclei in bone marrow cells of male NMRI mice dosed by gavage with up to 2000 mg/kg bw, given twice within 24 hours in a study performed in line with OECD TG 474 (BG Chemie, 1999). The bone marrow cells were evaluated at 24 hours after the last dose. The ratio between polychromatic and normochromatic erythrocytes were not substantially increased as compared to the corresponding vehicle controls, indicating that the test substance had no substantial cytotoxic effects on bone marrow cells. In a pretest with male and female mice performed to find an appropriated dose, reduced spontaneous activity, eyelid closure and apathy were observed as clinical signs of toxicity at 2000 mg/kg bw (both sexes).

Studies in Humans

There is no data available.

Conclusion

IBDU was tested negative in a standard and pre-incubation Ames test performed with *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 according OECD TG 471 (1983) both with and without metabolic activation (rat liver S-9 mix) up to 5000 µg/plate.

In vivo, IBDU did not induce micronuclei in male mice treated up to the highest guideline recommended dose (2000 mg/kg bw) in a study performed in accordance with OECD TG 474. Although the ratio between polychromatic and normochromatic erythrocytes was not changed thus lacking to show that the test substance has reached the bone marrow, there is evidence for systemic availability from the above mentioned repeated dose toxicity study in rats where kidney effects were observed in males at 300 mg/kg bw/day.

3.1.7 Carcinogenicity

No valid animal data are available and no epidemiological studies or case reports investigating the association of exposure to IBDU and cancer risk were identified.

It is noted that carcinogenic nitrosoureas may be produced from IBDU with nitrite; therefore, a carcinogenic potential - although expected to be very low - cannot be totally excluded.

In vivo Studies

Inhalation

No data available.

Dermal

No data available.

Oral

No valid data available.

Studies in Humans

No data available.

Conclusion

No valid animal data are available and no epidemiological studies or case reports investigating the association of exposure to IBDU and cancer risk were identified.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

IBDU was tested in two modern studies for its effects on the reproductive function (BASF AG, 2003a; BASF AG, 2003b).

The first study (BASF AG, 2003a) was performed in accordance with the OECD TG 422 (Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test; *cf* also chapter 3.1.5.). 10 male and 10 female Sprague-Dawley rats per group were treated by gavage with 0, 100, 300 or 1000 mg IBDU/kg bw/day. Males were treated during pre-mating (15 days), mating (max. 14 days) and post-mating for a total of 34 days, and females during pre-mating (15 days), mating (max. 14 days), and pregnancy and lactation until day 4 post partum. There were no substance related deaths, nor were there any substance related clinical signs observed. The high-dose females showed lower body weight gain during gestation (minus 10 % on days 0 - 20 of pregnancy as compared to the controls), and during lactation (minus 38 % on days 1 to 4 post-partum). They also had slightly lower food consumption during gestation. No effects on body weight or food consumption were seen in males up to and including the highest tested dose.

The mating index was 100 % for the pairs of the control, 100 and 300 mg/kg bw/day groups, but was lower in the 1000 mg/kg bw/day group (70 %). As no treatment-related morphological changes were noted in the reproductive organs, this finding was considered to be incidental. This evaluation is further supported by the results of a supplementary study (BASF AG, 2003b, see below), not

showing any effect on the mating index at an even higher dose (1,200 mg/kg bw/day) and using a higher number of animals (25 rats/sex instead of 10).

No effects of the substance were seen with regard to the time to insemination, fertility, duration of gestation, gestation index, number of implantation sites, and on postimplantation and neonatal losses. The number of corpora lutea was similar in the 0, 100 and 300 mg/kg bw/day groups. In the group treated with 1000 mg/kg bw/day the number was slightly lower (18 *versus* 23 per female). As the counts in all groups (including the high dose) were higher than the laboratory`s historical controls, and because there were no microscopic changes in the ovaries, this finding was considered as a chance event. The seminiferous tubules were lined with Sertoli cells only (minimal or slight) in 1/10 males given 300 mg/kg/day and in 2/10 males given 1000 mg/kg/day. For a third male from the same group, tubules lined with Sertoli cells only were considered to be tubuli recti as they were situated beneath the capsule. For 1/10 males given 300 mg/kg/day and another given 1000 mg/kg/day, minimal reduction in the number of spermatids was observed in very few seminiferous tubules. Minimal vacuolization of Sertoli cells was observed in 1/10 males given 1000 mg/kg/day. Although not found in the control males, these microscopic abnormalities recorded with minimal severity in few or very few seminiferous tubules in a few males were considered to be without relationship to the treatment and most probably fortuitous.

There were no stillborn pups or runts. The number of pups, which died during the four days of observation after birth was low (0 - 5 %) and similar in all groups. There were no notable clinical signs in the pups, and the pup body weights were similar in all groups. The treatment with IBDU had no effect on the sex ratio of the pups.

The following "No Observed Adverse Effect Levels" (NOAELs) were deduced from this study:

NOAEL, General Toxicity (male): 1000 mg/kg bw/day (highest tested dose)

NOAEL, General Toxicity (female): 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day).

NOAEL, Reproduction (male, female): 1000 mg/kg bw/day (highest tested dose).

The second study (BASF AG, 2003b) was performed as a one-generation study, and undertaken to further evaluate the toxicological relevance of the reduced mating index that was found at 1000 mg/kg bw/day in the earlier study (BASF AG, 2003a). 25 male and 25 female Sprague-Dawley rats per group were treated by gavage with 0, 600 or 1200 mg IBDU/kg bw/day. Females were treated throughout the pre-mating period (10 weeks), during mating (max. 2 weeks), and during pregnancy until day 14 post-coitum, inclusive. Males were treated throughout the pre-mating period (10 weeks), during mating (2 weeks), and until sacrifice (i.e. when most of the hysterectomies in females were completed).

There were no substance related deaths, nor were there any substance related clinical signs observed. Females showed lower body weight gain during pregnancy (minus 24 % in both dose groups), and during pre-mating (minus 11 %, only high-dose group). No significant effects were found in males. The food consumption was also slightly lower in females of the high-dose group during pregnancy (minus 14 %), and during pre-mating and pregnancy in the low-dose (not significant). There were no pathological findings at necropsy. Slight changes in organ weights (females: ovary and uterus, males: adrenals) as compared to the controls were not considered substance-related, as most of the values were within the range of the control group, and changes were only due to the contribution of a few individual values (females), or because of the lack of a dose-response (males). Seminology findings in the treated groups were not different from controls.

The female mating index and pre-coital interval were similar in all groups, as were the male mating index and the male fertility (female mating index: control, low, high-dose: 96 – 96 – 96 %; male mating index: control, low, high-dose: 100 - 96 - 96 %, male fertility index: 100 - 91.3 - 91.3 %). The treatment had also no effect on female fertility and gestation indices (female fertility index: 100, 87.5, 91.7 %). The number of corpora lutea was minimally lower in the treated groups when compared to the controls (control, low, high-dose: 17.6, 16.4, 16.0). Since the difference was small, not statistically significant, and within the range of the laboratory`s historical control values (15.9 - 18.9), this finding was considered as a chance event. The number of implantation sites and concepti was consequently also lower than in the controls, gaining statistical significance only at the top dose (control, low, high-dose: 16.6, 14.9, 14.5* ($p < 0.05$) and 15.2, 14.3, 13.0* ($p < 0.05$));. Also the values for implantation sites and concepti were within the laboratory's historical controls (13.8 - 17.1 and 12.8 - 16.3). The slight fluctuations in the pre- and post-implantation losses (5.7, 9.6, 9.1 % and 8.3, 4.2, 11.0 %) were not considered treatment-related, since they were not dose-related and/or not different from either the concurrent or historical controls (5.2 - 14.3 and 2.4 - 8.2).

The following "No Observed Adverse Effect Levels" (NOAELs) were deduced from this study:

NOAEL, General Toxicity (male): 1200 mg/kg bw/day (highest tested dose)

LOAEL, General Toxicity (female): 600 mg/kg bw/day (reduced body weight gain during pregnancy)

NOAEL, Reproduction (male, female): 1200 mg/kg bw/day (highest tested dose).

Developmental Toxicity

IBDU was evaluated for its developmental effects on Wistar rats in a study according to OECD TG 414 (BASF AG, 1993; Hellwig, Klimisch and Beth-Hübner, 1997) and in a screening test according to OECD TG 422 (BASF AG, 2003a).

In the developmental study (BASF AG, 1993; Hellwig, Klimisch and Beth-Hübner, 1997), the test substance was administered by gavage on days 6 through 15 of gestation at dose levels of 0, 100, 400 or 1000 mg/kg bw. No signs of maternal toxicity were observed. There were no substance-related effects in the dams with regard to food consumption, body weight, body weight gain, uterine weight and clinical or autopsy findings. The reproduction data revealed no biologically relevant differences between the control and treated groups. No effects on viability and weight of fetuses or other signs of developmental toxicity were induced by the treatment with IBDU. The incidence and type of the fetal external, soft tissue and skeletal findings, which were classified as malformations, variations and/or retardations observed in the treated fetuses were similar to the concurrent and/or historical control data.

The following "No Observed Adverse Effect Levels" (NOAELs) were derived from this study:

NOAEL, maternal toxicity: 1000 mg/kg bw/day (highest tested dose)

NOAEL, developmental toxicity: 1000 mg/kg bw/day (highest tested dose).

In the screening test (BASF AG, 2003a), there were no effects on pup mortality, and no notable clinical signs in the pups during the 4 day observation period. Pup body weights were similar in all groups on day 1 and day 4 post-partum. The treatment had no influence on the sex ratio (NOAEL, developmental toxicity: 1000 mg/kg bw/day; NOAEL maternal toxicity: 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day).

Studies in Humans

No data available.

Conclusion

In a reproductive/developmental toxicity screening test (OECD TG 422), and in a modern one-generation study, IBDU had no effects on the reproductive function of rats (NOAEL: 1200 mg/kg bw/day; highest dose tested). The NOAEL for general toxicity was 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day). No developmental effects were seen in a study performed in accordance with OECD TG 414 on Wistar rats (NOAEL developmental toxicity: 1000 mg/kg bw/day; NOAEL maternal toxicity: 300 mg/kg bw/day), and in the above mentioned screening test in rats according to OECD TG 422 (NOAEL developmental toxicity: 1000 mg/kg bw/day and NOAEL maternal toxicity: 300 mg/kg bw/day).

3.2 Initial Assessment for Human Health

IBDU had a low acute toxicity by the oral route. The only clinical signs noted after oral exposure to rats were tachypnoea and piloerection (LD_{50}, rat, oral: > 10 000 mg/kg bw, IBDU purity. 90 - 96 %). There are no valid acute studies available using the inhalation or dermal routes of exposure.

No eye or skin irritation studies of IBDU according to the current standard are available. Nevertheless the available studies with rabbits are considered of sufficient and good quality to allow the evaluation of these endpoints. IBDU (0.5 g) as a 50 % aqueous suspension was not irritating to the skin of rabbits under semi-occlusive conditions for 20 hours and 0.05 ml IBDU was slightly irritating to the eyes of rabbits.

After repeated oral administration over 4 weeks by gavage to rats in a screening study following OECD TG 422 (1996), the "No Observed Effect Levels" (NOAELs) were 300 mg/kg bw/day for females (reduced body weight gain during pregnancy and lactation at 1000 mg/kg bw/day), and 1000 mg/kg bw/day for males (highest tested dose level).

IBDU was tested negative in a standard and pre-incubation Ames test performed with *Salmonalla typhimurium* TA1535, TA1537, TA98 and TA100 according OECD TG 471 (1983) both with and without metabolic activation (rat liver S-9 mix) up to 5000 µg/plate. *In vivo*, IBDU did not induce micronuclei in male mice treated up to the highest guideline recommended dose (2000 mg/kg bw) in a study performed in accordance with OECD TG 474. Although the ratio between polychromatic and normochromatic erythrocytes was not changed thus lacking to show that the test substance has reached the bone marrow, there is evidence for systemic availability from the above mentioned repeated dose toxicity study in rats where kidney effects were observed in males at 300 mg/kg bw/day.

In a reproductive/developmental toxicity screening test (OECD TG 422), and in a modern one-generation study, IBDU had no effects on the reproductive function of rats (NOAEL: 1200 mg/kg bw/day; highest dose tested). The NOAEL for general toxicity was 300 mg/kg bw/day (reduced body weight gain in females during pregnancy and lactation at 1000 mg/kg bw/day). No developmental effects were seen in a study performed in accordance with OECD TG 414 on Wistar rats (NOAEL developmental toxicity: 1000 mg/kg bw/day; NOAEL maternal toxicity: 300 mg/kg bw/day), and in the above mentioned screening test in rats according to OECD TG 422 (NOAEL developmental toxicity: 1000 mg/kg bw/day and NOAEL maternal toxicity: 300 mg/kg bw/day)

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Concerning the aquatic effects short-term toxicity, tests for each trophic level are available.

For *Salmo gairdneri* a LC_{50} > 1000 mg/l after 96 h was obtained. The studies were conducted under static conditions according to OECD TG 203. The substance (1000 mg/l) was added to the test water without any pretreatment. Undissolved test substance was visible on the water surface and on the bottom of the aquarium. No symptoms were noted. No mortality occurred at this concentration (BASF AG, 1986).

A test on the acute toxicity of IBDU to the invertebrate *Daphnia magna* was performed according to the Directive 84/449/EEC, C. 2 in a static test system. For a test period of 48 hours an EC_{50} value of 500 mg/l was reported (BASF AG, 1988c). The highest test concentration was 500 mg/l and therefore, statistical analysis could not applied.

Acute toxicity of IBDU to the green alga *Scenedesmus subspicatus* was determined according to the German Industrial Standard Guideline DIN 38412, part 9, using five test concentrations ranging from 31.25 to 500 mg/l (nominal) and an untreated control. The E_rC_{50} (72 h) for the endpoint growth rate was > 500 mg/l (nominal) (BASF AG, 1990). After 96h a large pH-shift (7.6 to 10.4) could be observed, whereas no information about pH after 72 h is available.

The following valid acute toxicity data on aquatic organisms were available:

Table 2 Available Tests of Acute Toxicity for Aquatic Species

Aquatic Species	**LC_{50}/EC_{50}**	**Reference**
Fish: *Salmo gairdneri*	LC_{50} (96h), static test: > 1000 mg/l (nominal)	BASF AG, 1986
Invertebrates: *Daphnia magna*	EC_{50} (48h), static test: 500 mg/l (nominal)	BASF AG, 1988c
Algae: *Scenedesmus subspicatus*	E_rC_{50} (72h): static test: > 500 mg/l (nominal; growth rate)	BASF AG, 1990

A $PNEC_{aqua}$ of 500 µg/l can be derived from the EC_{50} value in the acute daphnia test with an assessment factor of 1000. This factor is chosen because only short term tests are available.

Chronic Toxicity Test Results

Results from prolonged or chronic studies are not available.

Toxicity to Microorganisms

IBDU at a concentration of 640 mg/l did not inhibit the growth of *Pseudomonas putida* when treated for 16 hours (BASF AG, 1987b).

4.2 Terrestrial Effects

Acute Toxicity Test Results

Vertraete et al. (1974) studied the influence of different slow-release fertilizers on some natural soil microbiological populations and compared the effect to those of urea. The influence of the fertilizers was evaluated by applying the compounds at a low and at a high dose, corresponding respectively with the application of 173 kg N/ha and 1215 kg N/ha (222 and 1550 mg IBDU/kg wet soil). Of the populations studied, none were significantly inhibited, but stimulations were noticed with Fungi, and with ammonifying- and nitrite-forming microorganisms. The slow-release fertilizers application reduced slightly and temporary urease, phosphatase, and saccharase activities of the treated soils.

Four natural organic fertilizers, alone or in combination with isobutylidenediurea (IBDU) were compared with IBDU alone for their effect on soil/root microbial populations associated with bermudagrass (*Cynodon* sp.) grown on a golf course putting green in southern Florida/USA. No significant differences in microbial populations were observed over a 2-year period (Elliott and Des Jardin, 1999).

No toxic response was noted in bermudagrass (*Cynodon* sp.) after application of up to 1900 kg IBDU/ha every week, whereas off-color was observed in *Lolium perenne* after 1 month of application of approximately 700 kg IBDU/ha (Volk and Dudeck, 1976). With IBDU, applied up to 323 kg per ha to *Boronia megastigma*, toxicity did not occur (Reddy and Menary, 1989).

Acute toxicity to *Eisenia fetida* was tested in a study according to OECD guideline 207. The 14d-LC_{50} value was 648 mg/kg soil (BASF AG, 2001).

Chronic Toxicity Test Results

Ma et al. (1990) studied long-term effects (20 y) on nitrogenous fertilizers usage on lumbricid earthworms in soil. This study (Ma et al., 1990) revealed that, IBDU (2 applications per year of 180 kg N/ha = 216 mg IBDU/kg soil) had effects on earthworm numbers and biomass. However, since experiments were conducted without controls and the observed effects, which were attributed to the lowering of pH observed in parallel with IBDU application in the absence of liming, were of secondary nature, the above-mentioned results must be viewed with caution. The effects were, however, attributed to the lowering of pH observed in parallel with IBDU application in the absence of liming (Ma et al., 1990).

4.3 Other Environmental Effects

No information available.

4.4 Initial Assessment for the Environment

IBDU is a solid substance, which melts at 205 °C under decomposition. The water solubility is in the range between 0.3 and 3.0 g/l at 20 °C. Henry's law constant was calculated as $4.11 * 10^{-13}$ Pa * m^3/mol from which a vapour pressure of $4.7 * 10^{-12}$ Pa can be derived. According to a fugacity model (Mackay level I), the main target compartment for IBDU is water (almost 100 %), with negligible amounts in the other compartments. The Henry Constant indicates a negligible volatility from water. In air the substance is indirectly photodegradated by hydroxyl radicals (0.5×10^6 OH/ cm^3 as a 24 h average) with a calculated half-life for photo-oxidation of 8.2 hours.

IBDU is potentially susceptible to hydrolysis because of its structure. The calculated half-life for hydrolysis, however, is more than one year. Adsorption to solid phase is not expected based on a calculated log K_{OC} of 1.4.

The substance is readily biodegradable as shown in a test according to OECD TG 301 C with non-adapted inoculum. At a test substance concentration of 100 mg/l, a biodegradation of 78 % was found within 28 days (72 % within 7 days, and 78 % within 14 days). In soil, IBDU is hydrolyzed to urea and isobutyraldehyde. These two substances are at least inherently biodegradable and have a low acute toxicity (urea: > 100 and isobutyraldehyde: > 10 mg/l). Urea is decomposed by urease into NH_3 and CO_2 (ammonification) and NH_3 then protonated into the ammonium ion. The latter volatilizes or is oxidized via nitrite into nitrate (nitrification). The measured log K_{OW} of –0.903 (at room temperature) for IBDU does not indicate a significant potential for bioaccumulation.

Short-term tests with fish, invertebrates and algae were available for IBDU. The effect values from the short term tests are: *Salmo gairdneri*: 96h-LC_{50} > 1000 mg/l, *Daphnia magna*: 48h-EC_{50} = 500 mg/l, *Scenedesmus subspicatus*: 72h-E_rC_{50} > 500 mg/l. Applying an assessment factor of 1000 according to the EU Technical Guidance Document, a $PNEC_{aqua}$ of 500 µg/l is derived from the 48h-EC_{50} for *Daphnia magna*.

The 14d-LC_{50} for *Eisenia fetida* was 648 mg/kg soil.

5 RECOMMENDATIONS

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

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

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I U C L I D

D a t a S e t

Existing Chemical ID: 6104-30-9
CAS No. 6104-30-9
EINECS Name N''-(isobutylidene)diurea
EC No. 228-055-8
Molecular Weight 174.20 g/mol
Molecular Formula C6 H14 N4 O2

Producer Related Part
Company: BASF AG
Creation date: 12-NOV-1992

Substance Related Part
Company: BASF AG
Creation date: 12-NOV-1992

Memo: master

Printing date: 02-FEB-2006
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Reliability (profile): Reliability: without reliability, 1, 2, 3, 4
Flags (profile): Flags: without flag, SIDS

1.0.1 Applicant and Company Information

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Flag: Critical study for SIDS endpoint
01-FEB-2006

Type: cooperating company
Name: Mitsubishi Chem. Corp.
Country: Japan

Flag: Critical study for SIDS endpoint
26-JAN-2005

Type: cooperating company
Name: The Nu-Gro Corp.
Country: Canada

Flag: Critical study for SIDS endpoint
26-JAN-2005

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: C6 H14 N4 O2
Mol. Weight: 174.20 g/mol

Flag: Critical study for SIDS endpoint
29-APR-2003

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: ca. 92 - % w/w

Remark: Typical composition:
As typical for technical products, the values can vary within
certain ranges.
Flag: Critical study for SIDS endpoint

02-FEB-2006 (1)

Substance type: organic
Physical status: solid
Colour: white
Odour: faint specific odour

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6),
magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
02-FEB-2006 (2) (1)

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,1'-Isobutylidenebisurea

Flag: Critical study for SIDS endpoint
02-DEC-1992

1,1-Diureidoisobutane

Flag: Critical study for SIDS endpoint
02-DEC-1992

Diureidoisobutane

Flag: Critical study for SIDS endpoint
02-DEC-1992

IBDU

Flag: Critical study for SIDS endpoint
02-DEC-1992

Isobutylenediurea

Flag: Critical study for SIDS endpoint
02-DEC-1992

Isobutylidendiharnstoff

Flag: Critical study for SIDS endpoint
02-DEC-1992

Isobutylidenebisurea

Flag: Critical study for SIDS endpoint
02-DEC-1992

Isobutylidenediurea

Flag: Critical study for SIDS endpoint
02-DEC-1992

Isodur

Flag: Critical study for SIDS endpoint
02-DEC-1992

N,N"-(Isobutyliden)diharnstoff

Flag: Critical study for SIDS endpoint
02-DEC-1992

N,N"-(Isobutylidene)bisurea

Flag: Critical study for SIDS endpoint
25-DEC-2001

N,N'-(2-Methylpropyliden)-bis-Harnstoff

Flag: Critical study for SIDS endpoint
11-NOV-2001

Urea, 1,1'-isobutylidenedi- (7CI, 8CI)

Flag: Critical study for SIDS endpoint
02-DEC-1992

Urea, N,N''-(2-methylpropylidene)bis- (9CI)

Flag: Critical study for SIDS endpoint
02-DEC-1992

1.3 Impurities

CAS-No: 57-13-6
EC-No: 200-315-5
EINECS-Name: urea
Mol. Formula: C H4 N2 O
Contents: ca. 5 - % w/w

Remark: typical composition
As typical for technical products, the values can vary within
certain ranges.
Flag: Critical study for SIDS endpoint
30-JUN-2003 (2)

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Mol. Formula: H2 O
Contents: ca. 2 - % w/w

Remark: typical composition
As typical for technical products, the values can vary within certain ranges.
Flag: Critical study for SIDS endpoint
30-JUN-2003 (2)

CAS-No: 7783-20-2
EC-No: 231-984-1

EINECS-Name: ammonium sulphate
Mol. Formula: H8 N2 O4 S
Contents: ca. .5 - % w/w

Remark: typical composition
As typical for technical products, the values can vary within certain ranges.
Flag: Critical study for SIDS endpoint
30-JUN-2003 (2)

CAS-No: 18939-43-0
EC-No: 242-691-3
EINECS-Name: magnesium sulphate
Mol. Formula: Mg O4 S
Contents: ca. .5 - % w/w

Remark: typical composition
As typical for technical products, the values can vary within certain ranges.
Flag: Critical study for SIDS endpoint
30-JUN-2003 (2)

1.4 Additives

1.5 Total Quantity

Remark: Production volume (year 2003):

30,000 - 50,000 metric t/a, referring to world market.

As there is only one producer in each region (Germany, Canada, Japan), no production volumes can be given for the regions.
Flag: Critical study for SIDS endpoint
02-FEB-2006 (3)

1.6.1 Labelling

Labelling: no labelling required (no dangerous properties)

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
02-FEB-2006 (1)

1.6.2 Classification

Classified: no classification required (no dangerous properties)

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
02-FEB-2006 (1)

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Flag: Critical study for SIDS endpoint
23-JUN-2004 (4)

Type: industrial
Category: Agricultural industry

Remark: used as slow-release nitrogen fertilizer
Flag: Critical study for SIDS endpoint
30-JAN-2006 (5)

Type: industrial
Category: Agricultural industry

Remark: used as nitrogen compound in slow-release fertilizers
Flag: Critical study for SIDS endpoint
01-FEB-2006 (6)

Type: use
Category: Fertilizers

Remark: Isobutylidenediurea is a slow-release nitrogen fertilizer used in various special fertilizer formulations.
Flag: Critical study for SIDS endpoint
10-JUN-2003 (7)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis

Remark: Isobutylidenediurea is obtained by condensation of urea with isobutyraldehyde in a molar ratio of 2 : 1 in a weakly acidic medium.
Flag: Critical study for SIDS endpoint
10-JUN-2003 (7)

Orig. of Subst.: Synthesis
Type: Production

Remark: Isobutylidenediurea is produced by a continuous process. According to a patent published by Mitsubishi Chemical Industries [153], urea is charged continuously with a screw feed via a belt weigher and is reacted with a stoichiometric quantity of isobutyraldehyde in the presence of semiconcentrated sulfuric acid in a mixer. In the last section of the mixer the reaction product is neutralized by injecting dilute aqueous potassium hydroxide solution. The product is dried by using plate driers and processed by sieving,

filtering, and grinding.
Source: [153] Mitsubishi Chem. Ind., US 3 322 528, 1961;DE 1 543 201, 1965 (M. Hamamoto, Y. Sakaki).
Flag: Critical study for SIDS endpoint

01-JUL-2003 (7)

Orig. of Subst.: Synthesis

Remark: accessible from urea and isobutyraldehyde
Flag: Critical study for SIDS endpoint
27-NOV-2003 (5)

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

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

Flag: Critical study for SIDS endpoint
10-JUN-2003 (8)

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)

Country: Germany
Remark: ID-Number: 1168
Flag: Critical study for SIDS endpoint
29-APR-2003 (9)

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. 228-055-8

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: ENCS
Additional Info: ENCS-No. 2-1742

Remark: ENCS CLASSIFICATION:
Low molecular chain-like organic compounds.

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: TSCA

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: DSL

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: PICCS

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: AICS

Flag: Critical study for SIDS endpoint
12-MAR-2004 (10)

Type: other: SWISS
Additional Info: SWISS No. G-5191

Remark: SWISS CLASSIFICATION:
Giftliste 1 (List of toxic substances 1), 20 May 2003.
Toxic category 5: Acute oral lethal dose of 2000-5000 mg/kg.
Flag: Critical study for SIDS endpoint
21-JUN-2004 (11)

Type: other: Inert Ingredients in Pesticide Products by Toxicity Category (Lists 3, 4A and 4B: inerts with unknown or minimal toxicity)
Additional Info: List Number (toxicity category): 3 (Inerts of unknown toxicity)

Country: USA
Flag: Critical study for SIDS endpoint
27-NOV-2003 (12)

Type: Annex I, Council Regulation (EEC) No. 793/93

Country: Europe
Source: EU. Annex I to Council Regulation 793/93 on the evaluation and control of the risks of existing substances: List of existing substances produced or imported within the Community in quantities exceeding 1000 tonnes/year. O.J. (L 84) 1, 5 Apr 1993.
Flag: Critical study for SIDS endpoint
27-NOV-2003 (12)

Type: other: OECD. Representative List of High Production Volume Chemicals (HPV)

Country: Europe
Flag: Critical study for SIDS endpoint
27-NOV-2003 (12)

Type: other: Switzerland. BAG Giftliste 1 (Stoffe), April 2002 [Toxics List 1 (Substances)]
Additional Info: as amended by 2003 BBl., number 42, page 7058, 28 October 2003

Swiss Identification Number: G-5191
Toxicity Category: 5

Country: Switzerland
Source: Toxicity Category 5 is determined by acute oral lethal doses of 2000 - 5000 mg/kg in small animals; however, other factors may be taken into consideration regarding data in other types of animals or other affects whether subacute, subchronic or chronic.
Flag: Critical study for SIDS endpoint
27-NOV-2003 (12)

1.9.1 Degradation/Transformation Products

Type: degradation product
CAS-No: 78-84-2
EC-No: 201-149-6
EINECS-Name: isobutyraldehyde

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
02-FEB-2006 (1)

Type: thermal breakdown products
EINECS-Name: NOx

Remark: When heated to decomposition it emits irritating or toxic fumes of NOx.
Source: Voprosy Pitaniya. Problems of Nutrition. (v/o Mezhdunarodnaya Kniga, Kuznetskii Most 18, Moscow G-200, USSR.) V.1- 1932-
Flag: Critical study for SIDS endpoint
23-JUN-2004 (13) (14)

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Environment: exposure from production
Exposure to the: Substance

Result: Emissions into wastewater from one German plant amount to approx. 2 tons/year (as TOC) and 8 tons/year (as NH4-N), respectively. The waste water is then treated by WWTP.
Flag: Critical study for SIDS endpoint
21-JUN-2004 (15)

Source of exposure: Environment: exposure from production
Exposure to the: Substance

Result: Emissions into the environment from production and formulation sites amount to a maximum of 5 tons per year in

Europe, not taking into account degradation in sewage treatment plants.
Flag: Critical study for SIDS endpoint
22-JUL-2004 (16)

Source of exposure: Environment: exposure from production
Exposure to the: Substance

Result: Approximately 488 kg/year are emitted into air from one German chemical production plant.
Flag: Critical study for SIDS endpoint
29-APR-2003 (17)

1.11 Additional Remarks

Memo: Conditions to avoid:
To avoid thermal decomposition do not overheat. Can decompose at above approx. 100°C.

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
29-APR-2003 (1)

Memo: When the product is ground (chopped), dust explosion regulations should be noted.

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: Critical study for SIDS endpoint
23-JUN-2004 (1)

1.12 Last Literature Search

Type of Search: External
Chapters covered: 3, 4, 5
Date of Search: 18-FEB-2003

Remark: TOXLINE, MEDLINE, AQUIRE, EPA Envirofacts
Flag: Critical study for SIDS endpoint
07-JUN-2004

Type of Search: Internal and External
Chapters covered: 5.10
Date of Search: 14-NOV-2002

Flag: Critical study for SIDS endpoint
07-FEB-2003

Type of Search: Internal and External
Chapters covered: 3, 4
Date of Search: 18-FEB-2003

Flag: Critical study for SIDS endpoint
22-APR-2003

Type of Search: Internal and External
Chapters covered: 1
Date of Search: 27-NOV-2003

Flag: Critical study for SIDS endpoint
21-JUN-2004

Type of Search: Internal and External
Chapters covered: 8
Date of Search: 27-NOV-2003

Flag: Critical study for SIDS endpoint
21-JUN-2004

Type of Search: External
Chapters covered: 2
Date of Search: 17-FEB-2004

Flag: Critical study for SIDS endpoint
21-JUN-2004

1.13 Reviews

Memo: Review

01-JUN-2004 (18)

Memo: Review

22-JUL-2004 (16)

2.1 Melting Point

Value: = 195 - 205 degree C

Reliability: (2) valid with restrictions
peer-reviewed source
31-JAN-2006 (13)

Value: 203 - 204 degree C

Test substance: Isodur
Reliability: (2) valid with restrictions
Reliable handbook
20-JUL-2004 (19)

Value: = 205 degree C
Decomposition: yes at = 205 degree C

Method: other
GLP: no
Test substance: other TS: IBDU (Isobutylidene diurea)

Reliability: (2) valid with restrictions
basic data reported
Flag: Critical study for SIDS endpoint
21-JUN-2004 (20)

Value: 207 - 208 degree C

Test substance: IBDU (Isobutylidene diurea)
Reliability: (2) valid with restrictions
Reliable handbook
22-JUN-2004 (19)

Value: = 236 degree C

Test substance: other TS: Isodur and Isodur 0-1.6 mm resp.

Remark: Decomposition at > 100 °C
Reliability: (4) not assignable
manufacturer/producer data without proof
21-JUN-2004 (1) (1)

2.2 Boiling Point

2.3 Density
Type: relative density
Value: = .55 g/cm³

Reliability: (2) valid with restrictions
peer-reviewed source
Flag: Critical study for SIDS endpoint
30-JAN-2006 (13)

Type: bulk density
Value: 500 - 600 kg/m3

Test substance: Isodur
Reliability: (2) valid with restrictions
Reliable handbook
20-JUL-2004 (19)

Type: bulk density
Value: ca. 550 kg/m3

Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
manufacturer/producer data without proof
25-DEC-2001 (1)

Type: bulk density
Value: 600 - 700 kg/m3

Test substance: IBDU (Isobutylidene diurea)
Reliability: (2) valid with restrictions
Reliable handbook
23-JUN-2004 (19)

2.3.1 Granulometry

Type of distribution: other

Test substance: other TS: IBDU, technical grade

Result: particle size 0.06 - 1.65 mm
Reliability: (2) valid with restrictions
basic data reported
Flag: Critical study for SIDS endpoint
23-NOV-2003 (20)

2.4 Vapour Pressure

Remark: Derived from Henry´s law constant of 4.11x10E-13 Pa x m3/mole a vapour pressure of 4.7x10E-12 Pa at 25°C was calculated. Not applicable for a solid.
Flag: Critical study for SIDS endpoint
21-JUN-2004 (21)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -.903

Method: other (measured)
Year: 1988
GLP: no

Method: test procedure in accordance to an internal BASF standard, comparable to OECD Guide-line 107
Result: All three concentrations tested gave similar Po/w values (0.127, 0.130, 0.118).
Test condition: measured at room temperature
Reliability: (2) valid with restrictions
Meets generally accepted scientific standard, acceptable for assessment
Flag: Critical study for SIDS endpoint
23-JUN-2004 (22)

Partition Coeff.: octanol-water
log Pow: = -.9

Reliability: (2) valid with restrictions
peer-reviewed source
30-JAN-2006 (13)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 2 g/l at 20 degree C

Reliability: (4) not assignable
secondary citation
22-JUN-2004 (23)

pH value: 4 - 7
Conc.: 2 g/l at 20 degree C

Reliability: (4) not assignable
manufacturer/producer data without proof
01-DEC-2001 (1)

Solubility in: Water
Value: = .3 - 3 g/l at 20 degree C

Remark: value given as "ca. 0.1 - 0.01 g/100 ml (as N) in neutral solution and at room temperature", corresponding to about 0.3 - 3.2 g IBDU / l.
Reliability: (2) valid with restrictions
basic data reported
Flag: Critical study for SIDS endpoint
01-DEC-2001 (20)

Solubility in: Water

Result: Isobutylidene diurea is very insoluble in water but once dissolution begins, hydrolysis proceeds rapidly.
Reliability: (4) not assignable
secondary citation
13-NOV-2001 (24)

Solubility in: Water
Value: = 99 g/l at 100 degree C

Reliability: (4) not assignable
manufacturer/producer data without proof
01-DEC-2001 (25)

Solubility in: Water
Value: .3 - 3 g/l at 25 degree C
pH value: = 5 - 8

Test substance: other TS

Remark: Concentration: 10 wt% suspension
value given as for "fertilizer grade"
Test substance: IBDU
Reliability: (2) valid with restrictions
Reliable handbook
Flag: Critical study for SIDS endpoint
30-JAN-2006 (19)

Solubility in: Organic Solvents

Result: hardly soluble
Test condition: solubility in alcohol and ether
Reliability: (2) valid with restrictions
Basic data reported
23-JUN-2004 (20)

pKa: 12.55 at 25 degree C

Method: other: (calculation) ACD Software Solaris v.4.67
Remark: most acidic
Reliability: (4) not assignable
not assignable
23-JUN-2004 (26)

pH value: 5 - 8

Test substance: other TS: IBDU

Test condition: Conc.: 10 wt% suspension
Reliability: (2) valid with restrictions
Reliable handbook
Flag: Critical study for SIDS endpoint
22-JUL-2004 (19)

Solubility in: Water
Value: = 2.7 g/l at 25 degree C
pH value: 6 - 8

Remark: Concentration: 10 wt% suspension
value given as for "fertilizer grade"
Test substance: Isodur
Reliability: (2) valid with restrictions
Reliable handbook
Flag: Critical study for SIDS endpoint
30-JAN-2006 (19)

pH value: 6 - 8

Remark: Conc.: 10 wt% suspension
Test substance: Isodur
Reliability: (2) valid with restrictions
Reliable handbook
Flag: Critical study for SIDS endpoint
20-JUL-2004 (19)

Solubility in: Water
Value: = 2 g/l at 20 degree C

Reliability: (2) valid with restrictions
peer-reviewed source
30-JAN-2006 (13)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

Result: other: At above 157 °C formation of inflammable gases possible

Year: 1987
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
22-NOV-2003 (27)

2.10 Explosive Properties

Result: other: dust explosible

Method: other: Hartmann apparatus
Year: 1987
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
26-DEC-2001 (27)

2.11 Oxidizing Properties

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .0000000000468328 cm³/(molecule * sec)
Degradation: = 50 % after 8.2 hour(s)

Method: other (calculated): AOP (v1.87)
Year: 1998
GLP: no

Reliability: (2) valid with restrictions
calculated with scientifically accepted method.
Flag: Critical study for SIDS endpoint
22-NOV-2003 (21)

3.1.2 Stability in Water

Method: other (calculated)
Year: 1998

Method: calculated with HYDROWIN v1.64
Remark: Hydrolysis rate extremely slow. t 1/2 > 1 year.
Reliability: (2) valid with restrictions
calculated with accepted method
Flag: Critical study for SIDS endpoint
22-JUN-2004 (28)

Method: other: lother (laboratory): see remark

Remark: In a laboratory approach 5 g of IBDU was added to 100 ml buffer solutions of varous pH values and left at 30 degree C for 12 days. The total and urea nitrogen in the solution was measured.
Result: The lower the pH the more the total and urea nitrogen in the solution was measured day by day. It was assumed that the dissolution of IBDU progresses by the hydrolysis of dissolved IBDU by H+.
Test substance: other TS: IBDU, purity not stated
Reliability: (4) not assignable
insufficient documentation
Flag: Critical study for SIDS endpoint
01-FEB-2006 (20) (29)

Method: other
Test substance: other TS

Result: After dissolving in water IBDU gradually undergoes hydrolysis. One mole of IBDU gives two moles of urea and one mole of isobutylaldehyde. Urea will be released without the aid of microbes, while other condensates of urea and aldehyde are decomposed only with the aid of aerobic microbes. In this respect IBDU may be characterized as urea with chemically-con-trolled solubility.
Test substance: IBDU, purity not stated

Reliability: (4) not assignable
not assignable, insufficient documentation
Flag: Critical study for SIDS endpoint
01-FEB-2006 (29)

3.1.3 Stability in Soil

Type: field trial
pH: = 7.2

Year: 1977
Test substance: other TS: Isobutylidene diurea (IBDU), materials of two particle sizes (0.7 - 2.5 mm and 0.5 - 1.0 mm)

Result: Nitrogen release from IBDU may be largely independent of biological processes, since good color and growth of Kentucky Bluegrass (Poa pratensis) were maintained in the cool months of spring and fall. It is, however, dependent on particle size. N release was quicker from fine IBDU than coarse IBDU.
Test condition: The soil was a Hagerstown silt loam (fine, mixed, mesic Typic Hapludalf) seeded with Baron Kentucky bluegrass (Poa pratensis).
Irrigation was applied following IBDU application and when initial signs of wilt appeared.
IBDU treatments were applied at a rate of 197 kg N per ha and year, split equally into spring and fall applications for 3 years.
Reliability: (4) not assignable
insufficient information
23-JUN-2004 (30)

Type: laboratory
Soil temperature: 29 degree C

Result: Isobutylidenediurea gave relatively complete breakdown to urea in sterilized soil in two weeks at 29 °C. The pronounced effect of soil moisture and IBDU granular size on the mineralization of isobutylidenediurea is attributed to the sensitivity of this compound to hydrolysis.
Reliability: (4) not assignable
insufficient information
23-JUN-2004 (20)

Type: laboratory
Soil temperature: 30 degree C
Content of clay: = 28 %
silt: = 14 %
sand: = 58 %
Organ. carbon: = 1 %
pH: = 7.1

Year: 1969
GLP: no
Test substance: other TS: Isobutylidenediurea from Mitsubishi Chemical Ind., Japan, purity not stated

Result: Data on conversion to nitrate on incubation with soil show

the rapid biological availability of isobutylidenediurea (in the absence of hydrolysis conditions) with a release rate intermediate between the rapid release for urea and the more gradual release from urea-formaldehyde condensates.

Test condition: The soil used in the study was taken from Delaware farm land which had not been recently fertilized. The pH (originally 6.1) was adjusted to 7.1 with calcium oxide before use and buffered with calcium carbonate.

Reliability: (2) valid with restrictions
Limited documentation

23-NOV-2003 (31)

Type: laboratory
Concentration: 1000 mg/kg

Year: 1976
GLP: no
Test substance: other TS: Isobutylidenediurea (IBDU), commercial product, purity not stated

Result: Nitrogen release patterns from 0.7 to 0.8 mm IBDU particles in soil at initial pH`s of 5.7, 6.8, and 7.7 were determined. After four weeks of incubation, the amount of N released was equivalent to one-third of the IBDU-N for soil at pH 5.7, however, less amounts were released in soil at pH`s 6.8 and 7.7. Differences in N release were due to differences in NH4+-N concentrations, whereas concentrations of NO3--N were not related to soil pH throughout the 10-week incubation period. Thus, N release from IBDU was affected by soil pH shortly after application, but this effect disappeared as soon as the NH4+- accumulation was exhausted by nitrifying organisms.
Particle size had pronounced effects on N release in soil of initial pH`s 5.7 and 7.4. Nitrogen recoveries of 75% after 10 weeks, 58% after 21 weeks, and 50% after 32 weeks were obtained for particle diameters of 0.6 to 0.7 mm, 1.0 to 1.2 mm, and 1.7 to 2.0 mm, respectively.

Test condition: Drummer silty clay loam soil from the horticultural research Farm at Urbana, Ill.
Soil temperature: 21 +/- 0.5 °C
Soil humidity: 28 +/- 2 % moisture

Reliability: (2) valid with restrictions
Limited documentation

Flag: Critical study for SIDS endpoint

20-JUL-2004 (32)

Type: laboratory
Soil temperature: 26 degree C

Test substance: other TS: Isobutylidene diurea (IBDU) powder, purity not stated

Result: In soils with a comparatively low pH such as brown forest (pH 4.8) and cinnamonic podzoic soils (pH 5.5) a certain depression in the rate of nitrification was found whereas ammonification was predominant.

In calcareous chernozem, IBDU was mineralized up to 88 %; nitrates were predominating. The gaseous losses and the nitrogen immobilized by soil microflora were low (6.4 %). 94

% of the total amount of IBDU nitrogen introduced underwent microbiological transformation until the end of the experiments.

In the grey forest soil, mineralization of nitrogen from IBDU took place and both nitrates and ammonia were formed. Certain losses were observed due to volatilization of ammonia between the first and the fourth week. The sum of nitrogen losses reached up to 21.5 % by the end of the study period. 99 % of the introduced nitrogen was mineralized.

In the brown forest soils the quantity of ammonia nitrogen released was much higher than that of nitrate nitrogen. Nitrogen losses due to volatilization of ammonia were also observed (13.8 %). Minute losses occured by volatilization of nitrogen oxides between the first and the fourth week, corresponding to the intensity of the mineralization process. The total amount of mineralised nitrogen reached up to 98 %.
In the podsolic soil, which is representative of light-textured soils, losses of nitrogen by volatilization of ammonia were observed during the whole mineralization period, amounting to 15.4 %. The quantity of undecomposed nitrogen was small, ca. 8 % of the amount of IBDU nitrogen introduced.

The most regular release of mineral nitrogen was observed under conditions of calcareous chernozem and grey forest soil, where the intensity of the mineralization process was continuously high up to the end of the investigation.

High amounts of mineralized nitrogen were also accumulated in the initial stages under conditions of the brown forest and cinnamonic podzolic soil.

Test condition: Samples from different soils were investigated: calcareous chernozem (pH 8.3), grey forest soil (pH 5.9), brown forest soil (pH 4.8) and cinnamonic podsolic soil (pH 5.5)

Investigations were carried out in a model incubation experiment, using 2-liter glass vessels (hermetic) under controlled conditions of soil moisture (60 % of the water holding capacity) and 26 °C.

The compounds studied were urea-formaldehyde condensate, nitroform, HTI-2 (specific synthetized laboratory sample), urea croton-aldehyde, Floranid and IBDU.

The test substances were added equivalent to 50 mg of nitrogen per 100 g of absolutely dry soil (corresponding to about 160 mg IBDU / 100 g soil).

Study period: 24 weeks.

Non-treated soil and urea were used as controls.

No. of replicates: no information

Reliability: (2) valid with restrictions

Limited documentation

Flag: Critical study for SIDS endpoint
20-JUL-2004 (33)

Type: laboratory

Result: N release from IBDU was much more rapid in acidic than alkaline soil. The authors concluded that N release occurred at sufficiently rapid rates in soil up to pH 8.3. Particle size had large effects and was considered a means of controlling N release rate. Incubation was carried out only for 19 days.
Reliability: (4) not assignable
Secondary citation
23-JUN-2004 (34)

Type: laboratory

Test substance: other TS: IBDU powder

Result: At 25 °C mineralization of IBDU powder (5 mg N / 20 g silt loam soil, 52 % H2O) was fast (about 80 % after 2 weeks), but at 10 °C the increase of nitrogen extended over eight weeks. Temperature dependence of IBDU mineralization is coupled with hydrolysis of urea.
Reliability: (4) not assignable
Secondary citation
23-JUN-2004 (35)

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 v3.00
Year: 1998

Method: bond estimation method
Result: Henrys Law Constant (calculated at 25 °C):
H = 4.07*10E-18 atm-m3/mole = 4.11*10E-13 Pa*m3/mole.
Reliability: (2) valid with restrictions
calculated with scientifically accepted method
Flag: Critical study for SIDS endpoint
22-NOV-2003 (36)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (measurement)
Year: 1966

Result: In the actual use of IBDU as a fertilizer on soil, dissolved IBDU will be hydrolyzed to urea and isobutyraldehyde. The

aldehyde will easily evaporate into air. A smaller amount will be oxidized to the acid and be adsorbed by soil or decomposed and consumed by soil microorganisms during relatively short periods (2-3 weeks).
Reliability: (4) not assignable
not assignable. Short summary lacking experimental details.
Flag: Critical study for SIDS endpoint
23-JUN-2004 (20)

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

Remark: calculated with Level 1, v2.11 Model.
Parameters used:
temperature = 25 °C,
log Kow = -0.903
water solubility = 2700 g/m3,
vapour pressure = 4.7*E-12 Pa,
Melting Point = 205 °C,
Amount of chemical = 1.00*E05 kg
Volumes (m3):
air = 6.00*E09,
water = 7.00*E06,
sediment = 21000,
soil = 45000,
susp. Sedmt. = 35.0,
fish = 7.0,
aerosol = 0.120
Result: water: 99.998 %,
air: 1.05E-11 %,
soil: 9.89E-04 %,
sediment: 1.00E-03 %
susp. sedmt.: 6.42E-06 %
fish: 6.25E-07 %
aerosol: 4.44E-06
Reliability: (2) valid with restrictions
scientifically accepted calculation method
Flag: Critical study for SIDS endpoint
20-JUL-2004 (37)

Media: other: Koc
Method: other (calculation)
Year: 1998

Result: log Koc: 1.418, estimated Koc: 26.19
Reliability: (2) valid with restrictions
calculated with scientifically accepted method
Flag: Critical study for SIDS endpoint
22-NOV-2003 (36)

Media: other: soil - water
Method: other (measurement)
Year: 1974

Result: Depending on soil quality between 0.1 and 0.9 per cent of the applied N from Isobutylidenediurea were lost as NO3- and 0.1 to 0.6 per cent as NH4+ in leachate (application rate: 146 kg IBDU/ha at several rates). Total losses (NO3- plus NH4+) ranged between 0.2 per cent of the applied N (sandy loam soil)

and 1.4 per cent (90% sand plus 10% peat). All NO3- concentrations resulting from IBDU application were low but continuous throughout the study. Concentrations of NO3- in runoff from soils greens treated with organic sources like IBDU never exceeded 7 mg/l. Concentrations of NH4+ in all samples analyzed were small occasionally exceeding 1 mg/l. The loss of NH4+ decreased as the amount of soil in mixtures increased.

Test condition: Different treatments (ammonium nitrate, ureaformaldehyde, 12-12-12, Milorganite, IBDU) were applied to individual 9 m2 golf greens constructed in 1972 and separated from each other by plastic sheets and equipped with subsurface tile drainage systems draining into 208-liter collection systems. The upper 30 cm of green profiles were constructed using mixtures of 90 % sand plus 10% peat moss, 85% sand plus 5% clay soil plus 10% peat moss, 80% sand plus 10% clay soil plus 10% peat moss, and 100% sandy loam soil. At least four replicates were included. All greens were sprigged with Tifdwarf bermudagrass (Cynodon dactylon) in the spring and overseeded inNovember with a mixture of ryegrass (Lolium perenne), bluegrass (Poa pratensis), fescue (Festuca arundinacea) and Bentgrass (Agrostis stolonifera).

Greens were irrigated 1 cm/day between May and September and 1 cm every other day during the remainder of the year. These rates were designed to be in excess of evapotranspiration and provide some leachate while remaining within the range of normal turf management procedures.

Test substance: Isobutylenediurea (IBDU), purity not stated

Reliability: (2) valid with restrictions
Limited documentation

Flag: Critical study for SIDS endpoint

30-JAN-2006 (38)

Media: other: soil - water

Method: other (measurement)

Year: 1991

Result: Depending on soil quality, up to 0.2 per cent of the applied N from Isobutylidenediurea were lost in mineralized form in leachate after 1.5 years (application rate: 220 kg Isodur/ha, 5 times per year; equivalent to about 733 kg N/ha).
After irrigation with 200 mm, approx. 8 % of the applied N were found in 20 cm depth. When the soil was irrigated with 80 mm during the same time period, only 0.2 % were found in this same soil layer.

Test condition: laboratory experiment with clay soil, not planted. application rate of isobutylidene diurea: 796 kg N / ha. Irrigation: 200 mm during 2 days.

Test substance: Isodur, purity not stated

Reliability: (4) not assignable
limited documentation, insufficient detail reported for assessment.

Flag: Critical study for SIDS endpoint

23-JUN-2004 (39)

Media: other: soil - water

Method: other (measurement)

Year: 1987

Result: Only small amounts (< 1%) of the applied N from Isobutylidenediurea were lost in leachate (application rate: 200 kg Isodur/ha, 3 times between November and June).
Test condition: Pot experiments, soil planted with Lolium perenne (40 %) and Poa pratensis (60%).
Test substance: Isodur, purity not stated (with 28 % IBDU)
Reliability: (4) not assignable
insufficient documentation
23-JUN-2004 (40)

21-JUN-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, non-adapted
Concentration: 100 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: 78 % after 28 day(s)
Result: readily biodegradable
Kinetic:

7 day(s)	72 %
14 day(s)	78 %
21 day(s)	78 %
28 day(s)	78 %

Control Subst.: Aniline
Kinetic:

7 day(s)	60 %
14 day(s)	72 %

Deg. product: not measured

Method: OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year: 2002
GLP: yes
Test substance: other TS: Source: Chemicals Evaluation and Research Institute (CERI), Japan (Lot No.: H1305, purity: 90%)

Result: Following results were reported.

In the test vessels N remained as NH3 form and after the cultivation and extents of biodegradation were calculated using ThOD based on NH3.

Biodegradation rates (28 days)

by BOD	77%	81%	77%	(Av. 78%)
by DOC	89%	90%	90%	(Av. 90%)
by HPLC	100%	100%		(Av. 68%)

Based on the BOD analysis, the 10-day window was fulfilled.

After the 28 days of cultivation, pH remained within the required range of 6.0 to 8.5.

Oxygen consumption of the blank vessels was 14.3 mg/l.

Test condition: Sludge samples were collected from the 10 sites such as sewage treatment works, industrial wastewater treatment works, rivers, lakes and sea throughout Japan and mixed thoroughly. A filtrate (500 ml) of the supernatant of the mixed sludge was then mixed with 5 l of the filtered supernatant of an activated sludge in the present use.

After the combined sludge solution (pH adjusted at 7.0+/-1.0) was aerated for 30 min, the supernatant corresponding to 1/3 of the whole volume was discarded. An equal volume of pure water was then added to the remaining portion and the supernatant (final concentration of 0.1 %) of the resulting sludge solution was mixed with sterile mineral medium and continuously aerated at 25+/-2 °C to allow minimization of residual dissolved organic carbon according to the procedure outlined in the TG. The test was conducted in triplicate with test substance insterile mineral medium at 100 mg/l and with a small volume of the activated sludge to give a final concentration of 30 mg/l in 300 ml.

A blank control (sterile mineral medium only), positive control (aniline as reference compound at 100 mg/l) and test substance control (test substance in pure water at 100 mg/l) in 300 ml were incubated simultaneously. Oxygen consumption resulting from biodegradation of the compounds was measured over 28-day test period using an Okura Electric Closed System Oxygen Consumption measuring apparatus (Coulometer). Percentage biodegradation was calculated based on BOD, TOC and HPLC analysis. The test solutions were maintained in a dark room at a temperature of 25+/-1 °C and continuously stirred bymagnetic stir bars over the 28-day test period. Degradation (%) was obtained from the following equations:

BOD:
Degradation (%) = (BOD-B)/ThOD x 100
BOD (mg): BOD in (sludge + test substance system)
B (mg): BOD in sludge blank
ThOD: theoretical oxygen demand required when test substance was completely oxidized (NH3-N).

HPLC:
Degradation (%) = (Sw-Ss)/Sw x 100
Sw (mg): Residual amount of test substance detected by HPLC in (water + o-toluidine system)
Ss (mg): Residual amount of test substance detected by HPLC in (sludge + test substance system)

Reliability: (2) valid with restrictions
All relevant data given in robust summary; original study requested but not jet available for review.

Flag: Critical study for SIDS endpoint

01-FEB-2006 (41)

Type: aerobic
Inoculum: activated sludge, domestic
Concentration: 19.5 mg/l related to DOC (Dissolved Organic Carbon)
Contact time: 28 day(s)
Degradation: = 85 % after 28 day(s)
Kinetic: 7 day(s) = 8 - 14 %

14 day(s) = 24 - 30 %
21 day(s) = 48 - 75 %
28 day(s) = 78 - 91 %

Control Subst.: other: not reported
Deg. product: not measured

Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year: 1988
GLP: no

Result: other: biodegradable, but not "readily biodegradable" according to OECD criteria (ready test pass level reached, but not the 10 day window)
Test condition: Inoculum: activated sludge from municipal waste water plant, not adapted.
Test Concentration: 47 mg IBDU/l
Test substance: Isodur, purity not stated
Reliability: (2) valid with restrictions
limited documentation
Flag: Critical study for SIDS endpoint
23-JUN-2004 (42)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

Species: other: aquatic organisms

Remark: No experimental data on bioaccumulation is available. However, the logKow of -0.903 indicates no significant potential for bioaccumulation.
01-FEB-2006 (43)

3.8 Additional Remarks

Memo: Isobutylidenediurea degradation by Rhodococcus erythropolis

Remark: The enzyme isobutylidenediurea amidinohydrolase was purified from biomass of Rhodococcus erythropolis, characterized and shown to hydrolyze the fertilizer to urea and isobutyraldehyde at a molar ratio of 2:1. Growth of the bacterium in the presence of isobutylidenediurea led to an increased expression of the constitutively synthetized enzyme.
Test substance: IBDU, purity not stated
Reliability: (2) valid with restrictions
Basic data given, meets scientific principles
21-JUN-2004 (44)

Memo: Nitrous oxide emission and denitrification nitrogen losses from soils treated with isobutylenediurea (=IBDU; fertiliser)

Remark: A diminished denitrification rate over time for all the treatments (distinct soil types and different soil moisture levels) was probably associated with decay of denitrifying

microbes. N2O emission could generally be correlated with the denitrification rate and the contribution of nitrification was estimated to be low. Generally the IBDU treatment gave rise to the greatest denitrification N loss, while losses due to N2O emission were lower than control in many of the trials. The ratio denitrification loss:N2O emission increased with the soil moisture and clay content of each type of soil.

Reliability: (2) valid with restrictions
Basic data given, meets scientific principles

21-JUN-2004 (45)

Memo: other

Remark: In a laboratory anaerobic incubation experiment Isobutylidenediurea was added to four representative agricultural soils of Bangladesh. IBDU enhanced ethylene formation in 3 of the 4 soils. With increasing pH of the soils the ethylene production decreases.

Test substance: IBDU, purity not stated

Reliability: (4) not assignable
Insufficient documentation and no standard method.

20-JUL-2004 (46)

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Oncorhynchus mykiss (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: 1000
LC0: 1000
LC50: > 1000
LC100: > 1000
Limit Test: yes

Method: other: OECD guideline 203 (1984)
Year: 1986
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Purity of test substance: 88%.
LC values related to nominal concentrations.
Result: No symptoms were noted. No mortality.

Undissolved test substance was visible on the water surface and on the bottom of the aquarium.
Test condition: Concentration tested: 1000 mg/L (this selection was based on the results of a range finding study which resulted in a LC50 after 96 hours of 1000 mg/L).

Preparation of the test substance: the substance was added to the test water without any pretreatment; subsequently the fish were placed into the aquaria.

Test animals:
body length between 4.9 and 6.5 cm, body weight between 1.4 and 3.4 g, corpulence factor 1.2.

Housing:
photoperiod: 16 hours light and 8 hours darkness.
Slight aeration.
water total hardness: about 2.5 mmol/L, Oxygen content: > 60% of air saturation value, pH: about 8.0
Water temperature: 12 °C
Adaptation period: 7 days
test vessels: glass aquarium with a stainless steel frame (80 cm x 35 cm x 46 cm), 0.22 g Fish / L test water.
no. of animals per test concentration: 10

Determination of mortality and symptoms: at 1, 4, 24, 48, 72, 96 hours.

Statistical analysis: probit analysis (Finney, 1971).
Reliability: (2) valid with restrictions

No information on stability of test substance under test conditions available, no analytical monitoring.
Flag: Critical study for SIDS endpoint
01-FEB-2006 (47)

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: = 250
EC50: = 500
EC100: > 500

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

Result:

Conc. [mg/l]	Immobile daphnids after 0h	24h	48h
Control	0	0	0
62.5	0	0	0
125	0	0	0
250	0	0	2
500	0	2	10

In the stock solution and in the test vessels test substance was visible over the whole test period.

Test condition: The test was performed according to 84/449/EEC, C.2 using daphnids from a in-house breeding stock in a static exposure procedure.

No solubilising agents were used.
After preparing a stock solution the following nominal concentrations plus an untreated control were tested: 62.5, 125, 250 and 500 mg/l. For each concentration and for the control and solvent control 4 replicates were used.
O2-concentrations and pH-values were measured in all test vessels. The oxygen concentrations were 7.74 - 8.9 mg/l, the pH values ranged from 7.84 to 8.08.

No chemical analysis of the test substance was carried out. The EC values are related to nominal concentrations.

Reliability: (2) valid with restrictions
standard guideline study, but no GLP and no analytics were performed

Flag: Critical study for SIDS endpoint
01-FEB-2006 (48)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: growth rate
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: > 500
EC20 : > 500
EC90 : > 500

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf

Gruenalgen
Year: 1988
GLP: no
Test substance: other TS: Isodur (Isobutylidendiharnstoff), purity not stated

Remark: EC values relate to nominal concentrations by which growth was inhibited by 20, 50 or 90 per cent (as compared to controls).

pH of untreated controls at 0 hrs : 7.7
pH of untreated controls at 96 hrs: 8.0 - 8.1

pH of treated cultures at 0 hrs (31.25 - 500 mg/L): 7.6
pH of treated cultures at 96 hrs (31.25 - 500 mg/L): 10.3 - 10.4

pH was measured after 96 h, but not after 72 h. The increase of pH (observed in all treatments) may be due to CO2 depletion, because after 72 h no exponential growth has been observed.
Biomass increased to a 100-fold at 72 h.

Result: At the exposure period of 72 h:

EC20 = 500 mg/l
EC50 > 500 mg/l
EC90 > 500 mg/l

Inhibition at 72 h was 20 % at 500 mg/l and 11 % at 250 mg/l. At 96 h no inhibition was observed, biomass increased by 10 % at 500 mg/l and 9 % at 250mg/l compared to the control.

Test condition: medium: as recommended by OECD guideline 201.
pH: about 8.
temperature: 23 +/- 2 °C.
light: 120 uE/m*m*s.
culture: 100 ml flasks, weekly passage.
growth period: 72 hours.
incubation: 10 ml of algae inoculum (1000 cells/ml), 96 hours.
measurements: fluorescence (685 nm) after 0, 24, 48, 72 and 96 hours; pH at 0 and after 96 hours.
acceptance criteria: cell growth of controls after 72 hours at least 16-fold.
test concentrations: 0, 31.25, 62.50, 125, 250, 500 mg/l.

Reliability: (2) valid with restrictions
standard guideline study, but no GLP and no analytics were performed

Flag: Critical study for SIDS endpoint
01-FEB-2006 (49)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: ca. 640

Method: other: growth inhibition test
Year: 1987

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

Remark: A saturated solution of Isodur contained 2.4 g of organic carbon. If diluted 1 : 8.5, this solution did not elicit any toxic reaction.
Reliability: (2) valid with restrictions
Test procedure comparable to national standard. Limited documentation.
Flag: Critical study for SIDS endpoint
08-JUN-2004 (50)

Type: soil
Species: other bacteria

Method: other: see Remark
Year: 1974
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The influence of the slow-release fertilizers ureaform, crotonylidenediurea and isobutylidenediurea on some natural soil microbiological populations and activities were studied and compared to those of urea. All measurements were done with the aid of pot experiments (2-liter pots containing 1.0 kg of wet soil). The soil used was a sandy loam with a pH of 6.5 and an organic matter content of 2.34 %. They were incubated in the dark at room
temperature. The soil moisture content was kept at 70 % of field capacity. The influence of the fertilizers was evaluated by applying the compounds at a low and at a high dose, corresponding respectively with the application of 173 kg N/ha and 1215 kg N/ha (222 and 1550 mg IBDU / kg wet soil). A control to which no fertilizer was added and a soil sample to which urea was added, were included. The degree of significance of the differences between the treated and the control soils was calculated by means of the Student Test on Paired Observations.
Result: Of the populations studied, none were significantly inhibited, but stimulations were noticed after 2 and 7 weeks with nitrite-forming microbes and with the fungi and cellulolytic microbes by isobutylidenediurea (IBDU) when applied at a rate of 1550 mg/kg wet soil (equivalent to about 1215 kg N / ha). The increase of the fungal population and of the number of cellulolytic propagules in the soil suggests that these groups might be directly involved in the degradation of IBDU. No significant increase of the Nitrobacter-population could be detected. IBDU did not significantly enhance the ammonifying microorganisms. All fertilizers reduced slightly and temporarily the urease, phosphatase and saccharase activity of the treated soils even when applied at the low dose. However, these reductions never surpassed 35 percent of the corresponding control values and the enzymatic activities gradually increased to control values at the twentieth week. Only 38 percent of the amount of carbon added, was recuperated as carbon dioxide. This indicated that IBDU was hydrolyzed into two urea molecules and one molecule of isobutyraldehyde and that this latter compound is not rapidly further metabolised. IBDU liberated immediately a small amount of ammonium and after 7

weeks about 72 percent of the amount of N added were detected as ammonium and, mainly, as nitrate (urea: 98 percent). Nitrite concentrations in soil were never increased. As to the pH, no significant shifts were observed with the low dose. When added at the high dose, a slow increase of 1.5 units followed by a return to the pH of the control soil was observed (no further details given in the publication).

Reliability: (2) valid with restrictions
Though not specifically mentioned in the publication, it seems that no replicates were used in this study.

Flag: Critical study for SIDS endpoint

08-JUN-2004 (51)

Species: activated sludge

Remark: An inhibition of activated sludge is not anticipated if IBDU is added in low concentrations.

Reliability: (4) not assignable
manufacturer/producer data without proof

22-NOV-2003 (52)

Result: Four natural organic fertilizers, alone or in combination with isobutylidenediurea (IBDU) were compared with IBDU alone for their effect on soil/root microbial populations associated with bermudagrass grown on a golf course putting green in southern Florida/USA. No significant differences in microbial populations were observed over a 2-year period.

Test condition: Plots (2m x 3m) were fertilized every 2 weeks (four replicate plots per treatment). A total of 879 kg N/ha was applied per year and the area was topdressed at least once per month to prevent thatch accumulation. Non-sterilized topdressing material was composed of the same material as the root-zone mix (80% sand, 20% Canadian shagnum peat). The study was conducted in sub-tropical climate (southern Florida, USA). Populations of total fungi, total bacteria, fluorescent pseudomonads, Stenotrophomonas maltophiia, actinomycetes and heat-tolerant bacteria were monitored every 3 months during the 2-year study period.

Test substance: Isobutylidenediurea blended with potassium magnesium sulfate

Reliability: (2) valid with restrictions
No appropriate negative control was used to evaluate IBDU effects. Summary lacking experimental details. The use of sand and peat topdressing material may have masked effects.

Flag: Critical study for SIDS endpoint

04-JAN-2002 (53)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: bermudagrass (Cynodon sp)

Year: 1975
GLP: no
Test substance: other TS: IBDU "fine", 0.7 to 1.4 mm diam. pellets

Result: There was no toxic response of bermudagrass to IBDU at soil pH 5.2 to 7.3 or at any combinations of IBDU with Ca(OH)2 and/or urea.
Test condition: Application at 1.5 to 5.9 kg N / are (approx. 485 - 1900 kg IBDU/ha) in all combinations with 0, 0.25, and 0.50 kg urea-N/are every week, and of 0 and 2.4 kg Ca(OH)2/are at initiation of tests.
Reliability: (2) valid with restrictions
Summary lacking experimental details
Flag: Critical study for SIDS endpoint
04-JAN-2002 (54)

Species: Lolium perenne (Monocotyledon)
Endpoint: other

Year: 1975
GLP: no
Test substance: other TS: IBDU "fine", 0.7 to 1.4 mm diam. pellets

Result: A 2.2 kg N/are rate (approx. 700 kg IBDU/ha) of IBDU resulted in chartreuse green ryegrass when soil pH was above 7.0. At 3.3 to 7.3 kg IBDU-N/are definite toxicity symptoms were produced at 1 month after applicaton, regardless of soil pH (chartreuse-yellow ryegrass). In all instances, toxicity symptoms had disappeared at 3 months after IBDU application. Tissue analysis showed an inverse correlation with Mn content. There was no off-color response to sulfur-coated urea or ureaform applied at equivalent N rates.
The toxic symptom exhibited by the ryegrass was not typical of that due to high ammonium. It was postulated that if ammonium rather than some toxic constituent unique to IBDU is involved, the symptoms are the result of the effect of an extended period (of otherwise nonlethal level) of ammonium on soil pH and thus Fe and Mn availability.
Test condition: single application at 1 to 7.3 kg N / are (approx. 322 - 2355 kg IBDU/ha) to triplicate plots (1.8 m x 2.7 m). The soil was a typical quartzipsamments loamy fine sand and the pH of individual plots varied from 6.4 to 7.2 depending on previous history. In a second experiment three replicates of plots of similar pH were each tested with four levels of IBDU-N, ranging from 1 to 4.9 kg N/are. In both experiments, turf color was evaluated both visually and by determination of chlorophyll by extraction of fresh clippings.
Reliability: (2) valid with restrictions
Summary lacking experimental details
Flag: Critical study for SIDS endpoint
04-JUN-2004 (54)

Species: other terrestrial plant: Boronia megastigma Nees
Endpoint: other

GLP: no data
Test substance: other TS: IBDU (31% N)

Result: With IBDU, applied up to 100 kg N per ha to Boronia (a typical Australian native plant), toxicity did not occur, because the N amount from IBDU solubilized and available to the plants at any given time was supposed to be small and thus would have been within the assimilation capacity of the plant.
Test condition: Application rates: 25, 50 and 100 kg N per ha (corresponding to approx. 81, 162 and 323 kg IBDU / ha). Each rate was applied either in one dose in spring or split into two or three equal doses, applied during the year.
Reliability: (2) valid with restrictions
Summary lacking experimental details
Flag: Critical study for SIDS endpoint
04-JUN-2004 (55)

4.6.3 Toxicity to Soil Dwelling Organisms

Type: artificial soil
Species: Eisenia sp. (Worm (Annelida), soil dwelling)
Endpoint: mortality
Exposure period: 14 day(s)
Unit: mg/kg soil dw
NOEC: = 250
LC0: = 250
LC50: = 648
LC100: = 1000
LOEC : = 500

Method: other: OECD guideline 207 (1984)
Year: 2001
GLP: yes
Test substance: other TS: Isobutylidendiharnstoff, purity 90.1 %

Result: LC50 (14 d): 648 (95% confidence limits 587-716) mg/kg
LC50 (7 d): 648 (95% confidence limits 591-712) mg/kg.

No particular behavioural or morphological changes were observed.

The validity criteria for acceptance of the test were fulfilled (LC50 of the control substance chloracetamide was 16.7 mg/kg).

pH of soil at day 0: 5.8
water content of soil at day 0: 33.3%
water content of soil at day 14: 33.1%

Test condition: The test substance was weighed and added directly to each parallel. No dilution series was prepared.
Concentrations tested: 125, 250, 500, 1000 mg/kg soil (nominal concentrations)
Mortality was assessed at day 7 and at day 14 after application.
The test animals were adults (they had a clitellum) and were less than 1 year old.
Water content of the soil was adjusted to 33 +/- 2% of dry

weight just before performance of the test.
Test soil: 69.7% quartz sand, 20% kaolin clay, 10% sphagnum peat, 0.3% CaCO3.
Test temperature: 18 - 22 °C
Test vessel: 1 liter glass jars with glass lids
Test volume: 750 g artificial soil (dry weight)
No of animals per vessel: 10
Total no of animals per concentration: 40
no of replicates per concentration: 4
no of replicates for control: 4
no of parallels without animals: 1 (for determination of water content, pH and temperature measurements)
age of animals at the beginning of test: 9 months
weight of animals: 300 - 600 mg (start of test)
Illumination: continuos illumination, about 400 - 800 lux
feeding: none
adaptation: 24 hrs before the test, in test substrate without test substance
measurement of temperature: continously during the test in a separate vessel close to the test vessels
measurement of pH: at the beginnning of the test according to DIN/ISO 10 390
measurement of water content of the test substrate: day 0 and day 14 in a separate vessel close to the test vessels
weight of animals: determined at day 0 and day 14
Statistics: Duncans multiple range test for the determination of NOEC/LOEC; the moving average method was used for the calculation of the LC50 value.
Validity criteria: mortality in controls below 10% at the end of the test; LC50 of control substance (chloracetamide) within acceptable range.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
08-JUN-2004 (56)

Species: Lumbricus sp. (Worm (Annelida), soil dwelling)
Endpoint: other

Test substance: other TS: IBDU, no purity stated

Result: Effects of fertilizers on lumbricid earthworms in uncultivated turfgrass on loamy sand soil were related to their effects on soil acidity. IBDU had effects on earthworm numbers and biomass and lowered pH dose-dependently by 1 to 1.5 units.
Endogaeic species of earthworms such as Aporrectodea spp. were more strongly affected than the epigaeic group of Lumbricus spp., although an exception was noted for A. caliginosa tuberculata. Strongly acidified soils contained more organic matter than soils which were less acidified, accumulations of soil organic matter were associated with accumulations of surface thatch.
The study indicates that the application of fertilizers to grasslands for long periods may have a deleterious effect on earthworms in the absence of liming, as the effects were related to changes in soil acidity.

Test condition: The loamy sand experimental site was situated in the Netherlands and had a turf consisting of mainly Agrostis capillaris, Lolium perenne, Poa trivialis and P. annua, with small amounts of Holcus lanatus and Festuca rubra. The site

was divided into a set of 2.5 x 3.0 m plots with 2 replications each of 18 fertilizer treatments, the factorial combinations of 6 different nitrogen fertilizers and 3 rates of applications equivalent to 60, 120 and 180 kg N per ha and year for a total period of 20 years.
All plots received a supplementary treatment of P2O5 (50 kg) and K2O (60 kg) per ha and year and lime was added in 1983 to stabilize the pH level. No organic fertilization or herbicides were applied.

IBDU was applied twice a year in mid-March and at the beginning of August.

Earthworms were sampled by hand-sorting of excavated soil blocks 30 cm2 x 15 cm deep, followed by extraction from deeper layers using formalin and their biomass determined. The populations were separated into (1) an epigaeic group of predominantly Lumbricus rubellus (Hoffm.) with some Lumbricus castaneus (Sav.) and (2) an endogaeic group consisting mainly of Aporrectodea caliginosa (Sav.) and Aporrectodea rosea (Sav.).

Samples for soil analysis were taken from the uppermost 0-5 cm horizon.

Statistical procedures consisted of analysis of variance (ANOVA) on log transformed data. Differences between means were assessed wth the method of least significant differences (LSD) among means.

Reliability: (4) not assignable
No data relating to untreated controls were provided.

Flag: Critical study for SIDS endpoint

30-JAN-2006 (57)

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Memo: The substance is used as fertilizer. If used according to the recommendations, no adverse effects on the environment are to be expected.

Reliability: (4) not assignable
manufacturer/producer data without proof

20-JUL-2004 (1)

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo: In vivo
Type: Absorption
Species: sheep
No. of animals, males: 5
No. of animals, females: 0
Doses, males: 60 g/d (ca. 1260 mg/kg bw)
Route of administration: oral feed

Result: Four mutton Merino wethers averaging 47.6 kg body weight were fed a semi-synthetic diet containing, as the only nitrogen source, 15N-labelled IBDU (60 g/day). The animals were killed 2 1/2, 7 1/4, 12 and 24 hours after isotope intake. The TCA-soluble and TCA-precipitable portions of blood plasma, urine and liver were analysed for 15N-content, the whole blood plasma for NH3, urea and IBDU, and urine for these 3 compounds in labelled and unlabelled form, respectively. From another wether provided with a ligature at the abomasus entry and killed 24 hours after isotope intake, the same analyses were taken. Whilst all sheep revealed an almost equal urea level ranging from 18 to 30 mg per 100 mL, IBDU was not detectable but in the animal killed 12 hours after the start of the experiment, amounting to 17.3 mg/100 mL blood plasma (ca. 2.2 % of the last IBDU - intake). The blood plasma of the wether with ligature was found to contain up to 18 mg IBDU / 100 mL. This finding is regarded as evidence of the possibility of IBDU to be absorbed through the rumen wall. The 15N-IBDU was incorporated into the blood plasma proteins. In the urine, only low amounts of unchanged IBDU (max. 1 % of intake) were recovered within 24 hours. Max. 4 % of 15N-intake were recovered in the livers (7.25 h sacrifice). After 24 h, about 50 % of the applied 15N were still present in the rumen.
However, it was not determined whether this was due to 15N-IBDU, or from labelled proteins or urea. The passing of nitrogen from IBDU into the body pool was assumed from the results of recovery experiments which demonstrated the presence of 15N in plasma proteins and liver.
Test substance: 15N-Isobutylidene diurea
Reliability: (2) valid with restrictions
limited documentation
07-JUN-2004 (58) (59)

In Vitro/in vivo: In vitro
Type: Absorption
Species: sheep
No. of animals, males: 5
No. of animals, females: 0
Doses, males: 60 g/d (ca. 1260 mg/kg bw) for 3 or 6 weeks
Route of administration: oral feed

Result: Result:
Six mutton Merino wethers (44.0-52.6 kg) were adapted for 3 or 6 weeks to a semisynthetic diet containing 60 g IBDU per animal and day.

First experiment:
Two sheep received 30 g IBDU with 1259 mg 15N-IBDU and 680 µCi

14C-IBDU(C1-labelled) via the rumen fistula. The animals were placed in respiration cages.
The peak of specific 14C-CO2 activity in the expired air (including ruminal gas) was observed 2 h after beginning of the experiment. Overall, about 50 % of the 14C applied was found in the expired air.
The 15N incorporation into the protein fraction of blood plasma reached a constant level between the 29th and 47th h of the experiment.
3.5 % of the 14C and 23 % of the 15N were excreted in the urine within 6 days. 20 % of the 15N in urine could be detected as 14C-isobutyl residues. An average of 22 % of the 15N applied was excreted in faeces (3.8 % of the applied 14C). When sacrificed on the 7th day of the experiment, atom %15N excess in liver, kidneys, heart and muscle were 0.17, 0.14, 0.08 and 0.05, respectively.

Second experiment:
Four sheep received 701 mg 15N IBDU excess per animal. After 2.5, 7.25, 12 and 24 hours, the animals were killed without having been fed again.
At the timepoints given, 15.6, 24.1 3.3, and 3.8 % of the 15N-intake were recorded in the rumen. At 7.25 h, 40 % of the 15N in the rumen was in the form of IBDU, after 12 hours it was 10 %. IBDU was only detectable in the blood of the animal sacrificed 12 h after dosing (concentration: 17.3 mg/100 ml plasma). The N15 was incorporated in blood plasma proteins. In the urine, small amounts of unchanged IBDU (max. 1 % of intake) were recovered.

Test substance: 15N-Isobutylidene diurea; 14C-Isobutylidene diurea (C1-labelled)
Reliability: (2) valid with restrictions
limited documentation
26-JAN-2005 (60) (59)

In Vitro/in vivo: In vivo
Type: Metabolism

Result: Only about 30% of IBDU is hydrolyzed in the rumen, 70% is hydrolyzed in the lower intestinal tract.
Reliability: (4) not assignable
insufficient documentation
22-JUL-2004 (61)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: no data
Sex: male/female
No. of Animals: 10
Vehicle: water
Value: > 10000 mg/kg bw

Method: other: BASF-Test

Year: 1967
GLP: no
Test substance: other TS: Isobutylidene diurea, purity ca. 90-96% (0-3% urea, 2% potassium sulfate)

Result:
- Results are given as dead animals/total number of animals at this dose at 24 h, 48 h and 7 days after dosing:
  800 mg/kg bw: 0/10, 0/10, 0/10
  1000 mg/kg bw: 0/10, 0/10, 0/10
  1600 mg/kg bw: 0/10, 0/10, 0/10
  3200 mg/kg bw: 0/10, 0/10, 0/10
  6400 mg/kg bw: 0/10, 0/10, 0/10
  10000 mg/kg bw: 0/10, 0/10, 0/10
- Symptoms per dose group: 800-1600 mg/kg bw : no symptoms
  3200-10000 mg/kg bw: piloerection and tachypnoea
  Necropsy: Four animals showed chronic bronchitis and bronchi ectases, all other animals without findings in the organs. Necropsy was performed by a pathologist.

Test condition:
- Doses: 800, 1000, 1600, 3200, 6400, 10000, mg/kg bw; The doses were applied as 10%, 16% or 30% preparations of the test substance in aqua dest.
- post-exposure observation period: 7 days
- Route of administration Oral; gavage
- Species/Sex: Rats ; Males and females
- No. of animals per sex per dose: 5 animals/sex/dose; no vehicle control

Reliability: (2) valid with restrictions
post observation period 7 days, no data on strain.
Flag: Critical study for SIDS endpoint
01-JUN-2004 (62)

Type: other
Species: cattle
Strain: other: Simmental-Rasse
Sex: male
Vehicle: water
Doses: 3000; 5000 mg/kg bw

Method: other: see test conditions
Year: 1980
GLP: no
Test substance: other TS: IBDU, N content 35.5 %

Remark: 3000 mg/kg bw: no clinical symptoms. Blood levels of NH3 increased from 0.5 mg/L to 3 mg/L, urea levels increased slowly from 189 to 515 mg/L during 24 hours. All changes were reversible within 5 days.
5000 mg/kg bw: caused toxicity symptoms which were reversible within 3 hours (defecation, increased breathing frequency, muscular fibrillations). NH3 blood levels increased 9-fold during the first hour after application and the increase in keton bodies was 2-fold. Urea levels increased from 197 to 712 mg/L after 1 day. The increases were observed for 3 days and returned to normal later on. The results demonstrated that at doses of 5000 mg/kg bw IBDU exerted its toxic effects mainly through its hydrolysis products (urea, NH3, isobutyraldehyd).

Test condition: Total No. of animals: 6
No. of animals per dose: no data

Blood samples were taken before, 1, 3, 6 and 24 hours after application. Daily samples were taken for the following 7 days. Blood samples were analysed for hemoglobin, erythrocytes, leucocytes, urea, NH3, keton bodies, GPT and GOT.

Reliability: (4) not assignable
limited documentation, no data on No. of animals per dose, no standard species for which no guideline and therefore no protocol is available

22-JUL-2004 (61)

Species: sheep
Sex: no data
Vehicle: water
Doses: 5000, 7500, 10000 mg/kg bw

Method: other: no data or see Test Conditions
Year: 1980
GLP: no
Test substance: other TS: IBDU, N content 35.5 %

Remark: 5,000 mg/kg bw: no clinical symptoms reported

7,500mg/kg bw were lethal for one out of two sheep within 2 hours after application. Clinical symptoms observed were defecation, muscular fibrillations, tachpnoea, tremor.

10,000 mg/kg bw were lethal for the two animals studied.

Necropsy of the animals that died showed inflated rumens, filled with liquor and gas. Oesophagus, trachea and bronchi were filled with foamy liquid and haemorrhagic infiltrations were observed in the duodenum and abomasum. Liver and spleen were hyperaemic, and petechiae were seen in the kidneys.

Test condition: Total No. of animals: 12
No. of animals per dose: 5000 mg/kg bw: 2 animals, 10000 mg/kg bw: 2 animals, no further data;
blood samples were taken before, 1, 3, 6 and 24 hours after application. Daily samples were taken for the following 7 days. Blood samples were analysed for hemoglobin, erythrocytes, leucocytes, urea, NH3, keton bodies, GPT and GOT.

Reliability: (4) not assignable
limited documentation, no data on No. of animals/dose, no standard species for which no guideline and therefore no protocol is available

22-JUL-2004 (61)

5.1.2 Acute Inhalation Toxicity

Type: other: Inhalatory Risk Test (IRT)
Species: rat
Sex: no data
No. of Animals: 12
Exposure time: 8 hour(s)

Method: other: as described by Smyth et al., Am. Ind. Hyg. Ass. J. 23, 95-107, 1962
Year: 1967

GLP: no
Test substance: other TS: Isobutylidene diurea, purity ca. 90-96% (0-3% urea, 2% potassium sulfate)

Remark: air saturated with isobutylidenediurea at room temperature (only a small amount of dust was formed; air was led through a 5 cm layer of isobutylidenediurea at a rate of 200 l/hour).
Post-exposure observation period: 7 days
Result: No deaths occurred.
No clinical symptoms. No pathological changes noted at necropsy.
Reliability: (3) invalid
Test system not applicable and not valid for solid test substances.
28-MAY-2004 (63)

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Strain: no data
Sex: male/female
No. of Animals: 10
Vehicle: water
Route of admin.: i.p.
Value: = 500 mg/kg bw

Method: other: BASF-Test
Year: 1967
GLP: no
Test substance: other TS: Isobutylidene diurea, purity ca. 90-96% (0-3% urea, 2% potassium sulfate)

Result:
- Number and time of death(s) per dose group: Results are given as dead animals/total number of animals at this dose at 24 h, 48 h, 7 days and 14 days after dosing:
  320 mg/kg bw: 0/10, 0/10, 2/10, 2/10
  400 mg/kg bw: 0/10, 1/10, 3/10, 3/10
  500 mg/kg bw: 0/10, 1/10, 3/10, 3/10
  640 mg/kg bw: 0/10, 7/10, 9/10, 9/10
  800 mg/kg bw: 0/10, 7/10, 10/10, -
  1000 mg/kg bw: 1/10, 9/10, 9/10, 9/10
  1600 mg/kg bw: 3/10, 10/10, 10/10, -
  3200 mg/kg bw: 5/10, 10/10, 10/10, -
  6400 mg/kg bw: 3/10, 10/10, 10/10, -
- Symptoms per dose group: 320-400 mg/kg bw: irregular respiration, piloerection, reduced general state, smeared eyelids, tremor
  500-800 mg/kg bw: as mentioned above but more pronounced
  1600-6400 mg/kg bw: convulsions, tremor, dyspnoe, piloerection, abdominal position, ptosis, apathy
- Necropsy: Animals that died showed pale kidneys and dark red kidney pulp.In animals that where sacrificed, one mouse showed pale kidneys; all other animals without

findings in the organs. Necropsy was performed by a pathologist.

Test condition: - No. of animals per sex per dose: 5 animals/sex/dose; no vehicle control
- Vehicle: Aqua dest.
- Doses: 320, 400, 500, 640, 800, 1000, 1600, 3200, 6400 mg/kg bw;
The doses were applied as 4 %, 8 %,10 %, 16% or 30% preparations of the test substance in aqua dest.
- Post dose observation period: 7 days (1600-6400 mg/kg bw)
14 days (320-1000 mg/kg bw)

Reliability: (2) valid with restrictions
post dose observation period only 7 days, no data on strain

01-JUN-2004 (63)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 50 % active substance
Exposure: Semiocclusive
Exposure Time: 20 hour(s)
No. of Animals: 2
Vehicle: water
Result: not irritating

Method: other: BASF-Test
Year: 1967
GLP: no
Test substance: other TS: Isobutylidene diurea, purity ca. 90-96% (0-3% urea, 2% potassium sulfate)

Result: - Systemic toxicity: No mortality occurred. There were no signs of clinical toxicity from the dermal exposure.
- Irritation score: No skin findings were observed at 1 min, 5 min, 15 min, 20 h and 8 days after application
- Summary: Semi-occlusive application for 20 hrs to rabbit skin did not lead to any signs of irritation.

Test condition: Rabbits: White Vienna, males, about 2.8 kg bw
ca. 0.5 g of a 50 % aqueous suspension was applied on the shaved skin for 1, 5, 15 minutes and 20 hours.
Application area 2.5 x 2.5 cm. Readings were performed at 24 hours and at 8 days after application.

Reliability: (2) valid with restrictions
limited documentation, substance tested only as 50% dilution, Observation/reading only at 1 min, 5 min, 15 min, 20 h, 24 hours and 8 days, only 2 animals tested

Flag: Critical study for SIDS endpoint

28-MAY-2004 (63)

5.2.2 Eye Irritation

Species: rabbit
Concentration: undiluted
Dose: 50 other: µl
No. of Animals: 2
Vehicle: none
Result: not irritating

Method: other: BASF-Test
Year: 1967
GLP: no
Test substance: other TS: Isobutylidene diurea, purity ca. 90-96% (0-3% urea, 2% potassium sulfate)

Result:
- Irritation Score: Cornea/Iris No findings at any of the observation time points.
- Irritation Score: ConjunctivaeRedness/Chemosis
  Redness: 1 hr: ++ (2); 24 hrs: + (1); 48 hrs: 0 (0); 72 hrs: 0(0); 8 days: 0 (0)
  Findings occurred to a comparable extent in both animalsThe same findings were made with talkum which was applied into the other eye.
- Summary: The treatment led to slight redness. All findings were reversible after 8 days of observation period. The control eyes which were treated with talkum did show the same reactions.

Test condition: Rabbits: White Vienna

Dose(s) used: 50 µl/animal of the test substance (powder). It was not washed out.

Observation times: Several time points after application including 1 hr, 24 hrs, 48 hrs, 72 hrs and 8 days after application

Reliability: (2) valid with restrictions
limited documentation, only 2 animals tested, only 50 µl applicated
Flag: Critical study for SIDS endpoint
28-MAY-2004 (63)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: Male: throughout pre-mating (15 days), and during the mating and post-mating periods until sacrifice (34 days in total).
Female: throughout pre-mating (15 days) and mating period, during pregnancy and lactation, until day 4 post partum.
Frequency of treatment: daily
Post exposure period: no

Doses: 0; 100; 300; 1,000 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL: = 300 mg/kg bw
LOAEL: = 1000 mg/kg bw

Method: other: OECD TG 422
Year: 2003
GLP: yes
Test substance: other TS: IBDU, 90.1 % purity

Remark: The repeated dose toxicity was assessed in a combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test according to OECD Test Guideline 422. This study is also described under Chapter 5.8.3 / TOXICITY TO REPRODUCTION, OTHER STUDIES.

Result: FO
MORTALITY: no substance related deaths.
OBSERVATIONS:
No substance related clinical signs observed. No effect on motor activity and reflexes.
BODY WEIGHT GAIN:
1000 mg/kg bw/day - females: lower body weight gain in the females during gestation (minus 10% on days 0 - 20 of pregnancy as compared to the controls), and during lactation (minus 38% on days 1 to 4 post-partum). Males: no effect.
FOOD CONSUMPTION:
1000 mg/kg bw/day - females: slightly lower food consumption in the females during gestation (minus 6% on days 0-20 of pregnancy). Males: no effect.
HEMATOLOGY: no notable changes.
BLOOD BIOCHEMISTRY:
Females: ALAT increased at top-dose (18 as compared to 10 in controls; $p<0.01$), value within historical control range, and not considered as of biological significance.
Males: significant, but not dose-related slight increases in Na, Cl, and ASAT values. All values were within historical control ranges and not considered as of biological significance.

URINALYSIS: no notable changes.
REPRODUCTIVE TOXICITY DATA: see section 5.8.3
NECROPSY FINDINGS
no substance related pathological changes.
ORGAN WEIGHTS
no substance related differences.
HISTOPATHOLOGY FINDINGS
Males: dose-related higher severity of acidophilic globules in the cortical tubular epithelium of the kidneys of the 300 and 1,000 mg/kg bw/day groups. As no tubular degeneration/necrosis was observed in the kidneys the presence of acidophilic globules was considered as due to the accumulation of the sex-linked alpha-2-u-globulin. This was confirmed by Mallory-Heidenhain and specific immunostaining (BASF, 2004b).
As a sex- and species-specific effect of male rats, this finding has no relevance for humans. It was therefore considered as of minor toxicological importance and it was not considered as an adverse effect.

The seminiferous tubules were lined with Sertoli cells only (minimal or slight) in 1/10 males given 300 mg/kg/day and in 2/10 males given 1000 mg/kg/day. For a third male from the same group, tubules lined with Sertoli cells only were considered to be tubuli recti as they were situated beneath the capsule. For 1/10 males given 300 mg/kg/day and another given 1000 mg/kg/day, minimal reduction in the number of spermatids was observed in very few seminiferous tubules. Minimal vacuolization of Sertoli cells was observed in 1/10 males given 1000 mg/kg/day. Although not found in the control males, these microscopic abnormalities recorded with minimal severity in few or very few seminiferous tubules in a few males were considered to be without relationship to the treatment and most probably fortuitous.

In summary, no treatment-related abnormalities were found in testes, epididymides, prostate, seminal/vesicles, ovaries, and uterus, and in all other investigated organs.
F1: results see section 5.8.3.
NOAELs:
Female: 300 mg/kg bw/day (reduced body weight gain during pregnancy at 1,000 mg/kg bw/day)
Male: 1,000 mg/kg bw/day (highest tested dose).

Test condition: ANIMALS: Crl CD(R) (Sprague-Dawley) IGS BR; at the beginning of the treatment 8 weeks (males) and 10 weeks (females) old, with a mean body weight of 276g (259-306g) for the males and 228g (213-248g) for the females. 10 males and 10 females / dose group.
VEHICLE: 0.5% carboxymethylcellulose.
MATING: females with males from the same dose group 1:1. The day of confirmed mating (vaginal plug) was designated day 0 post-coitum (p.c.).
PARAMETERS:
FO: mortality, symptoms, body weight, food consumption, (only pregnant dams were used for calculation of mean maternal food consumption, body weight and body weight change), motor activity, reactivity to stimuli, hematology (RBC, Hb, MCV, PCV, MCHC, Thrombos, WBC, differential white cell count, prothrombin time, activated partial thromboplastin time, fibrinogen), blood biochemistry (Na, K, Cl, Ca, phosphate, glucose, urea, creatininie, bilirubin, proteins, albumin, albumin/globulin, cholesterol, triglycerides, ALP, ASAT, ALAT, bile acids), urinalysis, necropsy, organ weights (adrenals, brain, heart, kidneys, liver, spleen, thymus, additionally in males: testes, epididymides; females: ovaries), histopathology (macroscopic lesions, adrenals, brain, colon, duodenum, epididymides, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes, ovaries, prostate, rectum, sciatic nerve, seminal vesicles, spinal cord, spleen , sternum, stomach, testes, thymus, thyroids and parathyroids, trachea, urinary bladder, uterus).
F1: see 5.8.3.
STATISTICAL METHODS: Dunnett, Fisher`s exact, Dunn, Mann-Whitney, Wilcoxon tests.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
26-JAN-2005 (64) (65)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA98 TA100 TA1535 TA1537
Concentration: 20 - 5000 µg/plate
Cytotoxic Concentration: > 5000 µg/plate
Metabolic activation: with and without
Result: negative

Method: other: OECD guideline 471 (1983)
Year: 1983
GLP: no
Test substance: other TS: Isobutylidene diurea, technical grade (purity ca. 92%)

Result: Positive controls were functional
No cytotoxicity and no mutagenic effects were detected.
No signs of precipitation of test substance.

Chemical	Dose (mg/plate)	Tester strain	-S9	+S9
	0	TA1535	15	20
	20		19	20
	100		17	23
	500		14	19
	2500		14	25
	5000		17	18
	0	TA100	151	156
	20		145	168
	100		130	165
	500		119	144
	2500		137	127
	5000		130	138
	0	TA1537	9	10
	20		11	10
	100		10	11
	500		10	12
	2500		8	14
	5000		9	11
	0	TA98	24	34
	20		22	33
	100		22	32
	500		19	32
	2500		17	29
	5000		19	31
	0	TA1535	18	20
	20		15	13
	100		20	14
	500		16	8
	2500		14	10
	5000		13	11
	0	TA100	126	138
	20		129	138
	100		124	125

500		126	131
2500		127	136
5000		122	126
0	TA1537	8	10
20		15	13
100		11	13
500		13	11
2500		12	8
5000		12	11
0	TA98	24	37
20		27	35
100		31	34
500		27	40
2500		28	35
5000		25	38

Test condition: Metabolic activation: liver S-9 mix from Aroclor 1254-induced rats. Standard plate and pre-incubation test. (20 min preincubation)

Vehicle: DMSO

Two independent experiments were performed (each with 3 plates). Incubation time (with and without metabolic activation): 48 hours.

Test doses: 0 ; 20 ; 100 ; 500 ; 2500 ; 5000 µg/plate

Positive controls: The following positive control substances are used to check the mutability of the bacteria and the activity of the S-9 mix:
with S-9 mix:
- 10 µg 2-aminoanthracene (dissolved in DMSO) for the strains TA 100, TA 98, TA 1537 and TA 1535

without S-9 mix:
- 5 µg N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) (dissolved in DMSO) for the strains TA 100 and TA 1535
- 10 µg 4-nitro-o-phenylendiamine (dissolved in DMSO) for the strain TA 98
- 100 µg 9-aminoacridine chloride monohydrate (dissolved in DMSO) for the strain TA 1537

Evaluation criteria: substance characterized as positive if
- doubling the spontaneous mutation rate (control)
- dose-response relationship
- reproducibility of results

Reliability: (2) valid with restrictions
not according to current but former guideline. Only 4 strains tested, (not tested with TA 102 or E.coli)

Flag: Critical study for SIDS endpoint

07-JUN-2004 (66)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse
Sex: male

Strain: NMRI
Route of admin.: gavage
Exposure period: two applications at an interval of 24 hours. Bone marrow cells were sampled 24 hours after the last application
Doses: 500, 1000, 2000 mg/kg bw
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 1997
GLP: yes
Test substance: other TS: Isobutylidenediurea, purity 90.1 weight %

Result: The test substance did not induce micronuclei in bone marrow cells of mice when tested in doses up to the limit dose recommended by current guidelines. In comparison to the corresponding vehicle controls there was no statistically significant or biologically relevant increase in the frequency of micronuclei. The mean values of micronuclei were in the same range as the vehicle control group and within the laboratory`s historical negative control range (0.04 - 0.16%).

The highest dose was the maximum guideline-recommended daily dose and was selected on basis of the results from a range-finding study. In the range-finding experiments 3 males were treated with 1000 mg/kg bw (twice at an interval of 24 hours) and 3 males and 3 females each were treated with 1500 or 2000 mg/kg bw, also given twice at an interval of 24 hours. All treated animals showed reduced spontaneous activity at 6 or 24 hours after the first and/or the second treatment and eyelid closure and apathy. With regard to toxicity, no difference between the sexes was noted.

The mean numbers of normochromatic erythrocytes were not substantially increased as compared to the corresponding vehicle controls (vehicle: 1922 NCEs, low dose: 1922, mid dose: 2217, high dose: 2017), thus the ratio between polychromatic and normochromatic erythrocytes is uneffected, indicating that the test substance had no substantial cytotoxic effects on bone marrow cells.

The positive and vehicle controls were functional, i.e. they were in the range of the respective historical controls. The stability of the test substance in the vehicle was analytically verified for the study period.

Test condition: Age of animals at start of acclimatization: 8-12 weeks
Acclimatization period: minimum 5 days.
Body weight at start of treatment: 35.0 g (SD +/- 2.1 g)
vehicle: 0.5 % aqueous carboxymethylcellulose.
control group: treated twice with the vehicle.
application volume: 10 ml/kg bw.
5 animals / dose.
Sampling time: 24 hours after last application.
2000 polychromatic erythrocytes (PCEs) were scored for micronulei per animal (except for animal no. 3, for which 2 independent evaluations of 2000 PCEs each were performed in order to verify the result).
cytotoxicity: expressed as the ratio between polychromatic and normochromatic erythrocytes.
All analyses were performed with coded slides.

positive control: cyclophosphamide, 40 mg/kg bw, single application.
Statistical analysis: non-parametric Mann-Whitney test.
Evaluation criteria: a test substance producing neither a dose-related increase in the number of micronucleated polychromatic erythrocytes nor a statistically significant positive response at any of the test points is considered non-mutagenic.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
28-MAY-2004 (67)

5.7 Carcinogenicity

Species: rat
Sex: male/female
Strain: no data
Route of administration: gavage
Exposure period: 20 weeks
Frequency of treatment: twice per week
Post exposure period: total study period: 92 weeks
Doses: 800 mg/kg bw
Result: negative
Control Group: yes

Method: other: see Test Conditions
Year: 1979
GLP: no
Test substance: other TS: Isobutylidene diurea, not further specified

Remark: The study result is summarized by Lewis Sen. JR as "questionable carcinogen with experimental tumorigenic data" and in RTECS as "tumorigen". Based on the results reported in the original publication, these conclusions cannot be followed.
Result: The dosage used is described as the MTD. However, no information is provided on clinical symptoms, body weights, food consumption and mortality.

According to the authors there was no statistically significant effect on the incidence, time of appearance or location of the observed tumours.

Tumour incidence:
control group (n=63): 7.9 %
treated group (n=82): 7.3 %

No information was provided as to the localization of the tumours.
Test condition: Rat strain not specified.
Animal weight at beginning of study: 80 g.
No. of Animals: 82 Treatment group, 63 control group.
The test substance was applied as aqueous suspendion.
Animals were macroscopically examined after 92 weeks. All pathological changes and tumour bearing organs were also examined microscopically.
Statistical method: not specified.
Reliability: (3) invalid

Not well documented study lacking critical information. Study does not meet current standards. Exposure period too short.

28-MAY-2004 (68) (69) (70)

Species: mouse
Sex: male/female
Strain: no data
Route of administration: gavage
Exposure period: 20 weeks
Frequency of treatment: twice per week
Post exposure period: total study period: 92 weeks
Doses: 1600 mg/kg bw
Result: negative
Control Group: yes

Method: other: see Test Conditions
Year: 1979
GLP: no
Test substance: other TS: Isobutylidene diurea, not further specified

Remark: The study result is summarized by Lewis Sen. JR as "questionable carcinogen with experimental tumorigenic data" and in RTECS as "tumorigen". Based on the results reported in the original publication, these conclusions cannot be followed.
Result: The dosage used is described as the MTD. However, no information is provided on clinical symptoms, body weights, food consumption and mortality.

In the 11th study month, the treatment group consisted of 108 male and 133 female animals. The control group had 76 male and 91 female animals. In animals that died or were killed before month 11, no tumours were observed (no further information on study design available).

According to the authors there was no statistically significant effect on the incidence, time of appearance or location of the observed tumours.

Tumour incidence:
control group: 23,4 %(male: 17.2, female: 29.6)
treated group: 22.4 %(male: 20.1, female: 24.1)

Lung adenoma:
control group: 11.3 %
treated group: 9.5 %

Lung adenomatous carcinoma:
control group: 1.7 %
treated group: 1.2 %

Mesothelioma:
control group: 1.7 %
treated group: 1.6 %

Mamma tumours:
control group: 4.7 %

treated group: 6.2 %

leukosis:
control group: 4.7 %
treated group: 2.4 %

Fibroma:
control group: -
treated group: 0.8 %

Test condition: Mouse strain not specified.

Animal weight at beginning of study: 18 g.

No. of Animals : 241 (108 males, 133 females) Treatment group, 167 (76 males, 91 females) control group.

The test substance was applied as aqueous suspension.

Animals were macroscopically examined after 92 weeks. All pathological changes and tumour bearing organs were also examined microscopically.

Statistical method: not specified.

Reliability: (3) invalid
Not well documented study lacking critical information. Study does not meet current standards. Exposure period too short.

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5.8.1 Toxicity to Fertility

Type: One generation study
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: males: throughout the pre-mating period, mating, and until sacrifice;
females: throughout the pre-mating period, mating, and pregnancy until day 14 post-coitum.
Frequency of treatment: daily
Premating Exposure Period
male: 10 weeks
female: 10 weeks
Duration of test: 14 weeks
No. of generation studies: 1
Doses: 0, 600, 1200 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL Parental: = 1200 mg/kg bw
other: NOAEL, systemic toxicity (male) : = 1200 mg/kg bw
other: LOAEL, systemic toxicity (female) : = 600 mg/kg bw

Method: other: similar to OECD TGs 421 and 416 (1995, 2001), but no second generation studied.
Year: 2003
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: The present study was initiated to further evaluate the toxicological relevance of a reduced mating index, which was found in a previous study (BASF AG 2003a).

Result:
MORTALITY:
no substance related mortality.
OBSERVATIONS:
no adverse effects observed.
BODY WEIGHT GAIN:
1,200 mg/kg bw/day - Females: slight effect during pre-mating (-11%, $p < 0.05$), and effect (-24%, $p < 0.001$) during pregnancy. Males: no significant effects.
600 mg/kg bw/day - Females: moderate decrease of body weight gain during pregnancy (-24%, $p < 0.001$). Males: no significant effects.
FOOD CONSUMPTION:
1,200 mg/kg bw/day - Females: slightly lower food consumption during pregnancy (-14%, $p<0.01$). Males: no effect.
600 mg/kg bw/day - Females: slight and non-significant decrease in food consumption during pregnancy (- 7%; n.s.). Males: no effect.
NECROPSY FINDINGS:
no pathological changes noted.
ORGAN WEIGHTS:
Females: significantly lower absolute and relative ovary and uterus weights (ovaries: low, high-dose/absolute: -12, -13%; low, high-dose/relative: -7, -4% as compared to controls; uterus: low, high-dose/absolute: -19, -21%; low, high-dose/relative: -14, -12% as compared to controls). These differences were considered not to be treatment related, as most of the values were within the range of the control group, and changes were only due to the contribution of a few individual values of two animals.
Males: significantly, but not dose-related higher absolute and relative adrenal weights (low, high-dose/absolute: +24, +18%; low, high-dose/relative: +29, +23% as compared to controls). Because of the lack of a dose-response and because only seen in males, these effects were considered as of no biological significance.
SEMINOLOGY:
not different from the controls.
MATING DATA:
The female mating index (mated/paired) and pre-coital interval were similar in all groups (control, low, high-dose: female mating index 96 - 96 - 96%, mean pre-coital interval 2.7 - 2.8 - 3.2 days). Most paired animals mated within 1 to 4 days of cohabitation except for a few pairs in each group, for which the duration was slightly longer. This finding is commonly recorded at this low incidence and is not related to the test substance.
MALE FERTILITY DATA:
The male mating index and the male fertility index were similar in all groups (male mating index: control, low, high-dose: 100 - 96 - 96 %, male fertility index: 100 - 91.3 - 91.3 %). The slight fluctuations were within the range of commonly recorded values in rats of this strain and are not related to the treatment with the substance.
FEMALE FERTILITY DATA:
The treatment had no effect on fertility and gestation indices. The following was obtained for the control, low,

and high-dose groups, respectively:
Mated females: 24, 24; 24;
Pregnant females: 24, 21, 22;
Female fertility index (%): 100, 87.5, 91.7;
Females with live concepti: 24, 21, 22;
Gestation index (%): 100, 100, 100.
NUMBER OF CORPORA LUTEA, NUMBER OF IMPLANTATIONS (control, low, high-dose groups):
corpora lutea: 17.6, 16.4, 16.0;
Implantation sites: 16.6, 14.9, 14.5* ($p<0.05$);
Pre-implantation loss (%): 5.7, 9.6, 9.1;
Concepti: 15.2, 14.3, 13.0* ($p<0.05$);
Post-implantation loss (%): 8.3, 4.2, 11.0.
The number of corpora lutea was minimally lower in the treated groups when compared to the controls. Since the difference was small, not statistically significant, and within the range of the laboratory`s historical control values (15.9 - 18.9), this finding was considered as a chance event. The number of implantation sites and concepti was consequently also lower than the controls, gaining statistical significance only at the top dose. Also the values for implantation sites and concepti were within the laboratory`s historical controls (13.8-17.1 and 12.8-16.3, respectively). The slight fluctuations in the pre- and post-implanatation losses were not considered treatment-related, since they were not dose-related and/or not different from either the concurrent or historical controls (historical controls for pre- and post-implantation losses (%): 5.2-14.3 and 2.4-8.2, respectively).
NOAELs:
Systemic Toxicity (male): 1,200 mg/kg bw/day.
Fertility, Gonadal Function, Reproduction (male, female): 1,200 mg/kg bw/day.
LOAEL:
Systemic Toxicity (female): 600 mg/kg bw/day (based on reduced body weight gain during pregnancy)

Test condition: ANIMALS: Crl CD(R) (Sprague-Dawley) IGS BR; at the beginning of the treatment 6 weeks old, with a mean body weight of 192g (171-210g) for the males and 161g (142-179g) for the females. 25 males and 25 females / dose group.
VEHICLE: 0.5% carboxymethylcellulose.
TREATMENT PERIOD, FEMALES: 10 weeks before mating, during mating (max. 14 days), and during pregnancy (until day 14 post-coitum inclusive).
TREATMENT PERIOD, MALES: 10 weeks before mating, during the mating period (2 weeks), and until sacrifice (when most hysterectomies were completed in females)
MATING: females with males from the same dose group 1:1. The day of confirmed mating (vaginal plug) was designated day 0 post-coitum (p.c.).
PARAMETERS:
mortality, symptoms, body weight, food consumption, necropsy, organ weights (males: testes, epididymides, prostate, seminal vesicles together with coagulation gland, pituitary gland and adrenals; females: uterus, ovaries, pituitary gland and adrenals), seminology (males) with analyses of epididymal and testicular (control and high-dose) sperm, hysterectomy (females) and determination of number of corpora lutea, number and distribution of dead and live concepti, of early and late resorptions, and of implanataion sites; reproductive tissues

were preserved, but not examined histopathologically as no substance related macroscopic lesions were found. Only pregnant dams were used for the calculation of mean maternal food consumption, bw, bw change and reproduction data. STATISTICAL METHODS: Dunnett, Fisher`s exact, Dunn, Mann-Whitney, Wilcoxon tests.

Conclusion: There were no substance-related effects on the male and female reproductive performance. In the light of these results, the lower mating index in a previous study (BASF, 2003a), is considered to be incidental and not related to the test substance.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

28-MAY-2004 (72)

Type: other: Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure Period: males: pre-mating, mating (14days) and post-mating, for a total of 34 days, females: pre-mating, mating, pregnancy and lactation until day 4 post partum
Frequency of treatment: daily
Premating Exposure Period
male: 15 days
female: 15 days
Duration of test: males: until sacrifice in the post-mating period, females: until day 4 post partum
No. of generation studies: 1
Doses: 0; 100; 300; 1000 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL Parental: = 1000 mg/kg bw
other: NOAEL, systemic toxicity female : = 300 mg/kg bw
other: NOAEL, systemic toxicity male : = 1000 mg/kg bw

Method: OECD Guide-line 422
Year: 2003
GLP: yes
Test substance: other TS: IBDU, 90.1 % purity

Remark: The study is described in detail under section 5.8.3 / TOXICITY TO REPRODUCTION, OTHER STUDIES

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

28-MAY-2004 (64)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat
Sex: female
Strain: Wistar
Route of administration: gavage
Exposure period: day 6 to 15 p.c.
Frequency of treatment: once daily

Duration of test: 20 days
Doses: 100, 400, 1000 mg/kg (in 10 mL/kg)
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 1000 mg/kg bw
NOAEL Teratogenicity: = 1000 mg/kg bw
NOAEL Fetotoxicity : = 1000 mg/kg bw
Result: not teratogenic, not fetotoxic, not maternally toxic

Method: OECD Guide-line 414 "Teratogenicity"
Year: 1981
GLP: yes
Test substance: other TS: IBUD, purity 90%

Result: No signs of maternal toxicity were observed. There were no substance-related effects in the dams with regard to food consumption, body weight, body weight gain, uterine weights and clinical or autopsy findings. The reproduction data (conception rate, mean number of corpora lutea and implantation sites, pre- and post-implantation loss, number of resorptions, number of viable fetuses) revealed no biologically relevant differences between the control and treated groups.

No embryo/foetotoxicity was induced by the treatment with isobutylidene diurea. The sex ratio did not differ significantly between the treated groups and controls and the mean placental and foetal weights were unaffected. Weight of placentae and weight of fetuses were comparable to the actual control values.

The examination of the foetuses for external malformations revealed brachygnathia and aglossostoma, both in one low-dose foetus. This was regarded as spontaneous occurrence since it is also present in the historical control data of this rat strain at a low frequency. No external variations were found in any group.

Soft tissue examination showed malformations such as hydrocephaly together with microphthalmia (left) and anophthalmia (right) in one foetus of the low dose group and dextrocardia in one foetus of the intermediate dose group. These were regarded as spontaneous occurrences since there was no dose response relationship and they are also present in the historical control data of this rat strain at a low frequency. Soft tissue variations (dilated renal pelvis and/or hydroureter) were seen throughout, without statistically significant differences between the groups (dilated renal pelvis incidence: 29/21/16/18; hydrourether incidence: 10/8/6/12).

Foetal skeletal analyses showed various malformations of the skull (mandible fused or various skull abnormalities), the vertebral column, the sternum, and/or the ribs (fused ribs). However, only the incidences of two types of skeletal malformations (thoracic vertebral body/bodies dumbbell-shaped (incidence: 0/5/10/5) and bipartite sternebrae with dislocated ossification centres (incidence: 0/1/4/2) and the overall number of malformations of the skeleton (incidence: 2/9/15/7) were significantly increased in the IBDU-treated groups, but

without a clear dose-response relationship. Moreover, the frequency of dumbbell-shaped thoracic vertebral bodies and bipartite sternebra(e) was unusually low in the concurrent controls. Hence, the observed malformations were not considered to be related to the treatment with IBDU.

Retardation of foetal skeletal development (incomplete or missing ossification of vertebral bodies/arches, sternebra(e), skull and/or the hyoid bone) occurred in all groups without biologically relevant differences between the groups.

Hence, the incidence and type of the foetal external, soft tissue and skeletal findings, which were classified as malformations, variations and/or retardations observed in the treated foetuses were similar to the concurrent and/or historical control data.

Test condition: In accordance with OECD TG 414.

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): 65-74 days, weight at study begin (day 0): 225 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 suspension in 0.5 % carboxymethylcellulose to 22-24 pregnant rats per group by gavage in the morning; a control group was dosed with the vehicle.
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 $p < 0.01$.

The test substance was applied as aqueous suspension in 0.5 % carboxymethylcellulose to 22-24 pregnant rats per group.

The control group received the vehicle only.

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
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Species: rat
Sex: female
Strain: Wistar
Route of administration: gavage
Exposure period: day 6 to 15 p.c.
Frequency of treatment: once daily
Duration of test: 16 days
Doses: 200, 600, 1200 mg/kg (in 10 ml/kg)
Control Group: yes, concurrent no treatment
NOAEL Maternal Toxity: = 1200 mg/kg bw
NOAEL Teratogenicity: = 1200 mg/kg bw
Result: no substantial treatment-related effects on the dams and foetuses

Method: other: range-finder for OECD 414
Year: 1991
Test substance: other TS: IBDU, 90 %, purity

Remark: Preliminary range-finding study.
Result: There were no substance-related effects on the dams concerning food consumption, body weight, body weight

change, uterine weights, corrected body weight change, clinical and necropsy observations and haematological, clinico-chemical and urine parameters.
There were no differences between the groups regarding conception rate, mean number of corpora lutea, total implantations, resorptions and live fetuses, and pre- and postimplantational losses.
No effects were seen on placental and fetal body weights.
The external examination of the foetuses showed one malformation in one low dose (exencephaly) and one high dose (micromely) foetus each. These effects were regarded as incidental as they are also present at low incidences in the historical control.

Test condition: Max. 10 pregnant animals per group.
The dams were sacrificed on the day following the last substance administration. Just before the scheduled sacrifice, blood and urine samples were collected for hematological and/or clinico-chemical examinations and liver, kidneys and the unopened uteri were weighed.
The following parameters were investigated:
dams- food consumption, body weight, various haematological and clinico-chemical paramerers, clinical and autopsy observations, reproduction data.
foetuses - placental and foetal weights or foetal observations.

Reliability: (1) valid without restriction
Due to the study design, only limited information on embryonic and fetotoxicity could be obtained.

28-MAY-2004 (75)

Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: males: pre-mating, mating (14 days) and post-mating, for a total of 34 days; females: pre-mating, mating, pregnancy and lactation until day 4 post partum.
Frequency of treatment: daily
Duration of test: males: until sacrifice in the post-mating period, females: until day 4 post partum
Doses: 0; 100; 300; 1000 mg/kg bw/day
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 300 mg/kg bw
NOAEL Teratogenicity: = 1000 mg/kg bw
Result: There were no indications for a substance-induced developmental toxicity up to and including the highest tested dose of 1,000 mg/kg bw/day

Method: other: OECD TG 422 (1996)
Year: 2003
GLP: yes
Test substance: other TS: IBDU, 90.1 %, purity

Remark: The study results and test conditions are described in detail under section 5.8.3 / TOXICITY TO REPRODUCTION, OTHER STUDIES
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
26-JAN-2005 (64)

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: Combined Repeated Dose Toxicity Study with Reproductin/Developmental Toxicity Screening Test
In Vitro/in vivo: In vivo
Species: rat
Strain: Sprague-Dawley
Sex: male/female
Route of administration: gavage
Exposure period: males: pre-mating (15 d), mating (14 d), and post-mating, for a total of 34 days.
females: pre-mating (15 d), mating, pregnancy and lactation until day 4 post-partum
Frequency of treatment: daily
Duration of test: males: until sacrifice in post-mating period,
females: until day 4 post-partum
Doses: 0; 100; 300; 1,000 mg/kg bw/day
Control Group: yes, concurrent vehicle

Method: other: OECD Guideline 422
Year: 2003
GLP: yes
Test substance: other TS: IBDU, 90.1 %, purity

Result: FO
MORTALITY: no substance related deaths.
OBSERVATIONS: No substance related clinical signs observed. No effect on motor activity and reflexes.
BODY WEIGHT GAIN: 1000 mg/kg bw/day - females: lower body weight gain in the females during gestation (minus 10% on days 0 - 20 of pregnancy as compared to the controls), and during lactation (minus 38% on days 1 to 4 post-partum).
Mean bw on day 0 of pregnancy and day 4 post-partum statistically differed from that of control group.
Males: no effect.
FOOD CONSUMPTION: 1000 mg/kg bw/day - females: slightly lower food consumption in the females during gestation (minus 6% on days 0-20 of
pregnancy). Males: no effect.
HEMATOLOGY: no notable changes.
BLOOD BIOCHEMISTRY: Females: ALAT increased at top-dose (18 as compared to 10 in controls; $p<0.01$), value within historical control range, and not considered as of biological significance.
Males: significant, but not dose-related slight increases in Na, Cl, and ASAT values. All values were within historical control ranges and not considered as of biological significance.
URINALYSIS: no notable changes.
MATING INDEX: The mating index was 100% for the pairs of the control, 100 and 300 mg/kg bw/day groups. The mating index was lower in the 1000 mg/kg bw/day group: 7/10 (70%) mated within the two weeks of cohabitation. As no reatment-related morphological changes were noted in the genital organs of the high-dose male and female animals, this finding was considered to be incidental. This evaluation is further supported by the results of a supplementary study (BASF AG, 2003b), not showing any effect on the mating index at an even higher dose (1200

mg/kg bw/day).
TIME TO INSEMINATION: similar in control and treated groups. All paired animals (except one control pair) mated within 1 to 4 days of cohabitation.
FERTILITY INDEX: similar in the control and treated groups, ranging from 90 to 100% without an indication of a relation to dose or treatment.
DURATION OF GESTATION: similar in the control and treated groups (21-22 days).
DELIVERY DATA: The gestation index was similar in the control and treated groups, ranging from 88.9 to 100%, without an indication of a relation to dose or treatment.
POST-NATAL and NEO-NATAL LOSSES: The number of corpora lutea was similar in the 0, 100 and 300 mg/kg bw/day groups, In the group treated with 1,000 mg/kg bw/day the number was slightly lower (18 vs. 23 per female). As the counts in all groups (including the high dose) were higher than the laboratory`s historical controls, and because there were no microscopic changes in the ovaries, this finding was considered as a chance event. No effect was found on the number of implantation sites, and on postimplantation and neonatal losses.
There was only a slightly lower mean value of implantation sites in high dosed females: 14.6 vs 16.3 per female. This value was within the range of historical control data: 12.5 to 15.1 implants/female. In addition the low value in the 1000 mg/kg bw/day group was attributed to the rather low value of a single individual with 8 implant sites.
NECROPSY FINDINGS: no substance related pathological changes.
ORGAN WEIGHTS: no substance related differences.
HISTOPATHOLOGY FINDINGS:
Males: dose-related higher severity of acidophilic globules in the cortical tubular epithelium of the kidneys of the 300 and 1,000 mg/kg bw/day groups. As no tubular degeneration/necrosis was observed in the kidneys the presence of acidophilic globules was considered as due to the accumulation of the sex-linked alpha-2-u-globulin. This was confirmed by Mallory-Heidenhain and specific immunostaining (BASF, 2004b). As a sex- and pecies-specific effect of male rats, this finding has no relevance for humans. It was therefore considered as of minor toxicological relevance, and not considered as an adverse effect.
The seminiferous tubules were lined with Sertoli cells only (minimal or slight) in 1/10 males given 300 mg/kg/day and in 2/10 males given 1000 mg/kg/day. For a third male from the same group, tubules lined with Sertoli cells only were considered to be tubuli recti as they were situated beneath the capsule. For 1/10 males given 300 mg/kg/day and another given 1000 mg/kg/day, minimal reduction in the number of spermatids was observed in very few seminiferous tubules. Minimal vacuolization of Sertoli cells was observed in 1/10 males given 1000 mg/kg/day. Although not found in the control males, these microscopic abnormalities recorded with minimal severity in few or very few seminiferous tubules in a few males were considered to be without relationship to the treatment and most probably fortuitous.
In summary, no treatment-related abnormalities were found in testes, epididymides, prostate, seminal/vesicles, ovaries, and uterus, and in all other investigated organs.

F1
MORTALITY: There were no stillborn pups or runts. The number of pups which died during the four days of observation after birth was low (0-5%) and similar in all groups.
CLINICAL OBSERVATIONS: There were no notable clinical signs in the pups.
PUP BODY WEIGTH: similar in the control and treated groups on day 1 and day 4 post-partum.
SEX RATIO OF PUPS: close to the theoretical value of 50% and similar in all groups.

NOAELs:
F0, General Toxicity (female): 300 mg/kg bw/day (reduced body weight gain during pregnancy at 1,000 mg/kg bw/day)
F0, General Toxicity (male): 1,000 mg/kg bw/day F0, Reproduction (male, female): 1,000 mg/kg bw/day
F1, Developmental Toxicity: 1,000 mg/kg bw/day

Test condition: ANIMALS: Crl CD(R) (Sprague-Dawley) IGS BR; at the beginning of the treatment 8 weeks (males) and 10 weeks (females) old, with a mean body weight of 276g (259-306g) for the males and 228g (213-248g) for the females. 10 males and 10 females / dose group.
VEHICLE: 0.5% carboxymethylcellulose.
MATING: females with males from the same dose group 1:1. The day of confirmed mating (vaginal plug) was designated day 0 post-coitum (p.c.).
PARAMETERS:
FO: mortality, symptoms, body weight, food consumption, (only pregnant dams were used for calculation of mean maternal food consumption, body weight and body weight change) motor activity, reactivity to stimuli, hematology (RBC, Hb, MCV, PCV, MCHC, Thrombos, WBC, differential white cell count, prothrombin time, activated partial thromboplastin time, fibrinogen), blood biochemistry (Na, K, Cl, Ca, phosphate, glucose, urea, creatininie, bilirubin, proteins, albumin, albumin/globulin, cholesterol, triglycerides, ALP, ASAT, ALAT, bile acids), urinalysis, necropsy, organ weights (adrenals, brain, heart, kidneys, liver, spleen, thymus, additionally in males: testes, epididymides; females: ovaries), histopathology (macroscopic lesions, adrenals, brain, colon, duodenum, epididymides, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes, ovaries, prostate, rectum, sciatic nerve, seminal vesicles, spinal cord, spleen , sternum, stomach, testes, thymus, thyroids and parathyroids, trachea, urinary bladder, uterus).
Mating: Mating index, time to insemination, fertility index
Gestation: Duration of gestation, delivery data, implantation sites, number of corpora lutea (only pregnant dams were used for calculation and summary of reproduction status)

F1: litter size, body weight, clinical signs, external examination for gross abnormalities.
STATISTICAL METHODS: Dunnett, Fisher`s exact, Dunn, Mann-Whitney, Wilcoxon tests.

Conclusion: There were no substance-related effects on the male and female reproductive performance and no indications for a substance-induced developmental toxicity up to and including the highest test dose of 1,000 mg/kg bw/day.

Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint

26-JAN-2005 (64)

5.9 Specific Investigations

Endpoint: other
Species: rat
Strain: no data
Sex: no data
Route of administration: in diet
Vehicle: no data
Doses: no data
Control Group: no data specified
Observation Period: no data

Method: other
GLP: no data
Test substance: other TS: isobutylidene diurea, not further specified

Result: A study was performed of the internal organs of rats fed the meat of agricultural animals whose diet included non-protein nitrogen-containing compounds - urea, isobutylidene diurea and a polymer, carbamide with polyacrylamide. Morphological studies have demonstrated that inclusion into the diet of experimental rats of the meat of young bulls given isobutylidene diurea and urea leads to structural alterations in the internal organs of rats, the most pronounced alterations being detected in experiments with the use of the meat of young bulls given isobutylidene diurea. The feeding of experimental rats with the meat of animals grown with the use of the polymer did not affect the morphofunctional status of their organs.
Reliability: (3) invalid
Invalid, since critical information is lacking. Not well documented, and non-validated test method.
Only English translation of abstract available (Russian publication).
28-MAY-2004 (76)

Endpoint: other
Species: cattle
Strain: no data
Sex: no data
Route of administration: in diet
Vehicle: other: in feed
Doses: 150 or 165 g/day
Control Group: no data specified
Observation Period: no data

Method: other
GLP: no data
Test substance: other TS: isobutylidene diurea, not further specified

Result: In the 1st period of 45 days, 2 groups of oxen of initial bodyweight 330 to 365 kg were given daily maize silage 20, barley straw 1, lucerne meal 0.3, coarsely ground barley 1, ground maize with cobs 1 kg and isobutylidene diurea (IBDU) 150 g or urea 100 g. In the 2nd period of 45 days the daily intake of IBDU, urea and coarsely ground barley was increased to 165, 110 g and 1.5 kg, respectively. At 2.5 h after the

morning feeding blood was taken for estimation of glucose, non-esterified fatty acids, ketone bodies, volatile fatty acids (VFA), citric acid, pyruvic acid and total protein and protein fractions; urine was collected for ketone body and uric acid measurement. There was no significant difference between the groups in values for carbohydrate and lipid metabolism or oxidative processes, but IBDU gave slightly less citric acid but more VFA and protein in blood than did urea. Compared to urea, IBDU caused 40% greater urine excretion, twice as much urinary ketone body concentration and 23% more citric acid in urine.

Reliability: (3) invalid
Invalid, since critical information is lacking. Not well documented, and non-validated test method. Only English translation of abstract available (Russian publication).

28-MAY-2004 (77)

Endpoint: other
Species: sheep
Strain: no data
Sex: no data
Route of administration: oral
Vehicle: other: in feed
Doses: no data
Control Group: no data specified
Observation Period: no data

Method: other
GLP: no data
Test substance: other TS: isobutylidene diurea, not further specified

Remark: Remark: Experiments were performed in sheep fed IBDU in order to investigate ruminal adaptation and microbial protein synthesis as well as the suitability of IBDU as a glucose precursor.

Result: Adaptation (8 weeks) improved rumen decomposition of DIBU as well as synthesis and quality of microbial protein. The results also indicate that IBDU meets the requirements for an efficient conversion into glucose.

Reliability: (3) invalid
Invalid, since critical information is lacking. Not well documented, and non-validated test method.

01-JUN-2004 (78)

5.10 Exposure Experience

Remark: no data available

24-AUG-2001

6.1 Methods Handling and Storing

Safe Handling: General safety and hygiene measures:
At the end of the shift the skin should be cleaned and skin-care agents applied.
Fire/Exp. Prot.: When the product is ground (chopped), dust explosion regulations should be noted.
Storage Req.: Keep away from heat. Protect against moisture. When stored loose do not mix with other fertilizers.
Transport Code: Not classified as hazardous under transport regulations.

Remark: Personal protective equipment:

If breathable dust is formed: dust mask.
Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint
23-JUN-2004 (1) (1)

6.2 Fire Guidance

Hazards: Can decompose at above 100 °C.
Thermal decomposition products: isobutyraldehyde.
Prot. Equipment: Possibly self-contained breathing apparatus.
Ext. Medium: If product is involved in fire:
dry extinguishing media, possibly: water, water spray.
Products arising: isobutyraldehyde

Test substance: Isodur and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint
23-JUN-2004 (1) (1)

6.3 Emergency Measures

Type: injury to persons (inhalation)

Remark: On inhalation of decomposition products (decomposition product at above 100°C: isobutyraldehyde): keep patient calm, remove to fresh air, summon medical help. If danger of loss of consciousness, place patient in recovery position and transport accordingly. Apply artificial respiration if necessary.
Test substance: ISODUR and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint
23-JUN-2004 (1) (1)

Type: injury to persons (skin)

Remark: Wash with soap and water.
Test substance: ISODUR and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint

21-JUN-2004 (1) (1)

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
10-JUN-2003 (1) (1)

Type: injury to persons (oral)

Remark: Immediately rinse mouth and then drink plenty of water, summon physician.
Test substance: ISODUR and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint
25-DEC-2001 (1) (1)

Type: accidental spillage

Remark: Personal precautions:
If breathable dust is formed: dust mask.

Environmental precautions:
Do not let product enter drains. Small spillages can be swilled away with water. Waste water must be disposed of correctly.

Methods for cleaning up:
Sweep/shovel up.
Test substance: ISODUR and ISODUR 0-1,6MM
contains: 1,1'-isobutylidene diurea, urea (CAS: 57-13-6), magnesium sulphate (CAS: 7487-88-9)
Flag: non confidential, Critical study for SIDS endpoint
23-JUN-2004 (1) (1)

6.4 Possib. of Rendering Subst. Harmless

6.5 Waste Management

6.6 Side-effects Detection

6.7 Substance Registered as Dangerous for Ground Water

6.8 Reactivity Towards Container Material

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