FOREWORD INTRODUCITON

Adipic acid, compound with hexane-1,6-diamine (1:1)

CAS N°: 3323-53-3

SIDS Initial Assessment Report

For

SIAM 16

Paris, France, 27 – 30 May 2003

1. Chemical Name:	Adipic acid, compound with hexane-1,6-diamine (1:1)
2. CAS Number:	3323-53-3
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn- Bad Godesberg
4. Shared Partnership with:	BASF AG, Germany; Asahi Kasei Corporation, Japan; DuPont, United States; Rhodia Polyamide Intermediates, France; Solutia Inc, United States
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	BASF AG, Germany Contact person: Dr. Hubert Lendle, GUP/CL - Z570 D-67056 Ludwigshafen
• Process used	see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 11. January 2003 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 10. September 2002 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
9. Date of Submission:	20. February 2003
10. Date of last Update:	

11. Comments:

OECD/ICCA - The BUA* Peer Review Process

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

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	3323-53-3
Chemical Name	Adipic acid, compound with hexane-1,6-diamine (1:1)
Structural Formula	$HOOC-(CH_2)_4-COOH.H_2N-(CH_2)_6-NH_2$

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Rationale

Adipic acid, compound with hexane-1,6-diamine (1:1) (AH salt) rapidly dissociates to form adipate and 1,6-hexanediammonium in an almost neutral aqueous solution. Depending on the exposure route (stomach: pH 1 to 3, intestines pH 7, lung: pH 6.9), adipate may be protonated to yield adipic acid (pKa1: 4.3, pKa2: 5.4). Therefore, according to the equation of Henderson-Hasselbalch, regardless of whether adipic acid or AH salt is applied, in the stomach adipic acid is formed, whereas in the lung adipate is formed. The cation 1,6-hexanediammonium has pKa values of 10.0 and 11.1 and therefore is formed when AH salt or 1,6-hexanediamine is applied regardless of the exposure route. Thus, it can be expected that systemic effects of adipic acid and 1,6-hexanediamine are representative for AH salt irrespective of the exposure route. However, local effects of 1,6-hexanediamine which are due to its alkalinity have no relevance for AH salt, which is almost neutral.
Since a fertility study with adipic acid is lacking, a one-generation study with di(2-ethylhexyl) adipate (DEHA) which is rapidly metabolized to adipic acid is used to cover this endpoint.

Additionally, 13-week studies with 1,6-hexandiamine and a 2 year study with adipic acid were used to assess subchronic and chronic effects. Ames tests with 1,6-hexanediamine and adipic acid have been additionally used for the endpoint mutagenicity *in vitro*.

Toxicologically, AH salt may be evaluated based on data available from adipic acid and 1,6-hexanediamine and DEHA.

Human Health

There are no toxicokinetic studies with AH salt but with its constituents: Adipic acid or adipate are partially oxidized in the lipid metabolism pathways and excreted via the kidney or the lungs. 1,6-Hexanediamine is partially oxidized by diaminooxidases and aldehydedehydrogenases to 6-aminohexanoic acid, which is excreted via the urine to some extent after N-acetylation. A small part is also excreted unchanged.

The oral LD50 of AH salt in rats was approximately 4,900 mg/kg bw. Clinical signs at sublethal doses included stiff gait, apathy, reduced appetite, diarrhea, and rough coat. The lowest lethal dose (LDlo) after 24 hour occlusive dermal exposure in rabbits was above 7,940 mg/kg bw for AH salt. Clinical signs included reduced appetite and activity, salivation and ocular discharge. No data are available on the inhalation toxicity (LC50) of AH salt.

In limited studies, a 50% aqueous preparation of AH salt was not irritating to the skin and slightly irritating to the eyes of rabbits.

After repeated administration of AH-salt to rats by gavage for 28 days liver (hepatocytic necrosis), kidney (renal tubular degenerative changes) and stomach (gastric mucosal necrosis) were target organs after exposures to high dose levels (5000 mg/kg bw). The NOAEL was 1000 mg/kg bw/day.

No further data for AH salt were available, therefore in some studies the components of AH salt were investigated.
Adipic acid (2 year study) and 1,6-hexanediamine (13 week study), gave no indication of specific target organs in dietary studies in rats. NOAELs of 500 - 1000 and 50 mg/kg bw/day, respectively, were obtained. Higher doses caused body weight retardation.

Inhalation of 1,6-hexanediamine dihydrochloride caused increased absolute and relative liver weights in male mice and no effects in female mice and Fischer rats of either sex besides local effects possibly due to the unphysiological pH. The local NOAEC was 5 mg/m^3, the systemic NOAECs were 16 mg/m^3 for mice and 160 mg/m^3 for rats. There is no inhalation toxicity information available on adipic acid, and therefore, it is not possible to predict a NOAEC for this endpoint for this substance, nor for AH salt.

On balance, sufficient data are available to assess the subchronic toxicity profile of AH salt, showing relevant effects only at very high exposure levels.

AH salt was not genotoxic in limited *in vitro* (Ames test, UDS test) and neither clastogenic nor aneugenic in a mouse micronucleus test (OECD 474) after intraperitoneal administration. Additionally, Ames tests for the two components of AH salt showed no mutagenic activity. AH salt is therefore considered to be non-genotoxic.

There are no data on carcinogenicity for AH salt.

Data for fertility and developmental toxicity are only available for the components of AH salt and for di(2-ethylhexyl) adipate, which is metabolized to adipic acid.

1,6-hexanediamine (or its dihydrochloride salt) had no effect on fertility of rats in a two-generation study after administration with the diet in doses up to 150 mg/kg bw/day and after inhalation of up to 160 mg/m^3 for 13 weeks in rats and mice. In the 2-generation study the top dose (500 mg/kg bw/day) was associated with a small reduction in litter size in the F1- and F2 generation, however, without histological changes in the sex organs of males and females and in the presence of paternal as well as maternal toxicity. With the exception of a slight reduction of the litter size reproductive parameters were not adversely influenced in rats fed with di(2-ethylhexyl) adipate up to exposure levels of 12,000 ppm in the diet (corresponding to ca. 240 480 mg adipic acid/kg bw/day). The second metabolite 2-ethylhexanol resp. its metabolite 2-ethylhexanoic acid might have contributed to the slight reduction of litter size seen at that dose. 1800 ppm (36 - 72 mg adipic acid/kg bw/day) was a clear NOAEL for fertility effects. This NOAEL corresponds to 65 -129 mg AH salt/kg bw/day.

The overall conclusion is that AH salt may present a hazard to fertility only at doses which are parentally toxic.

In various species (rat, mouse, rabbit), studies with adipic acid, one of the two constituents of AH salt, did not indicate an adverse effect on development up to the highest doses tested (gavage; 250 - 288 mg/kg bw/day). In none of these studies, signs of maternal or fetal toxicity have been observed. (NOAEL rat, mouse, rabbit (maternal/developmental toxicity) 250 - 288 mg/kg bw/day). Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results. The other constituent, 1,6-hexanediamine, caused some retardation in fetal development of rats in the presence of maternal toxicity. No teratogenic effects were found up to the highest tested dose level of 300 mg/kg bw/day, which was already associated with pronounced maternal toxicity (NOAEL maternal/developmental toxicity: 112 mg/kg bw/day). An impairment of body weight gain of rat pups in the postnatal period was shown for 1,6-hexanediamine at a dose of 500 mg/kg bw/day in the absence of maternal toxicity. The NOAEL for this effect is 150 mg/kg bw/day. These doses correspond to 1130 mg and 338 mg AH-salt/kg bw/day, resp. However, as no adverse effects on pup body weights occurred on the day of birth (day 0) and on the day 4 after birth, but only on day 21 after birth (less than 10 %; no data presented on days 7/14 after birth) it cannot be excluded that the effect on pup body weight data are a consequence of the food intake rather than lactation of the pups, particularly between days 14-21 after birth.

Therefore, there is insufficient evidence that AH salt may act as developmental toxicant by impairment of body weight gain of progeny during lactation found at non maternally toxic but high doses of 1,6-hexanediamine.

Environment

AH salt is a white solid, with a solubility in water of 468 g/l at 21 °C, a melting point of 202 °C, a density of 1201 kg/m^3, and a measured log Kow of –4.4. The vapor pressure is expected to be very low due to the salt character of the substance.

In a Zahn-Wellens test (OECD 302 B) conducted with industrial activated sludge a biodegradation of 96 % after 3 days was found. From this test result it can be concluded that AH salt is inherently biodegradable. There is no study available that indicates ready biodegradation of AH-salt. A BOD5/COD ratio of 0.61 was obtained using effluent from an industrial sewage treatment plant as inoculum. One component of AH-salt, adipic acid, is readily biodegradable while for the second component, 1,6-hexanediamine, no adequate test is available to determine

whether the chemical is readily biodegradable.

Due to the salt character of the substance the calculation of a fugacity model is not appropriate. Based on the physico-chemical properties, water is expected to be the main target compartment. Due to its salt character and physico-chemical properties, volatilization from surface waters and sewage treatment plants is not expected. The substance is also not expected to bioaccumulate based on its log Kow. The mobility in soil is expected to be high based on the log Kow. However, the soil absorption can be only roughly estimated because of possible ionic interactions of the cations with negatively charged particles in the soil that may reduce their mobility. Photochemical degradation in water with estimated half-lives of 10 – 67 days for the 2 components of AH- salt does not appear to be a relevant mechanism of elimination.

Static short-term tests have been conducted with species from three trophic levels. The following effect values were found:

Fish:	*Leuciscus idus:*	96h-LC50 = 10,000 mg/l;
	Salmo gairdneri, Lepomis macrochirus:	96h-LC50 > 470 mg/l;
Daphnids:	*Daphnia magna*:	48h-EC50 = 90 mg/l;
Algae:	*Scenedesmus subspicatus*:	72h-EC50 = 394.5 mg/l.

To derive the PNECaqua the EC50 from the test with *Daphnia magna* is used: PNECaqua = 90 mg/l / 1000 = 90 µg/l (for the derivation of the PNECaqua an assessment factor of 1000 is used according to the EU Technical Guidance Document as only short-term effect values are available).

Exposure

AH salt is the basic raw material for the production of nylon 66 polymers and copolymers, that are used in fibres and yarns for textiles, carpets, apparel, tire cord, and industrial applications, or in engineering resins, used for automotive parts, electrical and electronic applications, machine parts, films, and wire coatings.

The world-wide production capacity for AH salt is estimated to be 3,400,000 tonnes/year (1,000,000 tonnes/year in Western Europe, 1,900,000 tonnes/year in North & South America and 500,000 tonnes/year in Asia).

AH salt is not registered in the product registers of Denmark, Finland, Norway and Sweden. The Swiss product register contains 3 products: 1 industrial (100 % AH salt, chemical intermediate) and 2 consumer products (up to 1 % AH salt, detergents and soaps) without mentioning any quantities processed or used.

Releases into the environment may occur during production and processing. According to measurements in a German chemical plant releases are low. Releases to the environment from the use of end products containing AH salt are considered negligible, since AH salt is present in these products only in small amounts. Occupational exposure may occur during production and processing of AH salt. Workplace measurements are available from a European production plant and gave a 95 % percentile of 0.83 mg/m^3 (total dust: personal sampling). No exposure information is available with regard to processing sites.

One of the components, adipic acid, is approved as food additive.

AH salt is used in the production of numerous consumer end products. In these products, AH salt is generally bound into the polymer matrix and hence is not expected to be present above trace concentrations.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The components of the substance possess hazards concerning reproductive toxicity but only at high doses. Based on data presented by the Sponsor country exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

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

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 3323-53-3
IUPAC Name: Adipic acid, compound with hexane-1,6-diamine (1:1)
(AH salt)

Molecular Formula: $C_{12}H_{26}O_4N_2$.
Empirical Formula: $C_6H_{16}N_2.C_6H_{10}O_4$
Structural Formula: $HOOC\text{-}(CH_2)_4\text{-}COOH.H_2N\text{-}(CH_2)_6\text{-}NH_2$
Molecular Weight: 262.34
Synonyms: Adipic acid, compound with hexane-1,6-diamine (1:1)
Adipic acid - hexamethylene diamine salt (1:1)
AH salt
Hexanedioic acid, compound with 1,6-hexanediamine (1:1)
Hexamethylene diamine adipate (1:1)
Hexamethylene diammonium adipate
Nylon salt
Nylon 66 salt
1,6-hexanediamine, adipate
1,6-hexanediamine, hexanedioate

1.2 Purity/Impurities/Additives

Physical appearance: solid, white, odourless

degree of purity: 99 - 100 % w/w

Impurities: < =1 % w/w water

<= 0.002 % w/w o-diaminocyclohexane (BASF AG, 1999°;2002c)

1.3 Physico-Chemical properties

Summary of physico-chemical properties

Water solubility:	468 g/l at 21 °C (BASF AG, 1998)
pH (10% solution):	7.8 at 25 °C (BASF AG, 1988a)
Melting Point:	202 °C (BASF AG, 2000)
log Kow:	–4.4 (BASF AG, 1988a)
Vapor pressure:	The vapor pressure is expected to be very low due to the salt character
Density:	1201 kg/m^3 (BASF AG, 1999a)
Explosion:	Dust explosion hazard (BASF AG, 1987a)

1.4 Analogue rationale

For the following endpoints studies with AH salt were not available:

- fertility

- developmental toxicity

In order to evaluate these endpoints, studies of the two components of AH salt, namely adipic acid and 1,6-hexanediamine (and its dihydrochloride) were taken into account. This can be justified as follows:

AH salt rapidly dissociates to form adipate and 1,6-hexanediammonium in an almost neutral aqueous solution. Depending on the exposure route (stomach: pH 1 to 3, intestines pH 7 (Dekant and Vamvakas, 1994), lung: pH 6.9 (Joseph et al., 2002)), adipate may be protonated to yield adipic acid (pKa1: 4.3, pKa2: 5.4; Lettner, 1974). Therefore, according to the equation of Henderson-Hasselbalch, regardless of whether adipc acid or AH salt is applied, in the stomach adipic acid is formed, whereas in the lung adipate is formed. The cation 1,6-hexanediammonium has pKa values of 10.0 and 11.1 (Smiley, 1989) and therefore is formed when AH salt or 1,6-hexanediamine is applied regardless of the exposure route. Thus, it can be expected that systemic effects of adipic acid and 1,6-hexanediamine are representative for AH salt irrespective of the exposure route. However, local effects of 1,6-hexanediamine which are due to its alkalinity have no relevance for AH salt, which is almost neutral.

Since a fertility study with adipic acid is lacking, a one-generation study with di(2-ethylhexyl) adipate (DEHA) which is rapidly metabolized to adipic acid (see 3.1.0) is used to cover this endpoint.

Additionally, 13-week studies with 1,6-hexandiamine and a 2 year study with adipic acid were used to assess subchronic and chronic effects.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The worldwide production capacity for AH salt is estimated to be 3,400,000 tons/year:

approx. 1,000,000 tons/year in Western Europe,

approx. 1,900,000 tons/year in America (North + South)

approx. 500,000 tons/year in Asia).

AH salt is produced by mixing adipic acid and 1,6-hexanediamine (1:1), generally in aqueous solution and is then used, most often captively (approx. 95 %), as a 50 – 62 % aqueous solution to make nylon polymer by batch or continous melt polymerisation. Only about 5 % is crystallized and dried for shipment by 4 producers in Europe and Asia, accounting for approx. 170,000 tons/year of the isolated substance worldwide. AH salt is the basic raw material for the production of nylon 66 polymers and copolymers, that are used in fibres and yarns for textiles, carpets, apparel, tire cord, and industrial applications, or in engineering resins, used for automotive parts, electrical and electronic applications, machine parts, films, wire coatings, and monofilament (BASF AG, 2002b).

AH salt is not registered in the product registers of Denmark, Finland, Norway and Sweden (Danish Product Register, 2002; Finnish Product Register, 2003; Norwegian Product Register 2003; Swedish Product Register, 2002). The Swiss product register contains 3 products: 1 industrial

(100 % AH salt, chemical intermediate) and 2 consumer products (up to 1 % AH salt, detergents and soaps) without the mentioning of any quantities processed or used (Swiss Product Register, 2002).

2.2 Environmental Exposure and Fate

Releases into the environment may occur during production and processing of AH salt. According to measurements in a German chemical plant, during production and processing of aqueous solution max. 0.001 % of the production are emitted into the waste water and nothing into the air. During the production of the isolated (crystallized) substance approx. 0.007 % of the production are emitted into the air and 0.3 % into the waste water (BASF AG, 2002b). Releases to the environment from the use of end products containing AH salt are considered negligible, since AH salt is present in these products only in small amounts (see above).

Furthermore, environmental releases are possible from residual contents of monomeric AH salt in the polymeric product during further processing of the polymer as well as during use and disposal of end products. In a study that measured the extractable components from a foil used for food wrapping a concentration of hexanediamine of < 1 mg/kg (detection limit) in the extract was found. The total extract was determined to 0.2 % (2 g total extract/kg polymer). The main component of the extract was the cyclic dimere of hexanediamine and adipic acid. The study was performed over a period of 10 days with either water or isopropanol (BASF AG, 2002d). From this study it can be concluded that significant environmental releases of AH-salt from end products are unlikely to occur.

In neutral aqueous solution the substance dissociates forming adipate and 1,6-hexanediammonium.

Due to the salt-character of the substance the calculation of a fugacity model is not appropriate. Based on the physico-chemical properties of AH salt, water is expected to be the main target compartment. Due to its salt character and physico-chemical properties, volatilization from surface waters and sewage treatment plants is not expected. Also for the 2 components of AH salt a fugacity model cannot be estimated properly as both substances are dissociated under environmental relevant pH conditions.

In a Zahn-Wellens test (OECD 302 B) conducted with industrial activated sludge a biodegradation of 96 % after 3 days was found (BASF AG, 1986). From this test result it can be concluded that AH salt is inherently biodegradable.

In addition, a BOD5/COD ratio of 0.61 is available for AH-salt (BASF AG, 1986). As the inoculum used in this study was effluent from an industrial sewage treatment plant, it cannot be concluded from this test that AH-salt is readily biodegradable.

Studies on the ready biodegradation of adipic acid and 1,6-hexanediamine are available. In a MITI-I test a biodegradation of 68 - 90 % after 14 days was found for adipic acid. For 1,6-hexanediamine a biodegradation of 56 % (on the upward trend) after 14 days was obtained in the same test (CITI 1992). In addition, a BOD5/COD ratio of 104.8 % is available (Institut Kuhlmann, 1989). As the BOD5 was measured using industrial activated sludge, a statement concerning the ready biodegradability of 1,6-hexanediamine cannot be made based on this test.

No data are available for AH-salt on photochemical-oxidative degradation in the atmosphere by OH-radicals. For the 2 components of AH-salt, adipic acid and 1,6-hexanediamine, the following half-lives for photochemical-oxidative degradation can be estimated with AOPWIN (OH radical concentration: $5*10^5$ mol/cm³): adipic acid: about 69 hours; 1,6-hexandiamine: about 5.6 hours. However, as under environmental relevant pH conditions the both substances are dissociated

forming adipate and 1,6-hexanediammonium, this endpoint is not relevant for the assessment of the environmental behaviour of the substance.

Data on the oxidation of adipic acid and hexylamine by OH radicals in aqueous solutions are available (Buxton et al., 1988). Therefore, oxidative photochemical degradation of AH salt in aqueous solution can be expected. With a OH radical concentration of $6 * 10^{-17}$ mol/l (Mill, 1999), photochemical half-lives of 67 days for adipic acid and 10 days for 1-hexylamine (data for 1,6-hexandiamine not available), respectively, can be estimated. In comparison to its biodegradability, however, photochemical degradation of the AH salt in the aqueous phase does not appear to be relevant.

Based on a log K_{ow} of –4.4, bioaccumulation is not expected. The mobility in soil is expected to be high based on the log Kow. However, the soil adsorption can be only roughly estimated because of possible ionic interactions of the cations with negatively charged particles in the soil that may reduce their mobility.

2.3 Human Exposure

In the sponsor country, AH salt is produced in closed systems by mixing adipic acid and 1,6-hexanediamine in water at approx. 90 °C. Occupational exposure may occur during sampling (twice daily, sampling period approx. 1 min) and maintenance operations (BASF AG, 2002a). Appropriate personal protection measures are taken to avoid exposure to the hot solution. Some inhalational exposure may occur during filling of the crystalline salt into bags. However, exposure is minimized as a result of ventilation of the workplaces. No specific occupational exposure limits have been established in the sponsor country.

The following exposure levels for dust were measured for workplaces at a production plant in the sponsor country with personal sampling:

Production (1 plant, 9 measurements): 0.11 – 0.86 mg/m^3 (total dust; 8 h shift average)

Filling/Storage (1 plant, 9 measurements): < 0.083 – 0.52 mg/m^3 (total dust; 8 h shift average). The 95 % percentile for both sites was: 0.83 mg/m^3 (total dust) (BASF AG, 2002a)

For shipment, crystalline AH salt is filled into 25 kg bags. Aqueous solutions of AH salt are loaded at approximately 90 °C on tank trucks, ships or tank wagons and transported for further processing in insulated stainless steel tanks, so that the solution remains in the liquid state (BASF AG, 2002b).

AH salt is used in the production of numerous consumer end products. In these products, AH salt is generally bound in the polymer matrix and hence is not expected to be present above trace concentrations.

One of the components, adipic acid, is approved as food additive.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No data available for AH salt.

Data for the constituents of AH salt:

After administration of radioactive adipic acid to rats metabolic products identified as urea, glutamic acid, lactic acid, beta ketoadipic acid, citric acid and adipic acid were found in the urine. 70 % of the dose was exhaled as CO_2. The tissues showed very little radioactivity (Rusoff et al., 1960).

1,6-Hexanediamine is partially oxidized by diaminooxidases and aldehyde dehydrogenases to 6-aminohexanoic acid, which is excreted via the urine to some extent after N-acetylation. A small part is also excreted unchanged (Subramanyam et al., 1989; David and Heck, 1983).

Data for di(2-ethylhexyl) adipate (DEHA):

After oral administration of 665 or 1500 mg di(2-ethylhexyl) adipate/kg bw to male rats up to 95 % of the theoretical amount from DEHA was found as adipic acid in urine on day 1 after dosing. The urinary recovery was about 50 %. CO_2 exhalation was not studied. Other metabolites were oxidized and conjugated forms of 2-ethyl hexanoic acid (Cornu et al., 1988).

Conclusion

There are no toxicokinetic studies with AH salt but with its constituents: adipic acid or adipate are partially oxidized in the lipid metabolism pathways and excreted via the kidney or the lungs. 1,6-Hexanediamine is partially oxidized by diaminooxidases and aldehydedehydrogenases to 6-aminohexanoic acid, which is excreted via the urine to some extent after N-acetylation. A small part is also excreted unchanged.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

An LC_{50} for AH salt is not available.

Dermal

No deaths occurred during 24 hour occlusive treatment and throughout the 14-day observation period at a dermal dose of 7940 mg/kg bw in two rabbits. Clinical signs observed included reduced appetite and activity (for 2 to 8 days after dosing), salivation and ocular discharge. At necropsy, the viscera of all animals appeared normal (Solutia, 1978).

Conclusion

The lowest lethal dose (LDlo) after 24 hour occlusive dermal exposure in rabbits was above 7940 mg/kg bw. Clinical signs included reduced appetite and activity, salivation and ocular discharge.

Oral

AH salt is of very low acute oral toxicity. The oral LD_{50} in rats was approximately 4900 mg/kg bw. Clinical signs at sublethal doses included stiff gait, apathy, reduced appetite, diarrhea, and rough coat (BASF AG, 1956b). In a study, performed with the 50 % aqueous solution, at a dose level of 10,000 mg/kg bw no mortality was caused in 2 male and 3 female rats. The only clinical signs observed were reduced appetite and activity on the day of dosing; at necropsy (14 days after dosing) viscera appeared normal (Solutia, 1978). The LD_{50} in mice was 4700 mg/kg bw, clinical symptoms at sublethal doses included irritation of the gastro-intestinal tract, and intestinal bleeding, and diarrhea (BASF AG, 1956).

Conclusion

The oral LD50 in rat was approximately 4900 mg/kg bw. Clinical signs at sublethal doses included stiff gait, apathy, reduced appetite, diarrhea, and rough coat.

3.1.3 Irritation

Eye Irritation

A 50 % aqueous preparation of AH salt (limit of solubility) caused slight and transient conjunctivitis in two rabbits after exposure up to 3 hours. All effects were completely reversible within 24 hours (BASF AG, 1956a). Data on purity are lacking, but as there was no strong irritation observed, this is thought not to impair the evaluation of the eye irritation potential significantly. As a 50 % aqueous preparation is the limit of solubility, no higher concentrations would have been achieved if neat AH salt had been tested and this deviation from the test guideline is thought not to impair the evaluation of the eye irritation potential significantly.

Conclusion

A 50 % aqueous preparation of AH salt was slightly irritating to the eyes of rabbits.

3.1.4 Sensitisation

No data available.

3.1.5 Repeated Dose Toxicity

AH salt, as an aqueous preparation (48 - 50 %,w/w), was tested in a 28 day gavage study in Sprague-Dawley rats at dose levels of 0; 200; 1000 and 5000 mg/kg bw/day. 10 animals per sex/dose were used. The highest dose level caused the death or sacrifice in extremis of 10/10 males within 5 days and 6/10 females within 14 days of exposure. The surviving females of the high-dose group had lower mean body weights than the control group at day 8, but not at day 28. 1000 and 200 mg/kg bw/day produced no effects on body weight or food consumption in either sex, nor were any significant clinical observations noted. Organ weights among test animals of both sexes that survived to final necropsy, did not differ significantly from the control group. There was no difference in absolute and relative testes weights between treated groups and controls. Histopathological changes at the toxic level of 5000 mg/kg bw/day included renal tubular degenerative changes in both sexes (5/10 males and 3/10 females) and gastric mucosal necrosis in 3/10 males. Hepatocytic necroses were found in 2 males and 2 females of the high dose groups, and in 1 control female. No changes were found in all other organs including the pituitaries, testes and ovaries. There were no significant microscopic changes among mid dose males and females. Statistically significant increases in red blood cells and hematocrit in males at the mid- and low-dose levels were observed. However, the value remained within the normal limits and was therefore not considered as biologically significant. The serum chemistry was not altered. The NOAEL was 1000 mg/kg bw/day (Monsanto, 1982).

Additional information on the repeated dose toxicity of AH salt can be deduced from studies with adipic acid and 1,6-hexanediamine (see chapter 3.1) following current test guidelines. These studies gave no indication of specific target organs for systemic toxicity.

Inhalation of 1,6-hexanediamine or its dihydrochloride produced lesions in the upper respiratory tracts of Sprague Dawley rats (12.8 - 215 mg/m^3) or of Fischer 344 rats and B6C3F1 mice (1.6 - 160 mg/m^3) that could be attributed to the nonphysiological pH of these compounds. Significantly

increased absolute and relative liver weights were seen from 50 mg/m^3 onwards, only in male mice. The no observed adverse effect concentrations (NOAECs) for local irritation in these studies were 5 and 12.8 mg/m^3 for 1,6-hexanediamine dihydrochloride and 1,6-hexanediamine, respectively. The NOAECs for systemic toxicity were 160 mg/m^3 for rats and 16 mg/m^3 for mice respectively (NTP, 1993; Johannsen et al., 1987).

No gross or microscopic changes were seen in tissues of rats administered 1,6-hexanediamine with the diet at dose levels up to 500 mg/kg bw/day for 13 weeks. The only effects seen were a modest retardation in weight gain at 150 and 500 mg/kg bw. The NOAEL was 50 mg/kg bw/day (Johannsen and Levinskas, 1987).

Rats were fed either the basal laboratory diet, or the diet to which adipic acid was added (males: 0.1, 1, 3, 5 % = ca. 50 - 100; 500 - 1000; 1500 - 3000; 2500 - 5000 mg/kg bw/day, 20 animals/dose and 20 controls ; females: 1% = ca. 500 - 1000 mg/kg bw/day, 19 animals/dose group, 10 controls). After 2 years, surviving rats were weighed, killed, and examined grossly. Ten organ weights were recorded for approx. half of each group of males, and 4 organ weights were recorded for females. Microscopic examination of 15 tissues was done on a representative number of animals from each group. Thus, the study does not fully comply with the guidelines for a chronic study. In male rats, there were no body weight differences throughout the 2-year period in the 0.1 or 1 % exposure group. During the rapid growth period, the weight gains of the 3.0 and 5.0 % adipic acid groups were significantly less than the control groups. At the end of the study the body weight of males was reduced by 10 % and more in the two highest exposure groups. There was slight, but consistent, reduction in feed consumption at 5 % exposure. Throughout the study, the following clinical signs were observed among all groups, including controls: wheezing, blood-tinged crust about the noses and eyes, and body sores. The incidence of these findings did not appear to be significantly different among the groups although a lower incidence of signs indicative of respiratory infection and body sores occurred in the 5 % dose group. The incidence of lung pathology and tumor growth appeared to be equally distributed among all groups, including the controls. When the surviving males were sacrificed at the end of the study, there were no significant differences in organ weights or microscopic examination. In females, there were no significant differences in body weight gains or food consumption. Clinical signs noted in control and test groups included blood-tinged crust about the eyes and nose, unthriftiness, and body sores. There were no significant differences in organ weights, gross, or microscopic pathology (Horn, Holland and Hazleton 1957). The NOAEL for adipic acid was 1 % (500 - 1000 mg/kg bw/day).

Conclusion

After repeated administration of AH-salt to rats by gavage for 28 days liver (hepatocytic necrosis), kidney (renal tubular degenerative changes) and stomach (gastric mucosal necrosis) were the target organs after exposure to 5000 mg/kg bw/day. The NOAEL was 1000 mg/kg bw/day.

The components of AH salt were investigated in separate studies.

Adipic acid (2 year study) and 1,6-hexanediamine (13 week study), gave no indication of specific target organs in dietary studies in rats. NOAELs of 500 - 1000 and 50 mg/kg bw/day, resp. were obtained. Higher doses caused body weight retardation.

Inhalation of 1,6-hexanediamine dihydrochloride caused increased absolute and relative liver weights in male mice but no effects in female mice and Fischer rats of either sex besides local effects possibly due to the nonphysiological pH. The local NOAEC was 5 mg/m^3, the systemic NOAECs were 16 mg/m^3 for mice and 160 mg/m^3 for rats. There is no inhalation toxicity information available on adipic acid, and therefore, it is not possible to predict a NOAEC for this endpoint for this substance, nor for AH salt.

On balance, sufficient data are available to assess the subchronic toxicity profile of AH salt, showing relevant effects only at very high exposure levels.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

AH salt was not mutagenic in the Ames test in five Salmonella strains, both in the presence and in the absence of metabolic activation (liver S-9 mix up to 2500 ug/plate tested). The test did not include cytotoxic exposure levels (BASF AG 1980). The components adipic acid and 1,6-hexanediamine were negative in the Ames test up to and including 10 000 ug/plate (Mortelmans et al., 1986; Prival, Simmon and Mortelmans, 1991).

AH salt did not induce unscheduled DNA synthesis in primary rat hepatocytes in vitro in a test performed according to current standards (BASF AG, 1982). The test substance was not toxic at any of the applied concentrations (5 - 1000 µg/ml).

In vivo Studies

In a GLP micronucleus test performed via the intraperitoneal route (2 applications with a 24 h interval) in male mice (5 males/group) according to OECD TG 474, the administration of the test substance (purity 99 %) led to clinical signs of toxicity at 800 and 1600 mg/kg bw. No clinical signs were observed at 400 mg/kg bw. Because no differences in toxicity between the two sexes were found in a pre-test, only males were used in the main study. There was no increase in the number of polychromatic erythrocytes containing either small or large micronuclei. Therefore the test substance had no clastogenic effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells in vivo (BASF AG, 2001).

Conclusion

AH salt was not genotoxic in limited *in vitro* (Ames test, UDS test) and neither clastogenic nor aneugenic in a mouse micronucleus test (OECD 474) after intraperitoneal administration. Additionally, Ames tests for the two components of AH salt showed no mutagenic activity. AH salt is therefore considered to be nongenotoxic.

3.1.7 Carcinogenicity

There is no experimental data available for AH salt.

3.1.8 Toxicity for Reproduction

AH salt was not tested for its toxicity to fertility and development and there is only limited information available from a 28-day study on the effects on reproductive organs. As outlined in 3.1 studies with adipic acid and 1,6-hexanediamine (or its dihydrochloride), the two compounds that constitute AH salt are used to cover this endpoint.

Studies in Animals

Effects on Fertility

Repeated dose studies were performed with 1,6-hexanediamine (or its dihydrochloride salt), one component of AH salt. Dietary treatment with up to 150 mg/kg bw/day 1,6-hexanediamine for 56

days (F0) and 98 days (F1) prior to mating had no effect on fertility or reproduction in a two-generation study in Sprague-Dawley rats. The highest dose of 500 mg/kg bw/day which was tested, showed no influence on the animal mating performance and the number of litters. However, litter size in the F1 generation showed a significant reduction to 11.7 vs. 13.8 in the control, in the F2 generation there was a numerical reduction (11.0 vs. 13.0). The weight of male F0 and F1 parents was significantly reduced by about 10 % in this dose at the end of the treatment period. The body weight of the females was not altered at that time but the weight gain was reduced by about 10 % during gestation The pup weights were normal at birth, but significantly reduced at day 21 in male F1 and female F2 pups. There was no effect on their survival and they appeared normal during lactation. No macroscopic and microscopic effects on the sex organs were observed. NOAEL for fertility and all other parameter is 150 mg/kg bw/day (Short, Johannsen and Schardein, 1991). It is not known whether the reduced litter size is an effect on male or female fertility or a effect secondary to toxicity.

Inhalation of 1,6-hexanediamine dihydrochloride (as aerosol) 6 h/day, 5 d/week for 13 weeks at exposure levels of up to 160 mg/m^3 did not influence sperm motility and vaginal cytology in B6C3F1 mice or F344 rats. A subsequent mating trial did not impair the fertility and reproductive outcome of rats and mice (NTP 1993). 160 mg/m^3 corresponds to 38 mg/kg bw assuming an inhalation volume of 12 l/h, a bodyweight of 300 g and a retention of 100 %. The dose is therefore much lower than those used by Short et al. (1991).

A one-generation study with di(2-ethylhexyl)adipate is also taken to cover this endpoint as outlined in chapter 1.

DEHA was administered to ca. 21 day old rats, each dose and control group consisted of 30 female and 10 male rats. DEHA was given in the feed at 300, 1800 and 12,000 ppm. The authors do not state what the effective dose levels are, however as a general rule, the dose ranges within the experiment varied between 15 - 30, 90 - 180 and 600 - 1200 mg/kg bw/day, (according to a conversion factor of 10 and 20; WHO, 1987), depending on the age and body weight of the animals for a period of 10 weeks prior to mating, during mating and during the gestation and lactation periods. These doses correspond to 6 - 12, 36 - 72, 240 - 480 mg adipic acid/kg bw/day. Necropsy was performed on male animals immediately after successful mating, on females after the pups had been weaned, and on the progeny after day 36 of life. The following organs were histologically examined: cervix, epididymis, liver, mammary gland, ovaries, seminal vesicle, prostate, testes, uterus and all other organs if showing macroscopic changes. No clinical symptoms of intoxication occurred in the parent animals. Only the females in the high dose group suffered slight, but non-significant, inhibition of body weight gain during the pretreatment period (approx. 3 %) and a significant reduction during pregnancy. Data on body weight of females in the lactation period are lacking. The males of the high dose group showed a slight but significant increase in feed consumption from weeks 6 to 9 with simultaneous reduction in feed efficiency. Male and female fertility, length of gestation and the pre-coital interval were not affected. The parental animals did not show any signs of substance-related histopathological organ change. Both males and females in the high dose group, however, had significantly higher absolute and relative liver weights. There were four whole litter losses, none in control, one in the 300 ppm group, two in the 1800 ppm group and one in the 12,000 ppm dose group. Only in the high dose group was there a slight but non-significant reduction in litter sizes (day 1: 9.7 vs. 10.9; day 36: 8.5 vs. 10.0). None of the pups showed any clinical signs, substance-related macroscopic or histopathologic changes or gross malformations. Pup weight at birth was not different from controls. In the highest dose group a significant inhibition (10 - 23 %) of the mean body weight gain of pups in the postnatal follow-up period (day 1 - 36) was observed, as well as a reduction in the total litter weight of both males and females. The author derived a NOAEL for fertility parameters in both generations of 12,000 ppm; pup body weight reduction in the postnatal phase, however, was recorded at 12,000 ppm. There are

no data on maternal body weight gain during that phase and the pup body weight at term was not different from controls, thus maternal toxicity cannot explain this effect. However, the second metabolite 2-ethylhexanol might have contributed to retarded pup body weight gain. Thus, 1800 ppm, (36 - 72 mg adipic acid/kg bw/day) was shown as a clear-cut NOAEL for all effects (Tinston, 1988).

Conclusion

Data for fertility are only available for 1,6-hexanediamine and for di(2-ethylhexyl) adipate, which is metabolized to adipic acid.

1,6-hexanediamine (or its dihydrochloride salt) had no effect on fertility of rats in a two-generation study after administration with the diet in doses up to 150 mg/kg bw/day and after inhalation of up to 160 mg/m^3 for 13 weeks in rats and mice. In the 2-generation study the top dose (500 mg/kg bw/day) was associated with a small reduction in litter size in the F1 and F2 generation, however, without histological changes in the sex organs of males and females, and in the presence of paternal as well as maternal toxicity. With the exception of a slight reduction of the litter size, reproductive parameters were not adversely influenced in rats fed with di(2-ethylhexyl) adipate up to exposure levels of 12,000 ppm in the diet (corresponding to ca. 240 - 480 mg adipic acid/kg bw/day). The second metabolite 2-ethylhexanol might have contributed to the slight reduction of litter size seen at that dose. 1800 ppm (36 - 72 mg adipic acid/kg bw/day) was a clear NOAEL for fertility effects.

The overall conclusion is that AH salt may present a hazard to fertility only at doses which are parentally toxic.

Developmental Toxicity

Developmental toxicity studies have been conducted for adipic acid in rats, mice and rabbits, and for 1,6-hexanediamine (or its dihydrochloride) in rats.

Adipic acid was not embryo- or fetotoxic and not teratogenic after administration by gavage to rats (gd 6 - 15; up to 288 mg/kg bw/day), mice (gd 6 - 15; up to 263 mg/kg bw/day), and rabbits (gd 6 - 18; up to 250 mg/kg bw/day). In none of these studies signs of maternal or fetal toxicity have been observed (U.S. Food and Drug Administration, 1973, 1974).

NOAELs for rat, mouse and rabbit (maternal/developmental toxicity) are 250 - 288 mg/kg bw/day.

1,6-Hexanediamine dihydrochloride was not embryo- or fetotoxic in a limited study in Fischer 344 rats after gavage of up to 200 mg/kg bw/day (gd 0 - 15). Maternal toxicity (reduced body weight gain) was observed in this study at 200 mg/kg bw/day. Teratogenicity was not investigated (David and Heck, 1983).

In pregnant Sprague-Dawley rats treated with 112, 184 and 300 mg/kg bw/day of 1,6-hexanediamine by gavage (gd 6 - 15; n = 22) there was a significant decrease of body weight gain in the top dose. Incidence of implantation sites and resorptions was not affected, also fetal sizes were normal. Fetal body weights were reduced in both sexes and slight skeletal retardations were recorded. At 184 mg/kg bw/day there was numerical reduction (15 %) of maternal body weight gain during treatment and also a numerical reduction in fetal weight (5 %) and an increase in skeletal retardations. On balance, in the light of the pronounced maternal effects, the fetal effects observed do not indicate a selective fetal toxicity. Contrary to the author`s conclusions, 112 mg/kg bw/day is a NOAEL for both maternal and fetal toxicity, with 184 mg/kg bw/day being a LOAEL for both endpoints. 300 mg/kg bw/day is a NOAEL for teratogenicity and embryotoxicity (Johannsen and Levinskas, 1987).

An impairment of body weight gain of rat pups in the postnatal period was shown for 1,6-diaminohexane at a dose of 500 mg/kg bw/day, in the absence of maternal toxicity. The NOAEL for this effect is 150 mg/kg bw/day (Short, Johannsen and Schardein, 1991).

These doses correspond to 1130 mg and 338 mg AH-salt/kg bw/day, resp. However, as no adverse effects on pup body weights occurred on the day of birth (day 0) and on the day 4 after birth, but only on day 21 after birth (less than 10 %; no data presented on days 7/14 after birth) it cannot be excluded that the effect on pup body weight data are a consequence of the food intake rather than lactation of the pups, particularly between days 14-21 after birth.

Therefore, there is insufficient evidence that AH salt may act as developmental toxicant by impairment of body weight gain of progeny during lactation found at non maternally toxic but high doses of 1,6-hexanediamine.

Conclusion

Data for developmental toxicity are only available for the components of AH salt.

In various species (rat, mouse, rabbit), studies with adipic acid, one of the two constituents of AH salt, did not indicate an adverse effect on development up to the highest doses tested (gavage; 250 - 288 mg/kg bw/day). In none of these studies, signs of maternal or fetal toxicity have been observed (NOAEL rat, mouse, rabbit (maternal/developmental toxicity) 250 - 288 mg/kg bw/day). Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results.The other constituent, 1,6-hexanediamine, caused some retardation in fetal development of rats in the presence of maternal toxicity. No teratogenic effects were found up to the highest tested dose level of 300 mg/kg bw/day, which was already associated with pronounced maternal toxicity (NOAEL maternal/developmental toxicity: 112 mg/kg bw/day). An impairment of body weight gain of rat pups in the postnatal period was shown for 1,6-hexanediamine at a dose of 500 mg/kg bw/day in the absence of maternal toxicity. The NOAEL for this effect is 150 mg/kg bw/day. These doses correspond to 1130 mg and 338 mg AH-salt/kg bw/day, resp. However, as no adverse effects on pup body weights occurred on the day of birth (day 0) and on the day 4 after birth, but only on day 21 after birth (less than 10 %; no data presented on days 7/14 after birth) it cannot be excluded that the effect on pup body weight data are a consequence of the food intake rather than lactation of the pups, particularly between days 14 - 21 after birth.

Therefore, there is insufficient evidence that AH salt may act as developmental toxicant by impairment of body weight gain of progeny during lactation found at non maternally toxic but high doses of 1,6-hexanediamine.

3.1.9 Experience with Human Exposure

No data available.

3.2 Initial Assessment for Human Health

AH salt is easily soluble in water and therefore dissociates to form adipate and 1,6-hexanediammonium in an almost neutral aqueous solution. Depending on the exposure route (stomach: pH 1 to 3, intestines pH 7, lung: pH 6.9), adipate may be protonated to yield adipic acid (pKa1: 4.3, pKa2: 5.4). Therefore, according to the equation of Henderson-Hasselbalch, regardless of whether adipc acid or AH salt is applied, in the stomach adipic acid is formed, whereas in the lung adipate is formed. The cation 1,6-hexanediammonium has pKa values of 10.0 and 11.1 and therefore is formed when AH salt or 1,6-hexanediamine is applied regardless of the exposure route.

Thus, it can be expected that systemic effects of adipic acid and 1,6-hexanediamine are representative for AH salt irrespective of the exposure route. However, local effects of 1,6-hexanediamine which are due to its alkalinity have no relevance for AH salt, which is almost neutral.

Since a fertility study with adipic acid is lacking, a one-generation study with di(2-ethylhexyl) adipate (DEHA) which is rapidly metabolized to adipic acid is used to cover this endpoint.

Additionally, 13-week studies with 1,6-hexandiamine and a 2 year study with adipic acid were used to assess subchronic and chronic effects.

Toxicologically, AH salt may be evaluated based on data available from adipic acid and 1,6-hexanediamine and DEHA.

There are no toxicokinetic studies with AH salt but with its constituents: adipic acid or adipate are partially oxidized in the lipid metabolism pathways and excreted via the kidney or the lungs. 1,6-Hexanediamine is partially oxidized by diaminooxidases and aldehydedehydrogenases to 6-aminohexanoic acid, which is excreted via the urine to some extent after N-acetylation. A small part is also excreted unchanged

The oral LD_{50} for AH salt in rats was approximately 4900 mg/kg bw. Clinical signs at sublethal doses included stiff gait, apathy, reduced appetite, diarrhea, and rough coat.

The lowest lethal dose (LDlo) after 24 hour occlusive dermal exposure in rabbits was above 7940 mg/kg bw. Clinical signs included reduced appetite and activity, salivation and ocular discharge. An LC_{50} for AH salt is not available.

In limited studies, a 50 % aqueous preparation of AH salt was not irritating to the skin and slightly irritating to the eyes of rabbits. After repeated administration of AH-salt to rats by gavage for 28 days liver, kidney and stomach were target organs after exposures to high dose levels (5000 mg/kg bw). The NOAEL was 1000 mg/kg bw/day.

The components of AH salt were investigated in separate studies.

Adipic acid (2 year study) and 1,6-hexanediamine (13 week studies), gave no indication of specific target organs in dietary studies in rats. NOAELs of 500 - 1000 and 50 mg/kg bw/day, resp. were obtained. Higher doses caused body weight retardation.

Inhalation of 1,6-hexanediamine dihydrochloride caused increased absolute and relative liver weight in male mice and no effects in female mice and Fischer rats of either sex besides local effects possibly due to unphysiological pH. The local NOAEC was 5 mg/m^3, the systemic NOAECs were 16 mg/m^3 for mice and 160 mg/m^3 for rats .

On balance, sufficient data are available to assess the subchronic toxicity profile of AH salt, showing relevant effects only at very high exposure levels.

AH salt was not genotoxic in limited in vitro (Ames test, UDS test) assays and neither clastogenic nor aneugenic in a mouse micronucleus test (OECD 474) after intraperitoneal administration. Additionally, Ames tests for the two components of AH salt showed no mutagenic activity. AH salt is therefore considered to be non-genotoxic.

There are no carcinogenicity data for AH salt.

Data for fertility and developmental toxicity are only available for the components of AH salt and for di(2-ethylhexyl) adipate, which is metabolized to adipic acid.

1,6-Hexanediamine (or its dihydrochloride salt) had no effect on fertility of rats in a two-generation study after administration with the diet in doses up to 150 mg/kg bw/day and after inhalation of up to 160 mg/m^3 for 13 weeks in rats and mice. In the 2-generation study the top dose (500 mg/kg bw/day) was associated with a small reduction in litter size in the F1- and F2 generation, however, without histological changes in the sex organs of males and females, and in the presence of paternal as well as maternal toxicity. With the exception of a slight reduction of the litter size reproductive parameters were not adversely influenced in rats fed with di(2-ethylhexyl) adipate up to exposure levels of 12,000 ppm in the diet (corresponding to ca. 240 - 480 mg adipic acid/kg bw/day). The second metabolite 2-ethylhexanol might have contributed to the slight reduction of litter size seen at that dose. 1800 ppm (36 - 72 mg adipic acid/kg bw/day) was a clear NOAEL for fertility effects.

The overall conclusion is that AH salt may present a hazard to fertility only at doses which are parentally toxic.

In various species (rat, mouse, rabbit), studies with adipic acid, one of the two constituents of AH salt, did not indicate an adverse effect on development up to the highest doses tested (gavage; 250 - 288 mg/kg bw/day). In none of these studies, signs of maternal or fetal toxicity have been observed (NOAEL rat, mouse, rabbit (maternal/developmental toxicity) 250 - 288 mg/kg bw/day). Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results.

The other constituent, 1,6-hexanediamine, caused some retardation in fetal development of rats in the presence of maternal toxicity. No teratogenic effects were found up to the highest tested dose level of 300 mg/kg bw/day, which was already associated with pronounced maternal toxicity (NOAEL maternal/developmental toxicity: 112 mg/kg bw/day). An impairment of body weight gain of rat pups in the postnatal period was shown for 1,6-hexanediamine at a dose of 500 mg/kg bw/day in the absence of maternal toxicity. The NOAEL for this effect is 150 mg/kg bw/day.

Hence, AH salt is not expected to act as a developmental toxicant at non maternally toxic doses but may impair body weight development of the progeny during lactation at non maternally toxic doses.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Short-term tests have been conducted with species from three trophic levels. Although all tests were performed in static systems without analytical monitoring of the test substance concentration, the nominal concentrations are not expected to differ substantially from measured concentrations due to the low volatility. The following effect values were found:

a) fish

Leuciscus idus LC_{50} = 10,000 mg/l (96 h)

static, nominal concentrations, no mortality at 2500 mg/l (BASF AG, 1987b)

Salmo gairdneri LC_{50} > 470 mg/l (96 h)

static, nominal concentrations, no mortality at 470 mg/l (Monsanto, 1981c).

Lepomis macrochirus LC_{50} > 470 mg/l (96 h)

static, nominal concentrations, no mortality at 470 mg/l (Monsanto, 1981a).

b) invertebrates

Daphnia magna EC_{50} = 90 mg/l (48 h)

effect: mortality 10 % mortality at 50 mg/l (Monsanto, 1981b).

c) algae

Scenedesmus subspicatus EbC_{50} = 394.5 mg/l (72 h)

EbC_{20} = 269.3 mg/l (72 h)

EbC_{50} = 291.9 mg/l (96 h)

EbC_{20} = 102.9 mg/l (96 h)

effect: biomass, nominal concentration (BASF AG, 1987c).

d) microorganisms

Activated sludge EC_{50} > 900 mg/l (10 min)

effect: respiration inhibiton (BASF AG, 1986).

Pseudomonas putida EC_{50} > 2,000 mg/l (17 h)

effect: growth inhibition (BASF AG, 1987d).

e) Derivation of PNECaqua

For the derivation of the PNECaqua an assessment factor of 1000 is used according to the EU Technical Guidance Document, as only short-term effect values with species from three trophic levels are available.

To derive the PNECaqua the EC_{50} from the test with *Daphnia magna* is used: PNECaqua = 90 mg/l / 1000 = 90 µg/l.

4.2 Terrestrial Effects

No data available

4.3 Initial Assessment for the Environment

AH salt is a white solid, with a solubility in water of 468 g/l at 21 °C, a melting point of 202 °C, a density of 1201 kg/m^3, and a measured log K_{ow} of –4.4. The vapor pressure is expected to be very low due to its salt character.

In a Zahn-Wellens test (OECD 302 B) conducted with industrial activated sludge a biodegradation of 96 % after 3 days was found. From this test result it can be concluded that AH salt is inherently biodegradable. There is no study available that indicates ready biodegradation of AH-salt. A BOD5/COD ratio of 0.61 was obtained using effluent from an industrial sewage treatment plant as inoculum. One component of AH-salt, adipic acid, is readily biodegradable while for the second component, 1,6-hexanediamine, no adequate test is available to determine whether the chemical is readily biodegradable.

Based on the physico-chemical properties, water is expected to be the main target compartment. Due to its salt character and physico-chemical properties, volatilization from surface waters and sewage treatment plants is not expected. The substance is also not expected to bioaccumulate based on its log K_{ow}. The mobility in soil is expected to be high based on the log Kow. However, the soil adsorption can be only roughly estimated because of possible ionic interactions of the cations with negatively charged particles in the soil that may reduce their mobility.

Photochemical degradation in water with estimated half-lives of 10 – 67 days for the 2 components of AH salt does not appear to be a relevant mechanism of eliminiation.

Static short-term tests have been conducted with species from three trophic levels. The following effect values were found:

Fish: Leuciscus idus, 96h-LC_{50} = 10,000 mg/l;

Salmo gairdneri, Lepomis macrochirus, 96h-LC_{50} > 470 mg/l.

Daphnids: Daphnia magna: 48h-EC_{50} = 90 mg/l

Algae: Scenedesmus subspicatus: 72h-EbC_{50} = 394.5 mg/l

To derive the PNECaqua the EC_{50} from the test with Daphnia magna is used: PNECaqua = 90 mg/l / 1000 = 90 µg/l (for the derivation of the PNECaqua an assessment factor of 1000 is used according to the EU Technical Guidance Document as only short-term effect values are available)

5 RECOMMENDATIONS

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

Human Health: The chemical is currently of low priority for further work. The components of the substance possess hazards concerning reproductive toxicity but only at high doses. Based on data presented by the sponsor country exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the sponsor country.

6 REFERENCES

BASF AG (1956a). Department of Toxicology, unpublished study Bericht über die orientierende Hautreizprüfung von AH-Salz (VI/3), 17 Mar 1956.

BASF AG (1956b). Department of Toxicology, unpublished study Bericht über die orientierende toxikologische Prüfung von AH-Salz (VI/3), 19 Apr 1956.

BASF AG (1980). Department of Toxicology, unpublished study Bericht über die Prüfung von Hexamethylendiaminadipat im Ames-Test (79/518), 02 Jun 1980.

BASF AG (1982). Department of Toxicology, unpublished study Evaluation of Hexamethylenediamine adipate in the primary rat hepatocyte unscheduled DNA synthesis assay (81/230), 25 Jan 1982.

BASF AG (1986). Department of Ecology, unpublished study Prüfungen von AH-Salz für das Sicherheitsdatenblatt (01.408/86), 17.10.1986.

BASF AG (1987a). Sicherheitstechnische Kenndaten, unpublished study (SIK-Nr. 87/1629), 19 Oct 1987.

BASF AG (1987b). Department of Toxicology, unpublished study Bericht über die Prüfung der akuten Toxizität an der Goldorfe (87/131), 09 Sep 1987.

BASF AG (1987c). Department of Ecology, unpublished study Algentest (1104/87), 30.11.1987.

BASF AG (1987d). Department of Ecology, unpublished data Wachstumshemmtest in Anlehnung an Bringmann-Kühn (9/0242/87/2), 07.Apr 1987.

BASF AG (1988a). Analytics Department, unpublished study Octanol-Wasser-Verteilungskoeffizient (BRU 88.172), 29 Aug 1988.

BASF AG (1988b). Department of Ecology, unpublished data Bestimmung der akuten Wirkung von AH-Salz gegenüber dem Wasserfloh Daphnia magna Straus (1104/87), 22 .01.1988.

BASF AG (1998). Technische Entwicklung, Verfahrenstechnik, unpublished study Fest-Flüssig-Phasengleichgewicht (Meßbericht FE 98.401), 14 Oct 1998.

BASF AG (1999a). Crystalline AH-Salt: Specifications at a glance. http://www.basf.de/basf/html/e/produkte/gebiete/kunstst/fibre/products/intermed/ahsalz/spezah.html

BASF AG (1999b). Liquid AH-Salt: Keeps longer when well insulated. http://www.basf.de/basf/html/e/produkte/gebiete/kunstst/fibre/products/intermed/ahsalz/liquid.html.

BASF AG (2000). Material Safety Data Sheet AH Salt Crystalline (23.08.2000).

BASF AG (2001). Experimental Toxicology and Ecology: Cytogenetic study in vivo with AH-Salz kristallisiert in the mouse micronucleus test after two intraperitoneal administrations. unpublished report 26MO617/004157, 5 Dec 2001.

BASF AG (2002a). AH-Salt. Occupational Exposure Monitoring Data, 29 Jan 2002.

BASF AG (2002b). AH-Salt. Additional Informations, 24 May 2002.

BASF AG (2002c). Material Safety Data Sheet AH Salt Crystalline (23.05.2002)

BASF AG (2002d). department of analytical, unpublished data, laboratory notice, 26.07.2002.

Buxton GV, Greenstock, Helmann WP, Ross AB (1988). Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals in aqueous solution. J.Phys Chem Ref Data **17**, 513 - 883.

CITI (1992). Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan (1992).

Cornu MC, Keith Y, Elcombe CR and Lhugenot JC (1988). In vivo and in vitro metabolism of di-(2-ethylhexyl) adipate a peroxisome proliferator, in the rat, Arch. Toxicol. Suppl. **12**, 265-268.

Danish Product Register (2002). Communication to BUA.

David RM and Heck H (1983). Localization of 1,6-(14C)diaminohexane (HMDA) in the Prostate and the Effects of HMDA on Early Gestation in Fischer-344 Rats. Toxicol Letters **17**, 49-55.

Dekant W, Vamvakas S (1994). Toxikologie, Spektrum, Heidelberg, 113.

Finnish Product Register (2003). Communication to BUA.

Horn HJ, Holland EG and Hazleton LW (1957). Safety of adipic acid as compared with citric and tartaric acid. Agric Fd Chem **5**, 759-762.

Institut Kuhlmann (1989). Unpublished report 2-113-257/89, 08.05.1989.

Johannsen FR and Levinskas GJ (1987). Toxicological Profile of orally administered 1,6-hexane diamine in the rat. J Appl Toxicol **7**, 259-263.

Johannsen FR, Levinskas GJ, Ben-Dyke R and Hogan GK (1987). Subchronic Inhalation Toxicity of Hexamethylenediamine in Rats. Fund Appl Toxicol **9**, 504-511.

Joseph D, Tirmiz O, Zhang X-L, Crandall ED and Lubman RL (2002). Alveolar epithelial ion and fluid transport. Polarity of alveolar epithelial cell acid-base permeability. Am J Physiol Lung Cell Mol Physiol **282**, L675-L683.

Lettner H (1974). Adipinsäure. In: Ullmann's Enzyklopädie der technischen Chemie, Vol 7, VCH, Weinheim, 106.

Mill T (1999). Predicting photoreaction rates in surface waters. Chemosphere **38**, 1379 - 1390.

Monsanto Chemical Company (1981a). unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-096): Static Acute Bioassay Report #27358, 28 Apr 1981.

Monsanto Chemical Company (1981b). unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-097): Static Acute Bioassay Report #27359, 29 Apr 1981.

Monsanto Chemical Company (1981c). unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-095): Static Acute Bioassay Report #27357, 13 May 1981.

Monsanto Chemical Company (1982). Environmental Health Laboratory unpublished study: Four week Study of Nylon Salt 6/6 Administered by Gavage to Sprague-Dawley Rats. DMEH project no. ML-81-100. 27 Oct 1982.

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B and Zeiger E (1986). Salmonella Mutagenicity Tests: II. Results from the Testing of 270 Chemicals. Environ. Mutagen. **8** (Suppl 7), 1-119.

Norwegian Product Register (2003). Communication to OECD.

NTP (1993). Technical Report on Toxicity Studies of 1,6-Hexanediamine Dihydrochloride. NIH Publication 93-3347, March 1993. Toxicity Report No. 24.

Prival MJ, Simmon VF and Mortelmans KE (1991). Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. **260**, 321-329.

Rusoff I, Baldwin RR, Domingues FJ, Ohan WJ and Thiessen R (1960). Intermediary metabolism of adipic acid. Toxicol Appl Pharmacol **2**, 316-330.

Short RD, Johannsen FR and Schardein JL (1991). A Two-Generation Reproduction Study in Rats Receiving Diets Containing Hexamethylenediamine. Fund Appl Toxicol **16**, 490-494.

Smiley RA (1989). Hexamethylenediamine. **In**: Ullmann's encyclopedia of industrial chemistry, Vol A12, VCH, Weinheim, 629.

Solutia (1978). Unpublished study, Nylon 6/6 salt solution, acute oral and dermal toxicity report no. Y-77-355, 31 Jan 1978.

Subramanyam B, Callery PS, Geelhaar LA and Egorin MJ (1989). A cyclic imine intermediate in the in vitro metabolic conversion of 1,6 diaminohexane to 6-aminohexoic acid and caprolactam. Xenobiotica **19**, 33 – 42.

Swedish Product Register (2002). Communication to BUA.

Swiss Product Register (2002). Communication to BUA.

Tinston DJ (1988). Di-(2-ethylhexyl) adipate: Fertility study in rats: unpublished study,ICI Central Toxicology, Lab. Rep. CTL/P/2229.

U.S. Food and Drug Administration (1973a). Food and Drug Research Laboratories Inc., Teratologic evaluation of FDA 71-50 (Adipic Acid) in rats. Final Report, 26 Feb 1973.

U.S. Food and Drug Administration (1973b). Food and Drug Research Laboratories, Inc. Teratologic evaluation of FDA 71-50 (Adipic Acid) in mice. Final Report, 26 Feb 1973.

U.S. Food and Drug Administration (1974a). Food and Drug Laboratories, Inc. Teratologic Evaluation of Compound. FDA 71-50. Adipic Acid in Rabbits. Report PB-267 202, 26 Feb 1974.

U.S. Food and Drug Administration (1974b). Food and Drug Research Laboratories Inc., Teratologic evaluation of FDA 71-50 (Adipic Acid) in hamsters. Final Report, 26 Feb 1973.

WHO (1990). 1987/1990 IPCS Environmental Health Criteria Monograph No. 70 and No 40.

I U C L I D

D a t a S e t

Existing Chemical ID: 3323-53-3
CAS No. 3323-53-3
EINECS Name adipic acid, compound with hexane-1,6-diamine (1:1)
EC No. 222-037-3
Molecular Formula C6H16N2.C6H10O4

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: 19-NOV-2004
Revision date:
Date of last Update: **19-NOV-2004**

Number of Pages: **73**

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

1.0.1 Applicant and Company Information

Type: lead organisation
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Flag: Critical study for SIDS endpoint
11-JUN-2002

Type: cooperating company
Name: Asahi Kasei Corporation
Country: Japan

Flag: Critical study for SIDS endpoint
11-JUN-2002

Type: cooperating company
Name: DuPont
Country: United States

Flag: Critical study for SIDS endpoint
11-JUN-2002

Type: cooperating company
Name: Rhodia Polyamide Intermediates
Country: France

Flag: Critical study for SIDS endpoint
11-JUN-2002

Type: cooperating company
Name: Solutia Inc.
Country: United States

Flag: Critical study for SIDS endpoint
11-JUN-2002

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

1.1.0 Substance Identification

Remark: Empirical formula : C12 H26 O4 N2

Molecular formula : C6 H16 N2 (116.21 g/mol)

and weight C6 H10 O4 (146.14 g/mol)
Flag: non confidential, Critical study for SIDS endpoint
13-JAN-2003

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: 99 - 100 % w/w
Colour: white
Odour: odourless

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

1.1.2 Spectra

1.2 Synonyms and Tradenames

1,6-Hexanediamine, adipate (1:1) (8CI)

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

1,6-Hexanediamine, hexanedioate (1:1) (9CI)

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

Adipic acid hexamethylenediamine salt

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

Adipic acid, compd. with 1,6-hexanediamine (7CI)

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

Adipic acid, compound with 1,6-hexanediamine (1:1) (8CI)

Flag: non confidential, Critical study for SIDS endpoint
27-APR-2002

Adipic acid-hexamethylenediamine salt (1:1)

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

AH salt

Flag: non confidential, Critical study for SIDS endpoint
27-APR-2002

AH-Salz

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

Hexamethylenediamine adipate (1:1)

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

Hexamethylenediamine monoadipate

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

Hexamethylenediamine-adipic acid salt

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

Hexamethylenediammonium adipate

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

Hexanedioic acid, compound with 1,6-hexanediamine (1:1) (9CI)

Flag: non confidential, Critical study for SIDS endpoint
27-APR-2002

Nylon 66 salt

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

Nylon salt

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

1.3 Impurities

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water
Contents: <= 1 - % w/w

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (2)

EINECS-Name: o-diaminocyclohexane
Contents: <= .002 - % w/w

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

1.4 Additives

1.5 Total Quantity

Remark: Figure refer to calc. 100% of product

Western Europe : approx. 1.0 Mill. t/a
America (North + South): approx. 1.9 Mill. t/a
Asia : approx. 0.5 Mill. t/a
World : approx. 3.4 Mill. t/a

Almost all of the production stops at the aqueous solution stage of AH-salt. Only approx. 5% of the world production exists as crystallized salt.

Flag: Critical study for SIDS endpoint
11-JUN-2002

1.6.1 Labelling

Labelling: no labelling required (no dangerous properties)

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

1.6.2 Classification

Classified: no classification required (no dangerous properties)

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

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Flag: non confidential, Critical study for SIDS endpoint
02-FEB-1993

Type: industrial
Category: Chemical industry: used in synthesis

Flag: non confidential, Critical study for SIDS endpoint
02-FEB-1993

Type: industrial
Category: Polymers industry

Remark: Recommended use: for the production of homopolymerisates and copolymerisates.
Flag: non confidential, Critical study for SIDS endpoint
31-JAN-2003 (1)

Type: industrial
Category: Textile processing industry

Flag: non confidential, Critical study for SIDS endpoint
02-FEB-1993

Type: use
Category: Intermediates

Flag: confidential, Critical study for SIDS endpoint
02-FEB-1993

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

Orig. of Subst.: Synthesis
Type: Production

Remark: The most important salt (of hexamethylenediamine) is that produced by neutralization with adipic acid (salt strike): the so-called nylon salt or AH salt. This compound is the raw material for the preparation of nylon by thermal dehydration under vacuum.
Flag: non confidential, Critical study for SIDS endpoint
11-JUN-2002 (3)

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

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

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (4)

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

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

Remark: ID-number: 1342
Flag: non confidential, Critical study for SIDS endpoint
13-JAN-2003 (5)

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. 222-037-3

Flag: non confidential, Critical study for SIDS endpoint

12-DEC-2002 (6)

Type: ECL
Additional Info: ECL Serial No. KE-18686

Flag: non confidential, Critical study for SIDS endpoint
12-DEC-2002 (6)

Type: TSCA

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (6)

Type: DSL

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (6)

Type: PICCS

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (6)

Type: AICS

Flag: non confidential, Critical study for SIDS endpoint
29-MAY-2002 (6)

1.9.1 Degradation/Transformation Products

EINECS-Name: No thermal decomposition if used as directed.

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

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Human: exposure by production
Exposure to the: Substance

Result: The following exposure levels were measured by personal dust sampling for workplaces
at a production plant:
Production (1 plant, 9 measurements): 0.11 - 0.86 mg/m3 total dust (8 h shift average)
Filling/Storage (1 plant, 9 measurements): < 0.083 - 0.52 mg/m3 total dust (8 h shift average)
The 95% percentile for both sites was: 0.83 mg/m3 total dust.
Reliability: (1) valid without restriction
Flag: confidential, Critical study for SIDS endpoint
11-NOV-2004 (7)

1.11 Additional Remarks

Memo: Extractable components

Remark: Environmental releases are possible from residual contents of monomeric AH salt in the polymeric product during further processing of the polymer as well as during use and disposal of end products. In a study that measured the extractable components from a foil used for food wrapping a concentration of hexanediamine of < 1 mg/kg (detection limit) in the extract was found. The total extract was determined to 0.2 % (2 g total extract/kg polymer). The main component of the extract was the cyclic dimere of hexanediamine and adipic acid. The study was performed over a period of 10 days with either water or isopropanol.
From this study it can be concluded that significant environmental releases of AH-salt from end products are unlikely to occur.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
21-JAN-2004 (8)

Memo: Hazardous reactions: Dust explosion hazard

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

1.12 Last Literature Search

Type of Search: Internal and External
Chapters covered: 3, 4, 5

Remark: Date of Search: February 2002
Flag: Critical study for SIDS endpoint

27-APR-2002

Chapters covered: 1
Date of Search: 14-JAN-2003

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

Chapters covered: 8
Date of Search: 14-JAN-2003

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

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

07-FEB-2003

1.13 Reviews

2.1 Melting Point

Value: = 202 degree C

Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: only information for the salt
Reliability: (4) not assignable
manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
30-JAN-2003 (1)

Value: ca. 81 degree C

Test substance: other TS: AH salt solution, 62% (m)

Reliability: (4) not assignable
manufacturer/producer data without proof
30-JAN-2003 (9)

Value: = 183 - 197 degree C

19-JAN-2004 (10)

2.2 Boiling Point

Value: = 93.9 degree C at 700 hPa

Method: other
Year: 1991
GLP: no
Test substance: other TS: 50% aqueous solution

Result: = 100.8 at 900 hPa
= 103.7 at 1000 hPa
Reliability: (2) valid with restrictions
30-JAN-2003 (11)

Value: = 99.8 degree C at 700 hPa

Method: other
Year: 1991
GLP: no
Test substance: other TS: 75% aqueous solution

Result: = 108.0 at 900 hPa
= 111.7 at 1000 hPa
Reliability: (2) valid with restrictions
30-JAN-2003 (11)

2.3 Density

Type: density
Value: = 1.2014 g/cm³ at 20 degree C

Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: available information for the salt
Reliability: (4) not assignable manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
30-JAN-2003 (1)

Type: bulk density
Value: = 550 kg/m3

Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable manufacturer/producer data without proof
30-JAN-2003 (1)

Type: density
Value: = 1082 kg/m3 at 90 degree C

Test substance: other TS: AH salt solution (62%)

Reliability: (4) not assignable
30-JAN-2003 (12)

Type: density
Value: = 1.078 g/cm³ at 95 degree C

Method: Directive 84/449/EEC, A.3 "Relative Density"
Year: 1991
GLP: no
Test substance: other TS: 62% (m)

Reliability: (2) valid with restrictions
30-JAN-2003 (13) (9)

Type: density
Value: = 1201 kg/m3

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

Remark: Additional impurities of the test substance reported: volatile bases <= 1.0 mval/kg, iron <= 0.1 ppm, ash <= 4.0 ppm, nitric acid <= 1.0 ppm
Reliability: (4) not assignable manufacturer/producer data without proof
19-NOV-2004 (14)

2.3.1 Granulometry

Type of distribution: Volumetric Distribution

Method: other: particle size analysis
Year: 2001
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: only information on this parameter
Summary:
mv = 347.1
mn = 6.752
ma = 243.9
cs = 0.025
sd = 172.9

Result: Percentiles:
10 % = up to 155.1 microns
20 % = up to 200.7 microns
30 % = up to 238.6 microns
40 % = up to 278.5 microns
50 % = up to 325.6 microns
60 % = up to 382.1 microns
70 % = up to 443.7 microns
80 % = up to 505.7 microns
90 % = up to 570.2 microns
100 % = up to 616.2 microns

(0.11% = up to 11 microns)

Test condition: distribution: volume
progression: geometric Root4
upper edge: 1991
lower edge: 2750
residuals: disabled
number of channels: 38
run time: 20 seconds
fluid: water
loading factor: 0.0989
transmission: 0.94

Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-MAY-2002 (15)

2.4 Vapour Pressure

Value: 0 hPa at 20 degree C

Test substance: as prescribed by 1.1 - 1.4

Remark: The vapor pressure is expected to be very low due to the salt
character.

Reliability: (4) not assignable
manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
06-MAY-2002 (16)

Value: = 593 hPa at 90 degree C

GLP: no data
Test substance: other TS: AH salt solution (62%)

Reliability: (4) not assignable
manufacturer/producer data without proof
18-MAY-2002 (17) (12)

Value: = 3670 hPa at 150 degree C

Method: other (measured)
Year: 1991
GLP: no
Test substance: other TS: 62% aqueous solution

Result: = 4770 hPa at 160 °C
= 6200 hPa at 170 °C
= 7920 hPa at 180 °C
Reliability: (2) valid with restrictions
limited documentation
18-MAY-2002 (18)

Test substance: other TS: 62% w/w in water

Result: 5 mbar at 20 °C
Reliability: (4) not assignable
manufacturer/producer data without proof
06-MAY-2002 (9)

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -4.4 at 25 degree C
PH prec: = 7.7 - 7.8

Method: other (measured): equivalent to OECD 107 (1995)
Year: 1988
GLP: no

Remark: mean of 3 measurements
reason for flagging this data: only information on this parameter
Reliability: (2) valid with restrictions
limited documentation
Flag: Critical study for SIDS endpoint
06-JAN-2003 (19)

2.6.1 Solubility in different media

Solubility in: Water
Value: = 480 g/l at 20 degree C
pH value: = 7.8
Conc.: 100 g/l at 25 degree C

Remark: reason for flagging: experimentially derived data
Test substance: purity > 99.9 %
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
19-NOV-2004 (19)

Value: = 60 other: mass% at 71.1 degree C

Method: other: visual observation
Year: 1995
GLP: no
Test substance: purity 99.9%

Reliability: (2) valid with restrictions

discrepancy between documented test parameters and standard methods, but scientifically acceptable
06-MAY-2002 (20)

Solubility in: Water
Value: = 960 other: g/1000 g water at 25 degree C
pH value: = 7.7
Conc.: 100 g/l at 25 degree C

Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
19-JAN-2004 (21) (9)

Solubility in: Water
Value: 490 g/l at 25 degree C

Result: solubility at 25 °C
in methanol: 4 g/l
in ethanol. 0.2 g/l
Reliability: (4) not assignable
secondary citation: data from handbook
20-JAN-2004 (10)

2.6.2 Surface Tension

2.7 Flash Point

Value: > 240 degree C

Method: other: DIN 51755
Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging this data: only information on this parameter
Reliability: (4) not assignable
manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
20-MAY-2002 (1)

2.8 Auto Flammability

Value: 365 degree C

Method: other: DIN 51 794
Test substance: as prescribed by 1.1 - 1.4

Remark: Ignition temperature
Reliability: (4) not assignable
manufacturer/producer data without proof
20-MAY-2002 (1)

Value:

Method: other: VDI 2263, part 1, 2.6

Year: 1978
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: reason for flagging: experimentially derived data
Result: Ignition temperature: 380 °C (VDI 2263, part 1, 2.6)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
06-MAY-2002 (22)

2.9 Flammability

2.10 Explosive Properties

Result: other: dust explosion hazard

Method: other: open Hartmann tube
Year: 1978
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: Dust may form explosive mixtures with air
Reliability: (2) valid with restrictions
discrepancy between documented test parameters and standard methods, but scientifically acceptable
06-MAY-2002 (22)

Result: other: dust explosion hazard

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

Remark: particle size < 100 um
reason for flagging: experimentially derived data
Result: Dust may form explosive mixtures with air
Reliability: (2) valid with restrictions
discrepancy between documented test parameters and standard methods, but scientifically acceptable
Flag: Critical study for SIDS endpoint
06-MAY-2002 (23)

2.11 Oxidizing Properties

2.12 Dissociation Constant

Method: other

Result: dissociation constant

of adipic acid (CAS-No 124-04-9)
= 4,44/5,44 (approx, measured)

of hexamethylene diamine (CAS-No 124-09-4=
= 10,76/11,86 (measured, potentiometric)
Flag: Critical study for SIDS endpoint

03-DEC-2003 (24)

2.13 Viscosity

Value: = 10.1 mPa s (dynamic) at 90 degree C

Test substance: other TS: 62% w/w in water

Remark: reason for flagging this data: only information on the salt
Reliability: (4) not assignable
manufacturer/producer data without proof
Flag: Critical study for SIDS endpoint
06-MAY-2002 (9)

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³

Method: other (calculated): AOP WIN, v 1.90

Result: For the 2 components of AH-salt:

Adipic acid, CAS-No 124-04-9
t1/2 = 69 hours
1,6-Hexametylenediamine, CAS-No 124-09-4
t1/2 = 5,6 hours
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
21-JAN-2004

3.1.2 Stability in Water

Type: abiotic

Result: according to structural properties, hydrolysis is not expected
In neutral aqueous solution the substance dissociates forming adipate and 1,6-hexanediammonium.
Flag: Critical study for SIDS endpoint
01-DEC-2003

Result: Data on the oxidation of adipic acid and hexylamine by OH radicals in aqueous solutions are available (Buxton et al. 1988). Therefore, oxidative photochemical degradation of AH salt in aqueous solution can be expected. With a OH radical concentration of 6 · 10-17 mol/l (Mill 1999), photochemical half-lives of 67 days for adipic acid and 10 days for 1-hexylamine (data for 1,6-hexandiamine not available), respectively, can be estimated. In comparison to its biodegradability, however, photochemical degradation of the AH salt in the aqueous phase does not appear to be relevant.
03-JAN-2003 (25) (26)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: water - soil

Remark: for the components adipic acid and 1,6-hexanadiamine the Koc value can estimated (PCKOCWIN, V1.66):

Hexamethylendiamine, CAS-No. 124-09-4
Koc = 286 (log Koc = 2.46)
Adipic acid, CAS-No. 124-04-9
Koc = 21 (log Koc = 1.33) (this Koc may be sensitive to pH)
Result: The mobility in soil is expected to be high based on the log Kow (log Kow = -4.4).However, the soil adsorption can be only roughly estimated because of possible ionic interactions of the cations with negatively charged particels in the soil that may reduce their mobility.
Flag: Critical study for SIDS endpoint
21-JAN-2004

Type: volatility
Media: water - air

Result: Due to the salt-character and physico-chemical properties, volatilization from surface waters and sewage treatment plants is not expected.
Flag: Critical study for SIDS endpoint
01-DEC-2003

3.3.2 Distribution

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

Result: Due to the salt-character of the substance the calculation of a fugacity model is not appropriate.
Based on the physico-chemical properties of AH-salt, water is expected to be the main target compartment.
Reliability: (2) valid with restrictions
accepted calculation method
Flag: Critical study for SIDS endpoint
20-JAN-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, industrial
Concentration: 400 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: > 90 % after 3 day(s)
Result: inherently biodegradable
Kinetic: 3 day(s) = 96 %
6 day(s) = 93 %
1 day(s) = 62 %
3 hour(s) = 11 %

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year: 1986
Test substance: as prescribed by 1.1 - 1.4

Remark: One component of AH-salt, adipic acid, is readily biodegradable while for the second component, 1,6-hexanediamine, no adequate test is available to determine whether the chemical is readily bidegradable.
Studies on the ready biodegradation of adipic acid and 1,6-hexanediamine are available. In a MITI-I test a biodegradation of 68 - 90 % after 14 days was found for adipic acid. For 1,6-hexanediamine a biodegradation of 56 % (on the upward trend) after 14 days was obtained in the same test (CITI 1992). In addition, a BOD5/COD ratio of 104.8 % is available (Institut Kuhlmann 1989). As the BOD5 was measured using industrial activated sludge, a statement concerning the ready biodegradability of 1,6-hexanediamine cannot be made based on this test.
Reliability: (2) valid with restrictions
experimentially derived data
Flag: Critical study for SIDS endpoint
20-JAN-2004 (27)

3.6 BOD5, COD or BOD5/COD Ratio

B O D 5

Method:
Year: 1986
GLP: no
BOD5: = 1040 mg/l

C O D

Year: 1986
GLP: no
COD: = 1700 mg/g substance

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

BOD5/COD: = .61
Method:
Remark: Inoculum: effluent from industrial sewage treatment plant
Reliability: (2) valid with restrictions
experimentially derived data
Flag: Critical study for SIDS endpoint
20-JAN-2004 (28)
Method: other
Year:
Method:
Result: BOD5 = 0.53-0.7 mg/L (control) = 0.36-0.55 mg O2/mg AH-salt
Reliability: (4) not assignable
secondary citation
07-FEB-2003 (29)

3.7 Bioaccumulation

Method: other

Result: Based on a log Kow -4.4, bioaccumulation is not expected.
Reliability: (1) valid without restriction
only information on the salt

Flag: Critical study for SIDS endpoint
01-DEC-2003

3.8 Additional Remarks

Memo: The adipate salt of hexamethylene diamine was shown to have soil conditioning properties (studies on flocculation, aggregate stability, and permeability)

Reliability: (4) not assignable
27-APR-2002 (30)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50: > 470

Method: other: Committee on Methods for Toxicity Tests with Aquatic Organisms. Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, EPA, EPA-660/3-75-009, April 1975
Year: 1981
GLP: yes
Test substance: other TS:Nylon Salt, clear liquid with clear crystals;purity not stated

Method: Study conducted at 22 °C.
Reference substance: Antimycin.
Test substance: saturated solution (47 %), estimated by water solubility
Reliability: (2) valid with restrictions
no analytical monitoring
Flag: Critical study for SIDS endpoint
27-JAN-2003 (31)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
NOEC: = 2500
LC50: = 10000
LC100: > 10000
Limit Test: no

Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15 (1982)
Year: 1987
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: 10 fish/dose level.
Concentrations (nominal): 2500, 5000, and 10000 mg/L.
Result: Clinical symptoms: no abnormalities observed.
Test substance: AH-salt with purity of 100 %
Reliability: (2) valid with restrictions
no analytical monitoring
Flag: Critical study for SIDS endpoint
02-JAN-2003 (32)

Type: static
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:** no
LC50: > 470

Method: other: Committee on Methods for Toxicity Tests with Aquatic

Organisms. Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians, EPA, EPA-660/3-75-009, April 1975
Year: 1981
GLP: yes
Test substance: other TS:Nylon Salt, clear liquid with clear crystals;purity not stated

Method: Study conducted at 12 °C.
Reference substance: Antimycin.
Result: LC50 (24, 48 hours): > 470 mg/L.
The results with the standard substance were in the expected range of historical data.
Test substance: saturated solution (47 %), estimated by water solubility
Reliability: (2) valid with restrictions
no analytical monitoring
Flag: Critical study for SIDS endpoint
27-JAN-2003 (33)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: = 90
EC10 : = 55

Method: other: in accordance with the method outlined by the Committee on Methods for Toxicity Tests with Aquatic Organisms. U.S. EPA, Ecol. Res. Ser. 660/3-75009, 1975
Year: 1981
GLP: yes
Test substance: other TS: Nylon Salt, 50% aqueous solution

Method: statistical method: binomial, moving average and probit tests.
Remark: 95% C.I. = 80 - 105 mg/L.
Concentrations tested: 0; 50; 90; 320; 160; 500 mg/L.
Effect assessed: mortality.
Result: EC50 (24 h) = 165 mg/l
Test substance: concentrations in report refer to 50 % aqueous solutions of AH-salt
Reliability: (2) valid with restrictions
No analytical monitoring.

Flag: Critical study for SIDS endpoint
21-JAN-2004 (34)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC0: = 62.5
EC50: = 98.9
EC100: = 250

Method: Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"
Year: 1988
GLP: no

Test substance: as prescribed by 1.1 - 1.4

Remark: Toxicity may be due to the decrease of oxygen during the test.
Result: after 24 h:
EC0 = 250 mg/l
EC50 = 353 mg/l
EC100 = 500 mg/l

EC50 (48 hr), 95% confidence limits: 77.47 - 128.31 mg/L
Test condition: pH: 7.9
Test substance: purity not stated
Reliability: (3) invalid
No analytical monitoring.
The Test was regarded as invalid due to the decreased oxygen level.
21-JAN-2004 (35)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:** no
EC50: = 394.5
EC20 : = 269.3

Method: other: Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412, Teil 9, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen
Year: 1987
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: tested concentrations: 31.25; 62.5; 125; 250; 500 mg/L 10,000 cells / mL; 10 mL OECD medium; 20 °C; growth period: 72 hours; pH 7.4; 4 cultures / concentration plus 2 untreated controls / concentration.
Remark: reason for flagging this data: only study available on this endpoint
Result: EC20 (96h) = 102,9 mg/l
EC50 (96h) = 291,9 mg/l
EC90 (96h) = 479,1 mg/l
Test substance: purity not stated
Reliability: (2) valid with restrictions
no analytical monitoring
Flag: Critical study for SIDS endpoint
12-FEB-2003 (36)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 10 minute(s)
Unit: mg/l **Analytical monitoring:** no
EC50: > 900
EC20 : > 900

Method: other: similar to OECD TG 209
Year: 1986

Test substance: as prescribed by 1.1 - 1.4

Method: concentrations tested: 0, 150, 300, 600, 900 mg/L.
Remark: reason for flagging this data: only study available on this endpoint
Reliability: (2) valid with restrictions
OECD TG 209 requires 30 minutes and/or 3 hours incubation. Reference substance (3,5 - dichlorophenol): data not reported.
Flag: Critical study for SIDS endpoint
12-FEB-2003 (27)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 17 hour(s)
Unit: mg/l **Analytical monitoring:**
EC10: > 2000
EC50: > 2000
EC90 : > 2000

Method: other: growth inhibition test according to the method described in DIN 38412 Teil 8, Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Bakterien. Pseudomonas-Zellvermehrungs-Hemmtest.
Year: 1987

Remark: reason for flagging this data: only study available on this endpoint
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
12-FEB-2003 (37)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to Soil Dwelling Organisms

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo: In vitro

Remark: AH salt is a mixture of adipic acid and 1,6-hexane diamine (1:1).
For the endpoints
- repeated dose toxicity (13 week study)
- fertility
- developmental toxicity
no studies are availabe. To fill this endpoints, studies of the two compounds were taken.
Since di-2-(ethylhexyl)adipate is in vivo rapidly metabolized to adipic acid the one generation study with di-2-(ethylhexyl)adipate was taken to close the data gap for fertility for the component adipic acid:

After oral administration of 665 or 1500 mg di(2-ethylhexyl) adipate/kg bw to male rats up to 95 % of the theoretical amount was found as adipic acid in urine on day 1 after dosing. The urinary recovery was about 50 %. CO2 exhalation was not studied. Other metabolites were oxidized and conjugated forms of 2-ethyl hexanoic acid.

Flag: Critical study for SIDS endpoint
11-NOV-2004

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: other: no data
Sex: no data
Vehicle: other: not specified
Doses: 500; 1000; 2000; 4000; 5000; 8000; 10,000 mg/kg bw
Value: ca. 4900 mg/kg bw

Year: 1956
GLP: no
Test substance: other TS: AH salt"dry", purity not stated

Method: The test substance was administered via single dose gavage to groups of one to five animals per dose level. Animals were observed approximately 1-3 hours after dosing and then daily over a period of 8 days. At necropsy, all rats were examined for gross pathological changes. No further details available.

Result:

Dose (g/kg)	mortalitiy	death within
10	1/1	3 hours
8	5/5	1-2 days
5	4/5	1-8 days
4	0/5	
2	0/1	
1	0/1	
0.5	0/1	

Lethal doses caused seizures. Sublethal doses led to stiff gait, apathy, reduced appetite, diarrhoea, and rough coat. At necropsy, signs of gastro-intestinal tract irritation and intestinal bleeding were found.

Reliability: (2) valid with restrictions
short observation period; limited documentation

Flag: Critical study for SIDS endpoint

18-FEB-2003 (38)

Type: LD50
Species: rat
Value: = 5900 mg/kg bw

Test substance: no data

Reliability: (4) not assignable
Secondary citation

27-APR-2002 (39)

Type: LDLo
Species: rat
Strain: Sprague-Dawley
Sex: male/female
No. of Animals: 5
Doses: 10,000 mg/kg bw
Value: > 10000 mg/kg bw

Year: 1978
GLP: no
Test substance: other TS: Nylon 6,6 Salt solution (50 % aqueous solution)

Method: The test substance was administered undiluted via single dose gavage to a single group of five fasted rats (2 male, 3 female animals) at 10,000 mg/kg bw. Rats were observed approximately 1 hour after dosing and twice daily over a 14-day observation period. All rats were sacrificed at the end of the observation period and given a gross necropsy.

Result: No deaths occurred throughout the 14-day observation period. The only clinical signs observed were reduced appetite and activity during the day of dosing. The viscera appeared normal in all animals at necropsy.

Reliability: (2) valid with restrictions
limited documentation

Flag: Critical study for SIDS endpoint

02-JAN-2003 (40) (41)

Type: LD50
Species: mouse
Value: ca. 4700 mg/kg bw

Method: other: BASF-Test
Year: 1956
GLP: no
Test substance: other TS: AH salt "dry", purity not stated

Result: Lethal doses caused seizures. Sublethal doses were irritating to the gastro-intestinal tract, and caused intestinal bleeding and diarrhoea.

Reliability: (2) valid with restrictions
short summary report

19-MAY-2002 (38)

Type: LD50
Species: mouse
Value: = 1610 mg/kg bw

Test substance: no data

Reliability: (4) not assignable
Secondary citation
27-APR-2002 (39)

Type: LDLo
Species: rabbit
Vehicle: water
Doses: 1000; 3000 mg/kg bw
Value: ca. 3000 mg/kg bw

Method: other: BASF-Test
Year: 1956
GLP: no
Test substance: other TS: AH salt "dry", purity not stated

Result: 3000 mg/kg bw: Lethal for two rabbits within 24 hours, seizures.
1000 mg/kg bw: no clinical signs (1 rabbit). No effect on blood parameters (not specified) and urinalysis (no details given).
Reliability: (2) valid with restrictions
short summary report
19-MAY-2002 (38)

Type: LDLo
Species: cat
Doses: 750; 1000; 3000 mg/kg bw
Value: ca. 3000 ml/kg bw

Method: other: BASF-Test
Year: 1956
GLP: no
Test substance: other TS: AH salt "dry", purity not stated

Remark: 3000 mg/kg bw were lethal; seizures, vomiting, intestinal bleeding.
750; 1000 mg/kg bw: no mortality; vomiting, diarrhoe, bloody faeces. Blood parameters (unspecified) and urinalysis without abnormal findings.
Reliability: (2) valid with restrictions
short summary report
19-MAY-2002 (38)

Type: LD50
Species: guinea pig
Value: ca. 2000 mg/kg bw

Method: other: BASF-Test
Year: 1956
GLP: no
Test substance: other TS: AH salt "dry", purity not stated

Result: Lethal doses caused seizures. Sublethal doses were irritating to the gastro-intestinal tract, and caused

intestinal bleeding and diarrhoea.
Reliability: (2) valid with restrictions
short summary report
19-MAY-2002 (38)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

Type: LDLo
Species: rabbit
Strain: New Zealand white
Sex: male/female
Doses: 5010; 7940 mg/kg bw
Value: > 7940 mg/kg bw

Year: 1978
GLP: no
Test substance: other TS: Nylon 6,6 salt solution (50% aqueous solution)

Method: The test substance was administered to the shaved, intact skin of New Zealand Albino rabbits, using a gauze patch under an occluded plastic wrapping for 24 hours. Thereafter, the wrapping and patch were removed and the excess test material wiped free. One male animal was exposed to 5,010 mg/kg and two rabbits (1 male, 1 female) were exposed to 7,940 mg/kg. All rabbits were observed approximately 1 hour after dosing and twice daily over a 14-day observation period and given a gross necropsy.
Result: No deaths occurred throughout the 14-day treatment and observation period at either dose level. Clinical signs observed included reduced appetite and activity (for two to eight days after dosing), salivation and ocular discharge. At necropsy, the viscera of all animals appeared normal.
Reliability: (2) valid with restrictions
small number of animals, limited documentation.
Flag: Critical study for SIDS endpoint
17-FEB-2003 (40) (41)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: mouse
Route of admin.: i.p.
Value: = 1800 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: other TS: AH salt, purity not stated

Result: Lethal doses caused seizures. Sublethal doses were irritating to the gastro-intestinal tract, and caused intestinal bleeding and diarrhoea.
Reliability: (2) valid with restrictions
short summary report
17-FEB-2003 (38)

Type: LD50

Species: mouse
Route of admin.: s.c.
Value: = 1000 mg/kg bw

Method: other: BASF-Test
GLP: no
Test substance: other TS: AH salt, purity not stated

Result: Lethal doses caused seizures. Sublethal doses were irritating to the gastro-intestinal tract, and caused intestinal bleeding and diarrhoea.
Reliability: (2) valid with restrictions
short summary report
17-FEB-2003 (38)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Concentration: 50 % active substance
Exposure: Semiocclusive
No. of Animals: 2
Vehicle: water
PDII: 0
Result: not irritating
EC classificat.: not irritating

Year: 1956
GLP: no
Test substance: other TS: AH salt , purity not stated

Method: Exposure: 50% saturated solution, pH: 7.5;

exposure time: 1, 5 and 15 minutes; application site: back. The application sites were wiped with a mixture of acetic acid and polyethylene glycol after the end of the exposure period.
Remark: None of two animals showed any effects of irritation.
Reliability: (2) valid with restrictions
The short exposure time of 15 minutes is thought not to impair the evaluation of the skin irritation potential significantly aAs the eye irritation potential is very low (see 3.2.2) and a 10% aqueous solution of AH salt is neutral has almost a physiological pH value (see chapter 1), therefore, the negative result is plausiblethe short exposure time of 15 minutes is thought not to impair the evaluation of the skin irritation potential significantly. As a 50% aqueous preparation is the limit of solubility, no higher concentrations would have been achieved if neat AH salt had been tested and this deviation from the test guideline is thought not to impair the evaluation of the skin irritation potential significantly.
Flag: Critical study for SIDS endpoint
17-FEB-2003 (42)

Species: rabbit
Result: not irritating

Test substance: other TS: Nylon 6,6 salt solution, purity not specified

Result: Practically non irritating to skin of rabbits
Reliability: (4) not assignable
producer/manufacturer data without proof
28-APR-2002 (40)

5.2.2 Eye Irritation

Species: rabbit
Concentration: 50 % active substance
Comment: not rinsed
No. of Animals: 2
Vehicle: water
Result: slightly irritating

Method: other: BASF-Test
Year: 1956
GLP: no
Test substance: other TS: AH salt, purity not stated

Method: The eyes of 2 rabbits were examined 10 minutes, and 1, 3 and 24 hours after instillation of an 50% aqueous solution of the test substance into the right eye. The other eye served as control.
Result: Until 3 hours after administration of the test subsance, slight and transient conjunctivitis was observed in both tested animals. All effects were completely reversible at 24 hours after instillation (no effects were observed in the control eyes treated with physiological saline).
Reliability: (2) valid with restrictions
Data on purity are lacking, but as there was no strong irritation observed, this is thought not to impair the evaluation of the eye irritation potential significantly. As a 50% aqueous preparation is the limit of solubility, no higher concentrations would have been achieved if neat AH salt had been tested and this deviation from the test guideline is thought not to impair the evaluation of the eye irritation potential significantly.
Flag: Critical study for SIDS endpoint
17-FEB-2003 (42)

Species: rabbit
Result: slightly irritating

Test substance: other TS: Nylon 6,6 salt solution, purity not specified

Remark: no further information available
Reliability: (4) not assignable
producer/manufacturer data without proof
27-APR-2002 (40)

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Fischer 344

Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 6 hours/day; 5 days/week
Doses: 0; 1.6; 5; 16; 50; 160 mg/m3
Control Group: yes, concurrent vehicle
NOAEL: = 5 mg/m³

Method: other: NTP study
Year: 1993
GLP: yes
Test substance: other TS: 1,6-hexanediamine dihydrochloride, aerosol

Method: whole body exposure. 10 animals/sex per exposure group. In addition to the standard repeat dose protocol, sperm morphology and vaginal cytology evaluations were performed from the control group and the 3 highest exposure groups.
Result: Inhalation of the test substance produced lesions that could be attributed to the irritant effects of the compound.

Substance and concentration related effects were inflammation, erosion and necrosis of the larynx, degeneration, erosion, inflammation and squamous metaplasia in the respiratory and olfactory epithelia. 16 mg/m3 was a NOAEL for males, 5 mg/m3 for females. Effects were slight with the next higher concentrations tested.
No significant systemic toxicity was observed, and no specific target organs were identified.
All rats survived to the end of the study. The final mean body weights of most groups of rats exposed to the test substance were slightly lower than the mean body weights of the controls. These differences, however, were not statistically significant. No clinical signs of toxicity related to the test substance exposure were seen.
Administration of the test substance caused no changes in any of the sperm morphology or vaginal cytology parameters.
The NOAEC for systemic toxicity was 160 mg/m3, the NOAEC for irritating effects was 5 mg/m3
Test substance: 70% aqueous solution, purity 70.9%, pH 4.5-5.5
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
28-JAN-2003 (43) (44)

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 6 hours/day, 5 days/week
Post exposure period: no
Doses: 0; 12.8; 51; 215 mg/m3
Control Group: yes, concurrent vehicle
NOAEL: = 12.8 mg/m³

Method: other
Year: 1987
GLP: no data
Test substance: other TS: 1,6-hexanediamine, purity > 91% (remainder was 9% water)

Method: 15 rats/sex and group were exposed as a whole body exposure to target concentrations of 0, 12, 50 and 200 mg/m3 6h/day, 5

days/week for 13 weeks.
Clinical laboratory and hematological determination on 5 animals/sex/group pretest and after 5 weeks of treatment. No urine analysis was performed. Only 2 sections of nasal passages were examined.

Result: Because of exposure-related deaths in the 215 mg/m3 group, this group was terminated during the seventh week of the study. Clinical signs of respiratory and conjunctival irritation were observed in rats at both the 51 and 215 mg/m3 exposure levels. Body weight gain was significantly reduced in both sexes exposed to 215 mg/m3. At the 5-week study interval, slight hemopoietic stimulation of peripheral blood parameters was observed in rats of both sexes exposed to 215 mg/m3. Treatment-related microscopic lesions were seen only in rats exposed to 215 mg/m3 and were confined to the trachea, nasal passages, and lungs. No effects were reported with regard to ovaries and testes organ weights and with regard to the microscopic evaluation of testes, epididymides, mammary gland, prostate, seminal vesicles, ovaries, uterus and vagina.
The NOAEC for systemic toxicity was 51 mg/m3 and for irritating effects 12.8 mg/m3.

Test substance: substance concentration used for generated aerosol not stated; >97% were respirable (>10 µm), MMAD 1,1 µm

Reliability: (2) valid with restrictions
limited documentation, no incidences of histopathological lesions were given, limited examination of target organ nose, pH not given, concentration of substance in aerosol not given.

Flag: Critical study for SIDS endpoint

28-JAN-2003 (45)

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure period: 13 weeks
Post exposure period: no
Doses: 0; 50; 150; 500 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL: = 50 mg/kg bw

Year: 1987
GLP: no data
Test substance: other TS: 1,6-hexanediamine, purity not stated

Method: 15 rats/group and sex were fed at concentrations (in diet) of 50, 150, 500 mg/kg for 13 weeks. Clinical pathology tets were performed on blood samples from 10 rats/sex from both the high dose and control groups after 42 and 84 days of treatment. The organs of 10 rats/sex of the highest dose group were prepared by conventional histologic techniques and examined by light microscopy.

Result: No abnormal reactions or treatment-related toxic effects were observed and no changes were found in the peripheral blood picture and several clinical chemistry parameters examined in the highest dose level tested. The only finding was an apparent dose-related modest decrease in overall weight gain both in the mid and high dosage groups without statistical significance.
Urinalysis values were similar between the control and high dosage groups. No adverse gross or microscopic changes

related to treatment were observed at 500 mg/kg. No effects on gonads (examined by light microscopy) were reported.

Reliability: (2) valid with restrictions
limited documentation
Flag: Critical study for SIDS endpoint
07-JAN-2003 (46)

Type: Chronic
Species: rat **Sex:** male/female
Strain: other: Carworth farm albino
Route of administration: oral feed
Exposure period: 2 years
Frequency of treatment: daily
Doses: 0.1, 1, 3, 5% males and 1% females in the diet (ca. 50-100; 500-1000; 1500-3000; 2500-5000 mg/kg bw/day
Control Group: yes
NOAEL: 1 %

Method: other
Year: 1957
GLP: no
Test substance: other TS: adipic acid, purity not stated

Method: Rats were fed either the basal laboratory diet, or the diet to which adipic acid was added. Body weights, food consumption, and general appearance were recorded weekly throughout the experimental period. Whenever possible, animals that died were examined, and gross pathology was performed. After 2 years, surviving rats were weighed, killed, and examined grossly. Ten organ weights were recorded for approx. 1/2 of each group of males, and 4 organ weights were recorded for females. Microscopic examination of 15 tissues was done on a representative number of animals from each group.
Remark: the doses were calculated according the recommendation of WHO, IPCS Criteria No 70 (1987)
Result: Males: The percent survival for each test group was higher than for the control group. There were no body weight differences throughout the 2-year period in rats treated with 0.1 or 1% adipic acid. During the rapid growth period, the weight gains of the 3.0 and 5.0% adipic acid groups were significantly less than the control groups. At the end of the study the body weight of males was reduced by 10% and more in the two highest exposure groups. There was slight, but consistent, reduction in food consumption at 5%, Throughout the study, the following clinical signs were observed among all groups, including controls: wheezing, blood-tinged crust about the noses and eyes, and body sores. The incidence of these findings did not appear to be significantly different among the groups althrough a lower incidence of signs indicative of respiratory infection and body sores occurrent in the 5% dose group. The incidence of lung pathology and tumor growth appeared to be equally distributed among all groups, including the controls. When the surviving males were sacrificed at the end of the study, there was no significant differences in organ weights or microscopic examination. Females: There were no significant differences in body weight gains or food consumption. Clinical signs noted in control and test groups included blood-tinged crust about the eyes and noses, unthriftness, and body sores. There was no microscopic

pathology.
Reliability: (2) valid with restrictions
short description of the results, low number of animals, few organs examined, unclear number of animals examined, only one dose for females.
Flag: Critical study for SIDS endpoint
11-NOV-2004 (47)

Type: Sub-chronic
Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Post exposure period: no
Doses: 0; 200; 1,000; 5,000 mg/kg bw/d
Control Group: yes, concurrent vehicle
NOAEL: = 1000 mg/kg bw

Method: other: similar to OECD TG 407 (1981)
Year: 1982
GLP: yes
Test substance: other TS: Nylon Salt 6/6 solution, purity 48-50%

Method: 10 animals per sex were used per dose level.
Daily checks were made for mortality and obvious signs of toxicity. Weekly body weight and food consumption measurements were taken. All animals were necropsied. Survivors at study termination were bled for hematology and blood chemistry, and their livers, kidneys, and testes were weighed.
Control animals were gavaged with tap water.
The following parameters were examined:
Hematology - White blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
Serum Chemistry - Total protein, blood urea nitrogen, glucose, glutamic pyruvic transaminase, alkaline phosphatase, creatinine, cholesterol, calcium, and thyroxin.
Necropsy procedures included a thorough examination of the nasal, cranial, thoracic, abdominal and scrotal cavities.
The following tissues were examined histopathologically: Adrenals, esophagus, testes, ovaries, heart, kidneys, liver, lung with bronchi, duodenum, jejunum, ileum, colon, grossly evident lesions, mammary gland, pancreas, pituitary, prostate, stomach, trachea, thyroid.
Tissues from animals at the 0; 1,000 and 5,000 mg/kg/d levels were examined by light microscopy.

Statistics: Dunnett`s test (two-tailed) and by inspection for body weight and food consumption data. Bartlett`s test to assess the variability. Hematology and serum chemistry: Dunnett`s test and by inspection. Terminal body weights and absolute organ weights: analysis of variance and Dunnett´s test.
Organ weights/terminal body weight ratios: Mann-Whitney test using the Bonferoni Inequality Procedure. Incidence of microscopic abnormalities: Fisher Exact test with the Bonferoni Inequality Procedure.
Result: The highest dose level caused the death or sacrifice in

extremis of 10/10 males within 5 days and 6/10 females within 14 days of exposure.
The surviving females of the high-dose group had lower mean body weights than the control group at day 8, but their body weights were similar to the controls at study end. 1,000 and 200 mg/kg bw produced no body weight changes for either sex.

Initial food consumption data among females at the high dose level reflected a decrease when compared to their controls, but were similar to their controls during the remaining three weeks of testing. No food consumption effect occurred in either sex at 1,000 and 200 mg/kg bw.
No significant clinical observations were noted at the control, 200 or 1,000 mg/kg dose levels. Significant changes at the 5,000 mg/kg level included loose stools, rough coats, hypoactivity and red nasal and ocular discharges. Two high dose females also had urine stained fur. One of the females had difficulty in breathing, paleness and was sacrificed in extremis.
At necropsy, no changes were observed for the low level males. Animals of the high-dose group had gaseous distention of the stomach (assumed to be due to gasping during the terminal period of life). One mid dose female had renal congestion/redness at the corticomedullary junction. In the high dose group, enlarged adrenals, renal congestion/redness at the corticomedullar were each observed in one female. Two females that died prior to the end of the study had gastric dilatation, and three high dose females which survived to the end of the study had flattening of the gastric mucosal rugae. In the highest dose group 2 males and 3 females had lung congestion, 3 males had cortical congestion/hemorrhages of adrenals.
Organ weights among test animals of both sexes that survived to the final necropsy, did not differ significantly from the control group. There was no difference in absolute and relative testes weights between treated groups and controls.
Histopathological changes at levels of 5,000 mg/kg bw included renal tubular degenerative changes in 5 of 10 male rats and 3 of 10 female rats. The same dose level produced focal gastric mucosal necrosis in 3 of 10 male rats. Both focal changes were of a non-inflammatory necrotic nature. These changes were not detected in animals receiving 1000 mg/kg bw. Hepatocytic necroses were found in each 2 males and females of the high dose groups and in 1 control female. No changes were found in the pituitaries, testes and ovaries.
There were no significant microscopic changes in the mid dose males and females. Significant increases in red blood cells and hematocrits in males at the mid and low dose levels were observed (+12% for the mid-dose, +9.6% for the low dose group as compared to the control group). However, the values remained within normal limits of this strain and therefore is not considered as biologically relevant.Serum chemistry was not altered.
NOAEL: 1000 mg/kg bw

Reliability: (2) valid with restrictions
neurologic and immunotoxic effects not examined; limited hematology parameters; limited number of organs examined.

Flag: Critical study for SIDS endpoint

12-JUN-2003 (48) (40)

Type: Sub-chronic

Species: mouse **Sex:** male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure period: 13 weeks
Frequency of treatment: 6 hours/day; 5 days/week
Doses: 0; 1.6; 5; 16; 50; 160 mg/m3
Control Group: yes, concurrent vehicle
NOAEL: = 5 mg/m³

Method: other: NTP study
Year: 1993
GLP: yes
Test substance: other TS: 1,6- hexanediamine dihydrochloride, aerosol

Method: whole body exposure. 10 animals/sex per exposure group. In addition to the standard repeat dose protocol, sperm morphology and vaginal cytology evaluations were performed from the control group and the 3 highest exposure groups.
Result: Inhalation of the test substance produced lesions that could be attributed to the irritant effects of the compound. The observed NOAEL for respiratory damage was 5 mg/m3. No significant systemic toxicity was observed, and no specific target organs were identified.
All mice survived to the end of the study, and there were no exposure-related changes in body weight. A significant increase occurred in the absolute and relative lung weights of female mice in the highest exposure group. Absolute and relative liver weights were sigificantly increased in male mice in the 2 highest exposure groups.
Liver-weight-to-body-weight ratios were also increased in male mice in the 5 and 16 mg/m3 exposure groups, but were not concentration related. No exposure-related clinical signs were observed and no gross lesions were seen at necropsy.
Exposure related microscopic lesions were limited to the upper respiratory tract (larnyx and nasal passages) of both sexes. Substance and concentration related effects were inflammation, erosion and necrosis of larynx. hyaline degeneration, erosion and inflammation in the respiratory and olfactory epithelia.
The NOAEC for systemic toxicity was 16 mg/m3, for irritating effects 5 mg/m3.
Administration of the test substance caused no changes in any of the sperm morphology or vaginal cytology parameters with the exception of an increase in sperm motility in the 16 and 160 mg/m3 exposure groups. However, this change was not dose related, and the values for sperm motility were all well within the range for historical controls for NTP studies. Consequently, the increase in sperm motiity was not interpreted as an adverse effect.
Test substance: 70% aqueous solution, purity 70.9%, pH 4.5-5.5
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
28-JAN-2003 (43) (44)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium; TA1535 TA1537 TA1538 TA98 TA100
Concentration: 0; 4; 20; 100; 500: 2500 ug/plate

Cytotoxic Concentration: no cytotoxicity observed
Metabolic activation: with and without
Result: negative

Method: other: similar to OECD TG 471
Year: 1980
GLP: no
Test substance: other TS: AH salt, purity 100%

Method: metabolic activation: liver S-9 mix from Aroclor induced rats. Solvent: Aqua dest. Positive controls: 2-Aminoanthracene, Cyclophosphamid (with S9-mix). N-Methyl-N-nitro-N-nitroso-guanidine, 4-Nitro-o-phenylendiamine, 9-Aminoacridiniumchlorid (without S9-mix); an independent repeat experiment was performed with TA100 in the presence of metabolic activation.
A substance was considered positive in this test if the following was fullfilled:
- doubling of the spontaneous mutation rate (control)
- dose-response relationship
- reproducible resultes

Remark: The components adipic acid and 1,6-hexandiamine were negative in the Ames test up to and including 10000 ug/plate (Prival et al, 1991, Mutat. Res. 260, 321-329; Mortelmans et al. 1986, Env. Mutagen. 8, Suppl.7 1-119)

Result: The test substance did not induce mutations in any of the tester strains, both in the presence and in the absence of metabolic activation. The number of revertants were similar to the number of revertants in the control group. The positive controls were functional.

Reliability: (2) valid with restrictions
limited exposure concentration;

Flag: Critical study for SIDS endpoint

16-JUN-2003 (49)

Type: Unscheduled DNA synthesis
System of testing: rat hepatocytes
Concentration: 0; 5; 10; 25; 50; 100; 250; 500; 1000 ug/ml
Cytotoxic Concentration: no cytotoxicity
Metabolic activation: without
Result: negative

Method: other: in accordance with the method described by Williams G.M., Cancer Res. 37, 1845-1851, (1977)
Year: 1982
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Hepatocytes were obtained from adult Fischer 344 rats by perfusion of the liver in situ with a collagenase solution. The hepatocytes for the UDS assay were collected at approximately 73% viability (determined by trypan blue exclusion), and about 93% of the viable cells attached to the culture dishes during the 1.5-hour settling period. The treatments were initiated approximately 2 hours later.
Incubation period: 18 hours.
Positive control: 2-AAF, 0.05 ug/mL.
Solvent: WME culture medium, containing 1% fetal bovine serum.
The cells were examined microscopically at approximately 1500x magnitude under oil immersion. The mean net nuclear

grain count was determined from the triplicate coverslips (150 total nuclei) for each treatment conditon.
Viability and morphological appearance of the cells indicated that the hepatocyte cultures were in good metabolic condition for the UDS assay.

Result: None of the treatments with the test substance caused any significant changes in the degree of nuclear labeling relative to the negative control. The test substance was not toxic at any of the applied concentrations.
The positive control was functional.

Reliability: (2) valid with restrictions
highest concentration not cytotoxic

Flag: Critical study for SIDS endpoint

29-JAN-2003 (50)

Type: other: Cell transformation assay
System of testing: BALB/3T3 Clone A31 Mouse embryo cells
Concentration: 0; 10; 30; 100 ug/mL
Cytotoxic Concentration: not cytotoxic
Metabolic activation: with
Result: negative

Method: other: according to the method described by Schechtman and Kouri in: Progress in Genetic Toxicology Scott, Bridges, Sobels eds. Elsevier/North-Holland Biomedical Press, 307-316, (1977)
Year: 1980
GLP: yes
Test substance: other TS: AH salt, purity 100%

Method: Cells were treated in suspension for 2 hours at 36 +/- 2 °C with different concentrations of the test substance as well as positive and negative controls in the presence of a metabolizing system. The cells were then analyzed for the cytotoxic effects of the treatment and the induction of phenotypic transformations. The transforming potential of the test substance was determined 4-6 weeks after initiation of the assay by its ability to induce a significant increase in the number of morphologically transformed foci (type II and type III) when compared to the negative control.
metabolic activation: S-9 mix from Aroclor 1254 induced male Fischer rats.
positive control substance: Benzo(a)pyrene (BaP; 12.5 ug/mL).
vehicle: phosphate buffered saline (PBS).

Result: At 10 ug/mL, three morphologically transformed type III foci were found among 3.72 x 10e4 cells at risk, relative to the negative control (transformation frequency: 8.1 x 10 e-5). The induced transformation frequency was not statistically significant ($p > 0.05$). BaP (positive control) induced the formation of 3 morphologically transformed type II foci and 10 morphologically transformed type III foci per 3.075 x 10e4 cells at risk, relative to the negative control (transformation frequency: 3.25 x 10 e-4; statistically significant at $p < 0.05$).
The colony-forming efficiency of 3T3 cells exposed to the various concentrations of the test substance were comparable to those of the negative control.
In conclusion, no detectable tranforming activity was found.
(The acceptance criteria for the validity of the test were

fulfilled)
Reliability: (2) valid with restrictions
highest concentration not cytotoxic
29-JAN-2003 (51)

Type: other: Cell transformation assay
System of testing: BALB/3T3 Clone A31 Mouse embryo cells
Concentration: 0; 10; 30; 100 ug/mL
Cytotoxic Concentration: not cytotoxic
Metabolic activation: without
Result: negative

Method: other: according to the method described by Schechtman and Kouri in: Progress in Genetic Toxicology Scott, Bridges, Sobels eds. Elsevier/North-Holland Biomedical Press, 307-316, (1977)
Year: 1980
GLP: yes
Test substance: other TS: AH salt, purity 100%

Method: Cells were plated and treated for 20-24 hours at 36 +/- 2 °C with different concentrations of the test substance as well as positive and negative controls in the absence of a metabolizing system. The cells were then analyzed for the cytotoxic effects of the treatment and the induction of phenotypic transformations. The transforming potential of the test substance was determined 4-6 weeks after initiation of the assay by its ability to induce a significant increase in the number of morphologically transformed foci (type II and type III) when compared to the negative control.
positive control substance:
N-methyl-N`-nitro-N-nitrosoguanidine (MNNG; 0.5 ug/mL).
vehicle: aqueous cell culture medium.
Result: 100 ug/mL induced one morphologically transformed type III focus among 4.14 x 10e4 cells at risk, relative to the negative control (transformation frequency: 0.24 x 10 e-4). The induced transformation frequency was not statistically significant ($p > 0.05$). MNNG (positive control) induced the formation of 4 morphologically transformed type III foci per 23.25 x 10e3 cells at risk, relative to the negative control (transformation frequency: 1.72 x 10 e-4; statistically significant at $p < 0.05$).
Relative to the negative (medium) control, the colony-forming efficiency of 3T3 cells exposed to the various concentrations of the test substance ranged from 81-94%.
In conclusion, no detectable tranforming activity was found. (The acceptance criteria for the validity of the test were fulfilled)
Reliability: (2) valid with restrictions
highest concentration not cytotoxic
29-JAN-2003 (52)

Type: Ames test
System of testing: Salmonella typhimurium, TA 98, 100, 1535, 1537, 1538, E. coli WP2
Concentration: 0.033; 0.10; 0.33; 1.0; 3.3; 10 mg/plate
Cytotoxic Concentration: no data
Metabolic activation: with and without

Result: negative

Method: other: according Ames et al, 1975
Year: 1991
GLP: no data
Test substance: other TS: Adipic acid (CAS124-04-9)

Remark: metabolic activation: liver S-9 mix from Aroclor induced rats.
Solvent: potassium phosphate buffer.
Positive controls:
2-Anthramine (with S9-mix).
N-Methyl-N-nitro-N-nitroso-guanidine, 2-Nitrofluorene, 9-Aminoacridine, sodium acid, AF-2 (without S9-mix);
A substance was considered positive in this test if the following was fullfilled:
- doubling of the spontaneous mutation rate (control)
- dose-response relationship
- reproducible resultes

Result: The test substance did not induce mutations in any of the tester strains, both in the presence and in the absence of metabolic activation. The positive controls were functional.
Test substance: Adipic acid, Aldrich
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
16-JUN-2003 (53)

Type: Ames test

16-JUN-2003

Type: Ames test
System of testing: Salmonella typhimurium
Concentration: 33, 100, 333, 1000, 3333, 10000 ug/plate
Cytotoxic Concentration: 1000-3333 ug/plate
Metabolic activation: with and without
Result: negative

Method: other: NTP program
Year: 1986
GLP: no data
Test substance: other TS: 1,6 Hexanediamine

Remark: metabolic activation: liver S-9 mix from Aroclor induced rats.
Solvent: aqua.

A substance was considered positive in this test if the following was fullfilled:
- doubling of the spontaneous mutation rate (control)
- dose-response relationship
- reproducible resultes

Result: The test substance did not induce mutations in any of the tester strains, both in the presence and in the absence of metabolic activation. The positive controls were functional.
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
16-JUN-2003 (54)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: mouse **Sex:** male
Strain: NMRI
Route of admin.: i.p.
Exposure period: two injections within 24 hours
Doses: 0; 400; 800; 1600 mg/kg bw (total dose: 0; 800; 1600; 3200 mg/kg bw)
Result: negative

Method: OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year: 2001
GLP: yes
Test substance: other TS: AH Salt, crystalline, purity: 99%

Method: In this study, the ability of the test substance to induce chromosomal damage (clastogenicity) and to induce spindle poison effects (aneugenic activity) was investigated.
The test substance was dissolved in purified water.
In a pretest for determination of acute intraperitoneal toxicity, deaths were observed following two treatments down to a dose of 1700 mg/kg bw. 1600 mg/kg were survived by all animal, but led to evident signs of toxicity. There were no distinct symptomatic differences between the male and female animals. Thus, only male animals were used in the main study, 1600 mg/kg bw was selected as the highest dose.
test procedere in the main study:
Administration volume: 10 ml/kg bw.
5 male animals / dose group.
Negative control: purified water.
Positive controls: cyclophosphamide (20 mg/kg bw), vincristine (0.15 mg/kg bw).
The bone marrow of the two femora was prepared 24 hours after the second administration. After stainig of the preparations, 2,000 polychromatic erythrocytes were evaluated per animal and investigated for micronuclei. The normocytes with and without micronuclei occurring per 2,000 polychromatic erythrocytes were also registered.
Statistical method: Wilcoxon test, one-sided.

Result: The administration of the test substance led to signs of toxicity in the mid- and high-dose groups (800 mg/kg bw: squatting posture; 1600 mg/kg bw: squatting posture and poor general state).

There was no statistically significant increase in the number of polychromatic erythrocytes containing either small or large micronuclei.
The rate of micronuclei was close to the range of the concurrent negative control in all dose groups and within the range of the historical control data.
(The number of PCE's (%o) were: control 1.5; 400 mg/kg 1.6; 800 mg/kg 1.7; 1600 mg/kg 2.1; Cyclophosphamid 14.1; Vincristine 60.6; range of historical control: 1.0-2.7, mean 1.7)
No inhibition of erythropoiesis, determined from the ratio of polychromatic to normochromatic erythrocytes, was detected.
The test substance had no chromosome-damaging (clastogenic)

effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells in vivo.
Both of the positive control chemicals, i.e. cyclophosphamide for clastogenic effects and vincristine for induction of spindle poison effects, induced the expected significant increases in the rate of polychromatic erythrocytes containing small or large micronuclei.
The result for the negative control was within the historical control range.

Reliability: (1) valid without restriction
guideline study

Flag: Critical study for SIDS endpoint

27-JAN-2003 (55)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

Type: Fertility
Species: rat
Sex: male/female
Strain: other: Alpk:APfSD
Route of administration: oral feed
Exposure Period: 10 weeks
Frequency of treatment: daily
Doses: 300, 1800, 12000 ppm (ca. 15-30, 90-180, 600-1200 mg/kg bw/day)
Control Group: yes
NOAEL Parental: 1800 ppm
NOAEL F1 Offspring: 1800 ppm

Year: 1988
GLP: no data
Test substance: other TS: Di-(2-ethylhexyl)adipat

Method: Since di-2-(ethylhexyl)adipate (DEHA) is in vivo rapidly metabolized to adipic acid (after oral administration up to 95 % of di-2-(ethylhexyl)adipate was found as adipic acid in urine, Cornu 1988) the one-generation study with di-2-(ethylhexyl)adipate is also taken to cover this endpoint. DEHA was administered to ca 21 days old rats, each dose and control group consisted of 30 female and 10 male rats. DEHA was given in the feed at 300, 1800 and 12000 ppm. The authors do not precise the effective dose levels, however as a general rule, the dose ranges within the experiment varied between 15-30, 90-180 and 600-1200 mg/kg bw x day, (according to a conversion factor of 10 and 20, WHO 1987), depending on the age and body weight of the animals for a period of 10 weeks prior to mating, during mating and during the gestation and lactation periods. These doses correspond to 6-12, 36-72, 240-480 mg adipic acid/kg bw and day.
Necropsy was performed on male animals immediately after successful mating, on females after the pups had weaned, and the progeny after day 36 of life. the following organs were histologically examined: cervix, epididymis, liver, mammary gland, ovaries, seminal vesicle, prostate, testes, uterus and all other organs if showing macroscopic changes.

Remark: No data was available for AH salt itself and its component

adipic acid.
Since di-2-(ethylhexyl)adipate is in vivo rapidly metabolized to adipic acid (after oral administration up to 95 % of di-2-(ethylhexyl)adipate was found as adipic acid in urine, Cornu 1988) the one-generation study with di-2-(ethylhexyl)adipate was taken to close the endpoint fertility for the component adipic acid.

Result: No clinical symptoms of intoxication occurred in the parent animals. Only the females in the high dose group suffered slight, but non-significant, inhibition of body weight gain during the pretreatment period (approx. 3%) and a significant reduction during pregnancy. Data on body weight of females in the lactation period are lacking. The males of the high dose group showed a slight but significant increase in feed consumption from weeks 6 to 9 with simultaneous reduction in feed efficiency.
Male and female fertility, length of gestation and the pre-coital interval were not affected. The parental animals did not show any signs of substance-related histopathological organ changes. Both males and females in the high does group, however, had significantly higher absolute and relative liver weights.
There were four whole litter losses, none in control, one in the 300 ppm group, two in the 1800 ppm group and one in the 12000 ppm dose group. Only in the high dose group was there a slight but non-significant reduction in litter sizes (day 1: 9.7 vs 10.9; day 3: 8.5 vs 10.0). None of the pups showed any clinical signs, substance-related macroscopic or histopathologic changes or gross malformations. The pup weight at birth was not different from the controls.
In the highest dose group a significant inhibition (10-23%) of the mean body weight gain of pups in the postnatal follow-up period (day 1-36) was observed, as well as a reduction in the total litter weight of both males and females.
The author derived a NOAEL for fertility parameters in both generations of 12000 ppm; pup body weight reduction, however, was recorded at 12000 ppm, which is a dose level associated with some maternal toxicity. Thus, 1800 ppm (36-72 mg adipi acid/kg bw and day), was shown as a clear-cut NOAEL for all effects.

Test substance: Di-(2-ethylhexyl)adipat, CAS 103-23-1
The doses correspond to 6-12, 36-72, 240-480 mg adipic acid/kg bw and day.

Reliability: (2) valid with restrictions
limited data about body weight and body weight gain, no data about the precise effective dose levels.

Flag: Critical study for SIDS endpoint

29-JAN-2003 (56) (57)

Type: Two generation study
Species: rat
Sex: male/female
Strain: Sprague-Dawley
Route of administration: oral feed
Exposure Period: over two generations
Duration of test: 40 weeks
No. of generation studies: 2
Doses: 0; 50; 150; 500 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Parental: = 150 mg/kg bw

NOAEL F1 Offspring: = 150 mg/kg bw

Year: 1991
GLP: no data
Test substance: other TS: 1,6-hexane diamine, 78% aqueous solution

Method: 26 animals/sex were used per group.
After a minimum of 56 days of treatment, the F0 rats were mated to produce the F1 offspring. During the mating period each male was cohabitated with a female from the same treatment groups for up to 20 days. After the mating period, males were individually housed and continued on treatment until the completion of parturition, when fertility was evaluated. Pregnant F0 females were allowed to give birth to F1 pups and the day all pups were delivered was designated day 0 of lactation. Litters were examined for size, stillbirths, live births, and gross anomalies. Litter size was reduced to a total of 8 pups of equal size, when possible, on day 4 of lactation. Pups were housed with their mothers and weighed at intervals for 3 weeks after birth. Afterward, 26 pups of each sex from each group were selected to become F1 parents of the F2 offspring. After a minimum of 98 days treatment the F1 parents were mated to produce the F2 offspring. The F2 pups were sacrificed on day 21 of lactation. Gross necropsies were performed on F0 and F1 parents as well as F2 pups. The following tissues were evaluated from the F0 and F1 rats histopathologically: kidneys, liver, lungs, ovaries, prostate, seminal vesicles, spleen, testes with epididymes, uterus, and vagina.

Result: No treatment-related mortality was observed in any of the groups. The ability of rats to successfully mate and produce litters was not adversely affected by daily doses of up to 500 mg/kg.
The weight of male F0 and F1 parent animals was significantly reduced by about 10% at 500 mg/kg at the end of the treatment period. The body weight of the females was not altered at that time but the weight gain was reduced by about 10% during gestation (no further data). The litter size at birth was significantly reduced in the F1 generation (13.8 vs 11.7) and not significantly reduced in the F2 generation (13.0 vs. 11.0) at 500 mg/kg. Pup weight was normal at birth but was significantly lower at day 21 in male F1 pups and female F2 pups at 500 mg/kg. There
was no effect on their survival and they appeared normal during lactation.
The treatment with up to 150 mg/kg did not adversely affect reproduction or fertility. No differences between control and treated rats in either generation with regard to clinical observations, copulation, gestation length, nesting behaviour, appearance of pups.
No treatment related effects on testes weights, no microscopic and macroscopic effects on tissues.
No data about malformations.

Test substance: purity not stated
Reliability: (2) valid with restrictions
limited data
Flag: Critical study for SIDS endpoint
29-JAN-2003 (58)

Type: other: mating trial
Species: rat

Sex: male/female
Strain: Fischer 344
Route of administration: inhalation
Exposure Period: 13 weeks
Frequency of treatment: 6 hrs/day; 5 days/week
Doses: 0; 16; 50; 160 mg/m3 (aerosol)
NOAEL Parental: = 160 mg/m³
NOAEL F1 Offspring: = 160 mg/m³

Year: 1993
GLP: yes
Test substance: other TS: 1,6-hexanediamine dihydrochloride

Method: 20 males; 40 females (10 animals per dose level)
Mating trial animals were bred for a maximum of 10 nights (approx. study days 68 to 80, weekdays only) prior the end of the 13-week exposure period. Day 0 of gestation was considered to be the day sperm were observed in the lavage samples. Day of parturition was considered to be lactation day 0. Females and pups were killed on lactation day 21.
Adult female were weighed on gest. days 0 and 20. Adult males were weighed at the end of the mating period. Dams and pups were individually weighed on lactation days 0, 5, 14, 21. Pups were examined at birth for morphological abnormalities, viability and gender. The number of live/dead offsprings, percent neonatal survival, mean live pup weight, and sex ratio were recorded on lactation days 0,5,14,21.
Result: There was no effect on male or female fertility, body weights or body weight gains, gestation length, litter size, neonatal survival, pup weights, sex ratios of pups, or pup morphology.
Administration of the test substance caused no changes in any of the sperm morphology or vaginal cytology parameters.
The study was part of a larger investigation on the repeated dose toxicity of hexanediamine dihydrochloride (see section on repeated dose toxicity). The NOAEL for respiratory damage established in the 13 week repeated dose study was 5 mg/m3.
Test substance: 70% aqueous solution, purity 70.9%, pH 4.5-5.5
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
29-JAN-2003 (43) (44)

Type: other: mating trial
Species: mouse
Sex: male/female
Strain: B6C3F1
Route of administration: inhalation
Exposure Period: 13 weeks
Frequency of treatment: 6 hrs/day; 5 days/week
Doses: 0; 16; 50; 160 mg/m3 (aerosol)
NOAEL Parental: = 160 mg/m³
NOAEL F1 Offspring: = 160 mg/m³

Year: 1993
GLP: yes
Test substance: other TS: 1,6-hexanediamine dihydrochloride

Method: 20 males; 40 females (10 per dose level),
Mating trial animals were bred for a maximum of 10 nights (approx. study days 68 to 80, weekdays only) prior the end of the 13-week exposure period. Day 0 of gestation was considered

to be the day sperm were observed in the lavage samples. Day of parturition was considered to be lactation day 0. Females and pups were killed on lactation day 21.
Adult female were weighed on gest. days 0 and 20. Adult males were weighed at the end of the mating period. Dams and pups were individually weighed on lactation days 0, 5, 14, 21. Pups were examined at birth for morphological abnormalities, viability and gender. The number of live/dead offsprings, percent neonatal survival, mean live pup weight, and sex ratio were recorded on lactation days 0,5,14,21.

Result: There was no effect on male or female body weights or body weight gains, and no effect on male or female fertility. A statistically significant increase in the mean gestation length of mice in the two highest exposure groups was noted. However, in the absence of other reproductive toxicity, this effect was not considered biologically significant by the authors of the study. The test substance had no effect on litter size, neonatal survival, sex ratio of pups, or pup morphology. Pups in the highest exposure group had mean weights similar to that of controls at birth and on lactation day 5. However, mean weight of pups in this exposure group were lower than that of controls on lactation days 14 and 21. The cause for the lower litter weight at the 160 mg/m3 dose may be, that the litter size was slightly but not significantly higher than controls throughout lactation, which might also be an explanation for the slower body weight gain. This effect was also not considered of biological significance by the study authors.
Administration of the test substance caused no changes in any of the sperm morphology or vaginal cytology parameters with the exception of an increase in sperm motility in the 16 and 160 mg/m3 exposure groups. However, this change was not dose related, and the values for sperm motility were all well within the range for historical controls for NTP studies. Consequently, the increase in sperm motiity was not interpreted as an adverse effect.
The study was part of a larger investigation on the repeated dose toxicity of hexanediamine dihydrochloride (see section on repeated dose toxicity). The NOAEL for respiratory damage established in the 13 week repeated dose study was 5 mg/m3.

Test substance: 70% aqueous solution, purity 70.9%, pH 4.5-5.5
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
29-JAN-2003 (43) (44)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain: Fischer 344
Route of administration: gavage
Exposure period: days 0 through 15 of gestation
Frequency of treatment: daily
Doses: 0; 10; 100; 200 mg/kg bw
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: = 100 mg/kg bw
NOAEL Fetotoxicity : = 200 mg/kg bw
NOAEL Embryotoxicity : = 200 mg/kg bw

Year: 1983
GLP: no data

Test substance: other TS: hexamethylene diamine dihydrochloride, purity not stated

Method: Dams (13-14 per group) were killed on day 15 of gestation following 2 weeks of treatment and examined for the number of fetuses, resorptions, and corpora lutea. The results were analyzed using a one-way ANOVA at a probability level of 0.05.

Result: The study was undertaken to investigate a potential effect on early fetal development and implantation.

No significant differences between the groups were observed in reproductive parameters (corpora lutea, litter size and resorptions). A significant decrease in the weight gain during gestation occurred at the highest dose (200 mg/kg bw).
NOAEL Teratogenicity: not determined

Reliability: (2) valid with restrictions
limited documentation, limited number of animals, no teratogenicity examined.

Flag: Critical study for SIDS endpoint

16-JUN-2003 (59)

Species: rat **Sex:** male/female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: days 6 through 15 of gestation
Frequency of treatment: daily
Doses: 0; 112; 184; 300 mg/kg bw
Control Group: yes
NOAEL Maternal Toxity: = 112 mg/kg bw
NOAEL Teratogenicity: = 300 mg/kg bw
NOAEL Embryotoxicity : = 300 mg/kg bw
LOAEL Fetotoxicity : = 112 mg/kg bw

Year: 1987
Test substance: other TS: hexamethylene diamine

Method: Four groups of 22 pregnant rats were administered aqueous solutions of the test material by gavage. Distilled water was used to dose control animals. All animals were intubated at a constant volume of 10 mL/kg d. Body weights, actual and adjusted (=minus fetal, uterine and placental) weights were recorded on days 6-15 and 21. Daily food intake was recorded at 3-day intervals; dams were checked for survival twice daily. Dams surviving to day 21 were killed by CO2 overdose. Uterine horns were examined for number and placement of early resorptions, late resorptions and fetal survival. Live fetuses were sexed, weighed, measured and examined externally. Half of the fetuses in each litter were fixed in Bouin`s solution and examined for visceral abnormalities by the method of Wilson. The remaining fetuses were stained with alizarin-red-S and examined for skeletal abnormalities.
Statistics: Fischer Exact Probability Test (incidences of specific maternal and fetal observations), analysis of variance and, where necessary, tests for multiple comparison (body weight, food consumption, organ weights). Significance level: $p < 0.05$.

Result: In the 300 mg/kg dosage group, a single death and one animal killed in extremis were considered to have resulted from

treatment. Each one death in the control and 184 mg/kg bw group were considered the result of dosing accidents. Pregnant rats given 300 mg/kg and 184 mg/kg bw gained less weight (ca. 15 %) than control dams from gestation day 6 to 15. Adjusted weight on day 21 was reduced by 70 ($p<0.05$) and 15% resp. Statistically significant body weight gain reduction was also observed from gestation day 10- 15 for the 300 mg/kg group.
Transient reduction in food consumption were also noted at this test level.
The test substance had no effect on the number of implantation sites per dam, mean litter size, incidence of resorption, sex ratio or fetal length. A statistically significant decrease in fetal body weights of both male (8%) and female (7%) pups was observed at 300 mg/kg bw. At 184 mg/kg bw fetal body weight was reduced numerically (ca. 5%). The overall incidence of minor and major malformations observed in this study was low and none was judged related to treatment. The incidence of external observation of pups from each of the treated groups was not increased above background levels. Visceral examinations revealed a significant increase in the number of pups with spotty livers in the high dosage level. There also was a significant increase in bladder distension in the mid dosage group only. Since there was no dose-related pattern, it was concluded by the study authors that this latter observation is not related to treatment. Three types of anatomical variations and ossification delays differed significantly between control and treated groups. These were: poor development of hyoids, and, second, cervical vertebral centra and, third, the lack of fusion in the posterior sacral and anterior caudal vertebra. These retardations were limited in that no other significant correlative alterations in ossification were observed. There was no dose-related pattern for hyoid development. Thus, this was not considered related to treatment. The occurrence of fetuses with poorly or unossified cervical centra or sacral/caudal vertebra indicated slight retardation in skeletal development
observed at both the 184 and 300 mg/kg exposure levels.

Test substance: no data about purity of the substance
Reliability: (2) valid with restrictions
limited documentation of variations, data on skeletal redardation were not shown.
Flag: Critical study for SIDS endpoint
04-FEB-2003 (46)

Species: mouse **Sex:** female
Strain: CD-1
Route of administration: gavage
Exposure period: days 6 through 15 of gestation
Frequency of treatment: daily
Doses: 0; 2.6; 12; 56; 263 mg/kg bw as aqueous solution
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: 263 mg/kg bw
NOAEL Teratogenicity: 263 mg/kg bw
NOAEL Fetotoxicity : 263 mg/kg bw
NOAEL Embryotoxicity : 263 mg/kg bw

Year: 1973
GLP: no

Test substance: other TS: adipic acid, purity not stated

Method: 25 females per group were mated (31 in the high dose group); body weights were recorded on days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have ocurred as a result of anorexic effect in the pregnant females. On day 17 all dams were subjected to Caesarean section und the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical abnormality. All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examination employing 10x magnification. The remaining two-thirds were stained with alizarin red and examined for skeletal defects. Positive control: 150 mg Aspirin/kg bw; administration volume: 10 mL/kg bw.

Result: The administration of up to 263 mg/kg bw of the test substance to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occuring spontaneously in the sham-treated controls.
The results were not evaluated statistically, but inspection of the tablesshows no effects in the treated groups vs. control.

Reliability: (2) valid with restrictions
No statistical evaluation.
Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results.

Flag: Critical study for SIDS endpoint

17-FEB-2003 (60)

Species: rabbit **Sex:** female
Strain: Dutch
Route of administration: gavage
Exposure period: days 6 through 18 of gestation
Frequency of treatment: daily
Doses: 0; 2.5; 12; 54; 250 mg/kg bw
Control Group: yes
NOAEL Maternal Toxity: 250 mg/kg bw
NOAEL Teratogenicity: 250 mg/kg bw
NOAEL Fetotoxicity : 250 mg/kg bw
NOAEL Embryotoxicity : 250 mg/kg bw

Method: other: NTP study
Year: 1974
GLP: no
Test substance: other TS: adipic acid, purity not stated

Method: On day 0, each groups was given an injection of human chorionic gonadotropin, and was artificially inseminated 3 hours later. 11/19, 10/13, 11/16, 10/15, 14/20 pregnant/mated females were in the 0; 2.5; 12; 54 and 250 mg/kg treatment group, respectively.

Body weights were recorded, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight.
On day 29 all dams were subjected to cesarean section, and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each female was examined in detail for gross anatomical abnormality. The body weights of the live pups were recorded, and all fetuses were examined grossly for the presence of external congenital abnormalities. The live fetuses of each litter were placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were then sacrificed, and examined for visceral abnormalities. In addition, all fetuses were examined for skeletal defects.
6-Aminonicotinamide (2.5 mg/kg), dosed on day 9, was used as a positive control.
The resultes were not evaluated statistically, but inspection of tables shows no effects in the treated groups vs. control.

Result: The administration of the test substance up to 250 mg/kg bw had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No differences between treatment and control groups were found for corpora lutea, implantations, total no. of resorptions, total no. of fetuses, total no. of live litters and fetal weight.

Reliability: (2) valid with restrictions
study did not include a high dose that caused maternal toxicity, low number of animals per group, no statistical evaluation.
Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results.

Flag: Critical study for SIDS endpoint

17-FEB-2003 (61)

Species: hamster **Sex:** female
Strain: other: golden hamster
Route of administration: gavage
Exposure period: days 6 through 10 of gestation
Frequency of treatment: daily
Doses: 0; 2; 9.5; 44; 205 mg/kg bw
Control Group: yes

Year: 1973
Test substance: other TS: adipic acid, purity not stated

Method: 25-27 females / group.
Virgin adult females were mated with young adult males, and observation of motile sperm in the vaginal smear was considered day 0 of gestation. Body weights were recorded, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight. On day 14 all dams were subjected to cesarean section, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each female was examined in detail for gross anatomical abnormality. The body weights of the live pups were recorded, and all fetuses were examined grossly

for the presence of external congenital abnormalities. One third of the fetuses of each litter underwent detailed visceral examinations. The remaining 2/3 were examined for skeletal defects.
Aspirin, 250 mg/kg bw, was used as a positive control.

Result: No teratogenic effects, no skeletal or soft tissue findings. In this study an increase of resorption/implant sites from 3.5 to 7.7% in the highest dose group was observed. Consequently the average number of live fetuses was reduced from 12.6 to 11.4 a reduction as high as caused by the positive control substance aspirin. Without statistical evaluation it cannot be judged if this dose is a NOEL.

Reliability: (3) invalid
study did not include a dose that caused maternal toxicity, treatment period too short, no statistical evaluation, limited documentation.

29-JAN-2003 (62)

Species: **Sex:** female
Strain: Wistar
Route of administration: gavage
Exposure period: days 6 through 15 of gestation
Frequency of treatment: daily
Doses: 0; 2.9; 13; 62; 288 mg/kg bw as aqueous solution
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: 288 mg/kg bw
NOAEL Teratogenicity: 288 mg/kg bw
NOAEL Fetotoxicity : 288 mg/kg bw
NOAEL Embryotoxicity : 288 mg/kg bw

Year: 1972
GLP: no
Test substance: other TS: adipic acid, purity not stated

Method: 25 females / group, except for the high-dose where 24 animals were investigated.
Virgin adult females were mated with young adult males, and observation of a vaginal sperm plug was considered day 0 of gestation. Body weights were recorded, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight. On day 20 all dams were subjected to cesarean section, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each female was examined in detail for gross anatomical abnormality. The body weights of the live pups were recorded, and all fetuses were examined grossly for the presence of external congenital abnormalities. One third of the fetuses of each litter underwent detailed visceral examinations. The remaining 2/3 were examined for skeletal defects.
Aspirin, 250 mg/kg bw, was used as a positive control.

Result: The administration of the test substance up to the highest dose level had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No differences between treatment and control groups were found for corpora lutea, implantations, total no. of resorptions, total no. of fetuses, total no. of live litters and fetal weight.

The results were not evaluated statistically, but inspection of the tables shows no effects in the treated groups vs. control.

Reliability: (2) valid with restrictions
Study did not include a high dose that caused maternal toxicity, no statistical evaluation.
Data on purity of adipic acid are lacking, but as no effects were observed up to the highest dose tested this is thought not to impair the validity of the results.

Flag: Critical study for SIDS endpoint

17-FEB-2003 (63)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Remark: No studies were located in the open literature

20-MAY-2002

5.11 Additional Remarks

Type: Distribution

Remark: The following gavage administration of 1,6- [14C]diaminohexane (100-200 uCi of hexamethylendiamine, HMDA) to male Fischer 344 rats, approx. 20% of the administered dose was recovered as 14CO2 after 72h. Urinary and fecal excretion accounted for 47% and 27% of the administered radioactivity, respectively. Of several tissues examined, the highest concentration of residual radioactivity were found in the prostate at 24h and 72 h post-administration.

Test substance: 1,6-hexanediamine

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

16-JUN-2003 (64)

Type: Metabolism

Remark: Adipic acid is absorbed and metabolised by normal metabolic processes by the rat. When 50 mg radioactive adipic acid in 2-4 ml of water was fed by gavage to fasted rats, metabolic products identified as urea, glutamic acid, lactic acid, ß-ketoadipic acid, and citric acid, as well as adipic acid, were found in the urine collected overnight. 70% of the dose was exhaled as CO2 6h after application. The tissues showed very little radioactivity.

Test substance: adipic acid

Reliability: (2) valid with restrictions

Flag: Critical study for SIDS endpoint

16-JUN-2003 (65)

Type: Metabolism

Remark: 1,6 hexandiamine is metabolized in vitro by diamine oxidase to 3,4,5,6 tetrahydro-2H-azepineand this metabolized further by aldehyde dehydrogenase to 6-aminohexanoic acid and caprolactam in the rat liver.
Test substance: 1,6 hexandiamine
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

16-JUN-2003 (66)

Type: Metabolism

Remark: After oral administration of 665 or 1500 mg di(2-ethylhexyl) adipate/kg bw to male rats up to 95 % of the theoretical amount from DEHA was found as adipic acid in urine on day 1 after dosing. The urinary recovery was about 50%. CO2 exhalation was not studied. Other metabolites were oxidized and conjugated forms of 2-ethyl hexanoic acid.
Test substance: Di(2-ethylhexyl)adipate
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

16-JUN-2003 (56)

6.1 Analytical Methods

6.2 Detection and Identification

7.1 Function

7.2 Effects on Organisms to be Controlled

7.3 Organisms to be Protected

7.4 User

7.5 Resistance

8.1 Methods Handling and Storing

Safe Handling: Avoid dust formation. Protect against moisture.
Fire/Exp. Prot.: The product ist capable of dust formation.
Storage Req.: Store in unopened original containers in a, cool and dry place.
Transport Code: Not classified as hazardous under transport reguIations.

Remark: PERSONAL PROTECTIVE EQUIPMENT

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

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

General safety and hygiene measures:
Handle in accordance with good industrial hygiene and safety practice.

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

8.2 Fire Guidance

Ext. Medium: dry extinguishing media, foam, carbon dioxide, water
Add. Information: In case of combustion evolution of dangerous gases possible

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

8.3 Emergency Measures

Type: other: general advice

Remark: Immediately remove contaminated clothing.
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

Type: injury to persons (skin)

Remark: Wash off thoroughly with ample water.
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

Type: injury to persons (eye)

Remark: Immediately wash affected eyes for at Ieast 15 minutes under running water with eyelids held open,
consult an eye specialist.

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

Type: injury to persons (oral)

Remark: Rinse mouth and then drink pIenty of water.
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

Type: injury to persons (inhalation)

Remark: If difficulties occur after dust has been inhaled, remove to fresh air and seek medical attention.
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

Type: accidental spillage

Remark: Environmental precautions:
Do not discharge into drains/surface waters/groundwater.

Methods for cleaning up or taking up:
For small amounts: Sweep/shovel up.
For large amounts: Sweep/shovel up.
Flag: non confidential, Critical study for SIDS endpoint
14-JAN-2003 (1)

8.4 Possib. of Rendering Subst. Harmless

8.5 Waste Management

Memo: other: Incinerate in suitable incineration plant, observing local authority regulations.

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

8.6 Side-effects Detection

8.7 Substance Registered as Dangerous for Ground Water

8.8 Reactivity Towards Container Material

(1) BASF AG, Safety data sheet AH SALT CRYSTALLINE, 13.01.2003 (30056552)

(2) BASF AG (1999): Crystalline AH-Salt: Specifications at a glance

(3) Ullmann's Encyclopedia of Industrial Chemistry, Sixth Edition, 2000 Electronic Release

(4) TRGS 900 (Technical guidance for hazardous substances - Technische Regeln für Gefahrstoffe) (Germany) of 09/2001

(5) Catalogue of Substances Hazardous to Water - Umweltbundesamt Berlin, status Dec 15, 2002

(6) National Chemical Inventories, 2001 Issue 2

(7) BASF AG (2002): AH Salt. Occupational Exposure Monitoring Data. 29 Jan 2002

(8) BASF AG, department of analytical, unpublished data, laboratory notice, 26.07.2002

(9) BASF AG, Safety data sheet AH Salz LOESUNG, 13.01.2003

(10) Beilstein, 2004

(11) BASF AG, Technische Entwicklung - Verfahrenstechnik, unpublished study, 191.0384.1, 21 Jun 1991

(12) BASF AG (1999): Specifications for Liquid AH salt on internet http://www.basf.de/basf/html/e/produkte/gebiete/kunstst/fibre/products/intermed/ahsalz/

(13) BASF AG, Analytics Department, unpublished study, 90AO3832, 26 Mar 1991

(14) BASF AG (1999): Crystalline AH-Salt: The most important physical properties at a glance. http://www.basf.de/basf/html/e/produkte/gebiete/kunstst/fibreproducts/intermed/ahsalz/physah1.htm

(15) BASF AG, Analytics Department, unpublished data, 27 Nov 2001

(16) BASF AG, Material Safety Data Sheet AH Salt Crystalline (29.09.1999)

(17) BASF AG (1999): Liquid AH-Salt: The most important physical properties at a glance. http://www.basf.de/basf/html/e/produkte/gebiete/kunstst/fibreproducts/intermed/ahsalz/physah.html

(18) BASF AG, Analytics Department, unpublished study, report no. BRU 91.012, 22 Feb 1991

(19) BASF AG, Analytics Department, unpublished study (BRU 88.172), 29 Aug 1988

(20) BASF AG, Technische Entwicklung Verfahrenstechnik, unpublished study (Meßbericht BRU 95.084), 07 Nov 1995

(21) BASF AG, additional information, 24.05.2002

(22) BASF AG, Sicherheitstechnische Kenndaten, unpublished study (TLM/SIK 77/1398), 27 Jan 1978

(23) BASF AG, Sicherheitstechnische Kenndaten, unpublished study (SIK-Nr. 87/1629), 19 Oct 1987

(24) OECD, EDG - Comments from UK, 24.04.2003

(25) Buxton GV, Greenstock, Helmann WP, Ross AB (1988): Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms and hydroxyl radicals in aqueous solution. J.Phys Chem Ref Data 17: 513 - 883

(26) Mill T (1999): Predicting photoreaction rates in surface waters. Chemosphere 38: 1379 - 1390

(27) BASF AG, Labor Oekologie; unpublished study (Oekonr.01.408/86), 17 Oct 1986

(28) BASF AG, Labor Oekologie; unpublished study Nr.01.408/86, 17 Oct 1986

(29) Bruk ES at al.: Sanit Okhr Vodoemov Zagryaz Prom Stochnymi Vodami, No. 7, 56-58, from: Ref. Zh., Khim. 1966 Pt. II, Abstr. No. 17I229

(30) Ennis DM: Studies on the biodegradability of Polyamides nd low molecular weight amides and imides: Hexamethylenediamie Degradation and soil conditioning properties of Nylon Salt. Environmental Sciences Dissertation Abstract Int. B, Vol 37 (2), 676 (1976)

(31) Monsanto Chemical Company, unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-096): Static Acute Bioassay Report #27358, 28 Apr 1981

(32) BASF AG, Department of Toxicology: unpublihed study (87/131), 09 Sep 1987

(33) Monsanto Chemical Company, unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-095): Static Acute Bioassay Report #27357, 13 May 1981

(34) Monsanto Chemical Company, unpublished study (Analytical Bio Chemistry Laboratories Inc., project no. AB-81-097): Static Acute Bioassay Report #27359, 29 Apr 1981

(35) BASF AG, Department of Ecology, unpublished data (1104/87), 22 Jan 1988

(36) BASF AG, Department of Ecology, unpublished study (1104/87), 03 Dec 1987

(37) BASF AG, Department of Ecology, unpublished data (9/0242/87/2), Apr 1987

(38) BASF AG, Department of Toxicology, unpublished study (VI/3), 19 Apr 1956

(39) Marhold J.: Prehled Prumyslove Toxikologie; Organicke Latky, 444, Avicenum, Prag, (1986) cited in: RTECS, update Jan 2001

(40) Solutia Inc., Material Safety Data Sheet. Nylon 6,6 Salt Solution. 24 Aug 2001

(41) Solutia, unpublished study, report no. Y-77-355, 31 Jan 1978

(42) BASF AG, Department of Toxicology, unpublished study (VI/3), 17 Mar 1956

(43) Herbert et al. (1993): Fund Appl Toxicol 20, 348-359,

(44) NTP Technical Report on Toxicity Studies of 1,6-Hexanediamine Dihydrochloride. NIH Publication 93-3347, March 1993. Toxicity Report No. 24

(45) Johannsen FR et al. (1987): Subchronic Inhalation Toxicity of Hexamethylenediamine in Rats. Fund Appl Toxicol 9, 504-511

(46) Johannsen FR and Levinskas GJ (1987): Toxicological Profile of orally administered 1,6-hexane diamine in the rat. J Appl Toxicol 7, 259-263

(47) Horn HJ et al. (1957), J. Agric Fd Chem 5, 759-62.

(48) Monsanto Chemical Company, Environmental Health Laboratory unpublished study: Four week Study of Nylon Salt 6/6 Administered by Gavage to Sprague-Dawley Rats. DMEH project no. ML-81-100. 27 Oct 1982

(49) BASF AG, Department of Toxicology, unpublished study (79/518), 02 Jun 1980

(50) BASF AG, Department of Toxicology, unpublished study (81/230), Jan 1982

(51) BASF AG, Department of Toxicology, unpublished study: Activity of T 1624 in the in vitro mammalian cell transformation assay in the presence of exogenous metabolic activation (79/518), 29 Oct 1980

(52) BASF AG, Department of Toxicology, unpublished study: Activity of T 1624 in the in vitro mammalian cell transformation assay in the absence of exogenous metabolic activation (79/518), 31 Dec 1980

(53) Prival MJ et al. (1991). Bacterial mutagenicity testing of 49 food ingredients gives very few positive results, Muat. Res. 260, 321-329.

(54) Mortelmans K. et al.(1986). Salmonella Mutagenicity Tests: II. Results From the Testing of 270 Chemicals. Environ. Mutagen. 8, Suppl. 7, 1 - 119.

(55) BASF AG (2001), Experimental Toxicology and Ecology: Cytogenetic study in vivo with AH-Salz kristallisiert in the

mouse micronucleus test after two intraperitoneal administrations. Unpublished Report 26MO617/004157, 5 Dec 2001

(56) Cornu M.C. et al. (1988): In vivo and in vitro metabolism of di-(2-ethylhexyl) adipate a peroxisome proliferator, in the rat, Arch. Toxicol. Suppl. 12, 265-268

(57) Tinson D.J.: unpublished data ICI Central Tox. Lab., citet in BUA Report 196, Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart

(58) Short RD et al. (1991): A Two-Generation Reproduction Study in Rats Receiving Diets Containing Hexamethylenediamine. Fund Appl Toxicol 16, 490-494

(59) David RM and Heck H (1983): Localization of 1,6-(14C)Diaminohexane (HMDA) in the Prostate and the Effects of HMDA on Early Gestation in Fischer-344 Rats. Toxicol Letters 17, 49-55.

(60) U.S. Food and Drug Administration. Food and Drug Research Laboratories, Inc. Teratologic evaluation of FDA 71-50 (Adipic Acid) in mice. Final Report, 26 Feb 1973

(61) U.S. Food and Drug Administration. Food and Drug Laboratories, Inc. Teratologic Evaluation of Compound. FDA 71-50. Adipic Acid in Rabbits. Report PB-267 202, June 1974

(62) U.S. Food and Drug Administration. Food and Drug Research Laboratories Inc., Teratologic evaluation of FDA 71-50 (Adipic Acid) in hamsters. Final Report, 26 Feb 1973

(63) U.S. Food and Drug Administration. Food and Drug Research Laboratories Inc., Teratologic evaluation of FDA 71-50 (Adipic Acid) in rats. Final Report, 26 Feb 1973

(64) David RM and Heck H (1983): Localization of 1,6-(14C)diaminohexane (HMDA) in the Prostate and the Effects of HMDA on Early Gestation in Fischer-344 Rats. Toxicol Letters 17, 49-55.

(65) Rusoff et al. (1960) Intermediary metabolism of adipic acid. Toxicol Appl Pharmacol 2: 316-330

(66) Subramanyam B. et al. (1989), A cyclic imine intermediate in the in vitro metabolic conversion of 1,6 diaminohexane to 6-aminohexoic acid and caprolactam. Xenobiotica 19, 33-42