FOREWORD INTRODUCTION

ADIPIC ACID

CAS N°: 124-04-9

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, 20-23 April 2004

1. Chemical Name:	Adipic acid
2. CAS Number:	124-04-9
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Gebäude 9115
• Process used	The BUA Peer Review Process : see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 30 October 2003 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 15 October 2003 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search termsOECD/ICCA
8. Quality check process:	As basis for the SIDS-Dossier the IUCLID was used. All data have been checked and validated by BUA.
9. Date of Submission:	Deadline for circulation: 23 January 2004
10. Date of last Update:	Last literature search: IUCLID Chapters 1-4: 2003-01-02 Chapter 5: 2003-10-30

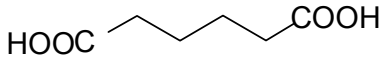
11. Comments:

OECD/ICCA - The BUA* Peer Review Process

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

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

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	124-04-9
Chemical Name	Adipic Acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

In limited studies in animals and humans it was shown that adipic acid is absorbed after oral administration, partially metabolized to various metabolites and CO_2 which are excreted via urine and breath, resp. None of the studies was conducted according to GLP.

Adipic acid is of very low acute toxicity. The oral LD_{50} in rats in a study similar to OECD TG 401 is approximately 5560 mg/kg bw. Clinical signs at lethal doses included acute dilatation of the heart and acute congestive hyperaemia, ulceration of glandular stomach (bleeding-corrosive gastritis), intestinal atony, pale liver and reddening of intestinal mucosa. The LD50 for mice was reported to be 1900 mg/kg bw. In an inhalation test similar to OECD TG 403 in rats neither mortality nor symptoms were observed during and after 4 hour exposure to 7700 mg/m^3 of adipic acid. Reduced appetite and activity were the only effects reported following occlusive dermal administration of 7940 mg/kg bw of adipic acid to 2 rabbits for 24 hours.

In rabbits, 50 % adipic acid suspensions were slightly irritating to the intact skin and moderately irritating to scarified skin. The neat material was a severe eye irritant in rabbits, with symptoms being reversible within 16 days. Respiratory irritation in animals is not sufficiently examined. Workers exposed over an extensive period (av. 9.2 years) complained of respiratory irritation at adipic acid concentrations of 0.47-0.79 mg/m^3. Due to the acidic character of the substance, a local irritation potential is plausible.

Despite the wide dispersive use of adipic acid, only very few cases of skin or respiratory tract sensitisation reactions are reported in humans. A sensitisation study in animals according to validated guidelines is not available. Overall, sensitisation is not expected for adipic acid.

There is no repeated inhalation toxicity study with histopathological examination of the nose available. Systemic effects after repeated inhalation have not been investigated in fully valid studies. There are no studies on repeated dermal application available. In a limited 2-year oral study adipic acid was of low repeated dose toxicity, however it was not tested according to modern standards. The NOAEL was 1 % for male rats (approx. 750 mg/kg bw/day) and higher doses (3 and 5 %) caused body weight retardation with no indication of specific target organ toxicity. The NOAEL for female rats was 1 % (approx. 750 mg/kg bw/day), the highest dose tested in females. In one volunteer no overt toxic symptoms were seen after oral administration of 7 g adipic acid per day for 10 days.

A variety of mutagenicity tests in vitro and in vivo have failed to demonstrate that adipic acid possesses genotoxic potential. A number of good quality Ames tests in *Salmonella typhimurium* similar to OECD TG 471 and an examination of chromosome damage in human lung cells in culture produced negative results. In gavage studies in male rats it did not induce chromosome damage in the bone marrow or dominant lethal mutations in a dose-response or time-trend pattern.

Adipic acid was not carcinogenic in a limited two-years feeding study where male rats were fed with up to 5 % (3750 mg/kg bw/day) adipic acid and female rats with 1 % (750 mg/kg bw/day).

No specific studies on fertility have been conducted. In a two-year feeding study in rats histopathological examination of testes, ovaries, and uterus revealed no evidence of an adverse effect on the reproductive organs up to

the highest doses tested (males approx. 3750 mg/kg bw/day, females approx. 750 mg/kg bw/day). Based on the available data there is no reason to expect specific reproductive toxicity of adipic acid.

Adipic acid was not embryo- or fetotoxic and not teratogenic up to the highest tested doses of 288, 263, and 250 mg/kg bw/day via oral administration to rats, mice, and rabbits, respectively. In none of these studies signs of maternal toxicity have been observed and the highest dose was well below the limit dose of 1000 mg/kg bw which would be a precondition for a fully valid negative study. In view of the low systemic toxicity of the compound, however, this endpoint seems to be adequately covered despite the limitations of the studies.

Environment

Adipic acid is a white, crystalline solid with a melting point of 152 °C, and a boiling point of 337.5 °C. The density of the solid is 1.36 g/ml at 25 °C. The vapor density in relation to air is 5.04. The vapor pressure is 9.7 Pa at 18.5 °C. The measured log K_{ow} is 0.093 at 25 °C. The solubility in water is 23 g/l at 25 °C. The flash point is 196 °C, the auto flammability (ignition temperature) 420 °C. Decomposition starts at 230 °C. pKa values of 4.34 and 5.44 indicate that under environmental conditions adipic acid is largely deprotonated.

With regard to its chemical structure adipic acid is not expected to hydrolyze under environmental conditions. According to a Mackay calculation level I the favorite target compartment of the substance (uncharged molecule) is water with 97 %. It has to be considered, that at very low concentrations of adipic acid expected in the environment, the substance is mostly present as anion (i.e. deprotonated). As anions are neither subject to volatilization nor to adsorption, the hydrosphere is also the target compartment for the deprotonated molecule. The Henry's law constant of 9.7×10^{-7} Pa m^3 mol^{-1} (Bond method) and of 8.8×10^{-2} Pa m^3 mol^{-1} (ratio of vapor pressure versus solubility) at 25 °C indicates that the compound has a low potential for volatilization from surface waters. The calculated half-life of adipic acid in air due to indirect photodegradation is $t_{1/2}$ = 2.9 days.

Adipic acid is readily biodegradable (MITI, comparable to OECD TG 301C: biodegradation 68 - 90 % after 14 days, OECD TG 301B: 91 % after 28 days, closed bottle test OECD TG 301D: 83 % after 30 days).
The bioconcentration factor BCF = 3 for adipic acid calculated from the octanol-water partition coefficient indicates that there is only a low potential for bioaccumulation in aquatic organisms. With a calculated K_{oc} value of 22, adipic acid can be regarded as a substance without geoaccumulation potential.

Concerning the toxicity of adipic acid to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The lowest valid effect data on acute fish toxicity was > 1000 mg/l for *Danio rerio* (96 h-LC_{50}) (pH 7.4 – 7.7). With *Daphnia magna* a 48 h-EC_{50}-value of 85.6 mg/l was observed. As the pH in the test solutions was in the range of 4 (500 mg/l) to 7.7 (15.6 mg/l), pH related effects on the daphnids cannot be excluded. In an algae growth inhibition test with *Desmodesmus subspicatus* the 96 h-E_bC_{50} was 26.6 mg/l and the 72 h-E_bC_{50} was 31.3 mg/l. The pH for the concentration of the EC50 was 6.0 at test begin and 8.2 after 96 h. Therefore, it can be concluded that the effects found in this study are likely not caused by pH effects. No tests are available on chronic toxicity of adipic acid.

Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the lowest acute effect concentration, the 96 h-EC_{50} of 26.6 mg/l of *Desmodesmus subspicatus*, a $PNEC_{aqua}$ of 27 µg/l was determined.

Exposure

Adipic acid is manufactured from a mixture of cyclohexanol (93 %) and cyclohexanone (7 %) by oxidative ring cleavage using concentrated nitric acid. Alternatively, it is manufactured from cyclohexane by catalytic oxidative ring cleavage. The global adipic acid manufacturing volume was estimated to be 1.8 million tonnes in 1995, and the manufacturing capacity amounted to 2.3 Mio tonnes in 1996 (USA 0.78 Mio. t/a, Japan 0.1 Mio. t/a, and Western Europe 0.92 Mio. t/a). In 2000, the global manufacturing volume is estimated to be about 2.7 Mio. tonnes by 19 adipic acid plants (Brazil 1, Canada 1, China 3, France 1, Germany 2, Italy 1, Japan 2, Korea 1, Singapore 1, Ukraine 1, United Kingdom 1, USA 4).

Adipic acid is a basic chemical but is also used in consumer products. The most important product manufactured from adipic acid is nylon 66 (up to 70 % of the production). In foodstuffs adipic acid is used e.g. as a dietetic food additive, as acidulating agent for gelatine and jams, and as a neutralizing agent and buffer, in concentrations up to 10,000 mg/kg foodstuff. Adipic acid is present in marketed preparations registered in the product registers of Switzerland, Sweden, Denmark, Finland and Norway.

The exhaust gases of the manufacturing plant of the Sponsor company are lead to a thermal exhaust purification plant. Exhausts from the manufacturing and processing areas, where particulate adipic acid might occur, are led to air filters. Waste from the manufacturing and processing of adipic acid is incinerated in an incinerator for hazardous wastes. Wastewater is lead to a wastewater treatment plant. No adipic acid is detected in its effluent (detection limit 20 µg/l).

No information is available on the occurrence of adipic acid in the hydrosphere. Adipic acid was detected in soil samples (215 - 568 and 2,050 µg/kg). Adipic is formed in the atmosphere by photooxidation. Atmospheric concentrations vary from 0.9 ng/m^3 to 9 µg/m^3 (background to urban smog). Adipic acid is a component of tobacco smoke. It was detected in particle emissions from wood and foliage combustion. Adipic acid occurs in beet juice, ripe fruits of Morinda citrifolia, and rice straw, indicating biotic formation.

In the Sponsor company, regular surveys in the working area for any possible exposure to a dangerous substance at different work situations and appropriate control measures are performed. To protect workers from exposure several precautionary and protective measures are taken by the Sponsor company. Since exposure of manufacturing workers to adipic acid is unlikely to occur, no workplace measurements are available. In another company in the sponsor country there is no exposure of manufacturing workers either. Due to filling operations there was observed a dust concentration of 1 mg/m3 (8 h TWA) in the storage area. However, in another country data exist indicating occupational exposure potential.

Based on the ready biodegradability and the low bioaccumulation potential of adipic acid, a significant indirect exposure of the general public via the environment is not expected.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health
The chemical possesses properties (eye and respiratory tract irritation) indicating a hazard for human health. Although these hazards do not warrant further work, they should nevertheless be noted by chemical safety professionals and users, especially at the workplace.

Environment
The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure level, they should nevertheless be noted by chemical safety professionals and users.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number:	124-04-9
IUPAC Name:	Hexanedioic Acid
Molecular Formula:	$C_6H_{10}O_4$
Structural Formula:	$HOOC\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}COOH$
Molecular Weight:	146.14 g/mol
Synonyms:	Adipic acid
	1,4-Butanedicarboxylic acid
	1,6-Hexanedioic acid
	Adipinic acid

1.2 Purity/Impurities/Additives

Purity of the commercial product (Davis 1985):	> 99.6 % w/w (food-grade product)
Purity of the commercial product (CCOHS 2003):	Adipic acid is commercially produced on large scale with a purity of 99.8 % because of the extreme sensitivity of polyamide synthesis to impurities. Typical impurities include other acids (monobasic acids and lower dibasic acids) (60 ppm), nitrogenous materials, trace metals such as iron (2 ppm) and other heavy metals (10 ppm), arsenic (3 ppm) and hydrocarbon oil (10 ppm)
Impurities (Davis 1985):	water (< 0.2 % w/w)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference	IUCLID
Substance type	Organic compound		1.1.1
Physical state	White, odorless, crystalline solid*	Kennedy 2002	1.1.1
Melting point	152 °C	Merck 2001	2.1
Boiling point at 1013 hPa	337.5 °C	Davis 1985; Merck 2001	2.2
Density at 25 °C	1.36 g/cm³	Beilstein 2003	2.3
Vapour pressure at 18.50 °C	9.7 Pa	Kirk-Othmer 1991	2.4
Octanol/water partition coefficient (log K_{ow}) at 25 °C	0.093 (OECD TG 107)	BASF 1988a	2.5
Water solubility at 25 °C	23 g/l	MITI 1992	2.6.1
Flash point (Closed cup)	196 °C	Davis 1985	2.7
Auto flammability (ignition temperature)	420 °C	Davis 1985	2.8
Ionization constants at 25 °C	pKa1 = 4.34 pKa2 = 5.44	Davis 1985	2.12
Conversion factors at 25 °C (calculated)	1 ppm = 5.96 mg/m^3 1 mg/m3 = 0.168 ppm	CCOHS 2003	2.14
Lower flammable (explosive) limit	35 g/m3	Davis 1985	2.14
Dust cloud ignition temperature	550 °C	Davis 1985	2.14
pH value at 25 °C	2.7 (saturated solution) 3.2 (0.1% solution)	Davis 1985	2.14
Vapour density in relation to air	5.04	Kirk-Othmer 1991	2.14
Thermal decomposition (decarboxylation)	230 °C	Verschueren 1996	2.14

* In crystalline form, the substance appears colourless, while as a powder, it appears white

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

2.1.1 Production

There are several methods to produce adipic acid.

The method applied by Bayer starts from cyclohexane, which is used to produce KA-oil, a mixture of cyclohexanol (93 %) and cyclohexanone (7 %). KA-oil is then oxidised with nitric acid to yield adipic acid (Bayer Polymers 2003).

The first step of another process - used in Eastern Germany – is the hydration of phenol to obtain cyclohexanol, which is further oxidised to adipic acid (NRI 2003).

The organic oxidation products are (BUA 1994):

ca. 95 % adipic acid
ca. 3 % glutaric acid
ca. 2 % succinic acid

During the oxidation process, NO_2, NO, N_2O and N_2 are formed. The main product is nitrous oxide (N_2O) (Mainhardt and Kruger 2001).

In the third method, adipic acid is manufactured from cyclohexane by catalytic oxidative ring cleavage (BUA 1994).

Weissermel and Arpe (1998) report the world wide manufacturing capacity of adipic acid to amount 2.3 million metric tonnes in 1996. These authors also specify the regions and the production capacities (Table 2).

Table 2 Production capacities and volumes in 1995/1996

Region/Country	Capacity 1996 (million metric tonnes)	Production 1995 (million metric tonnes)
USA	0.78	0.863
Japan	0.1	0.077
Western Europe	0.92	0.528
thereof Germany	0.3	0.25
others	0.5	0.33*
Total volume	2.3	1.8*

*data from Mainhardt and Kruger (2001), all other data from Weissermel and Arpe (1998)

Mainhardt and Kruger (2001) estimate the worldwide production volume to be 2.7 million tonnes in 2000, compared to 1.8 million tonnes in 1995. Worldwide, there are 19 adipic acid plants (Brazil 1, Canada 1, China 3, France 1, Germany 2, Italy 1, Japan 2, Korea 1, Singapore 1, Ukraine 1, United Kingdom 1, USA 4; Mainhardt and Kruger 2001). In Germany, a third plant became operational in 2002 (NRI 2003).

In Germany adipic acid is manufactured in an industrial scale by three producers. The Bayer adipic acid production unit is in the Bayer AG Uerdingen industrial park (Bayer Polymers 2003).

In 2002 quantities of adipic acid manufactured in Germany were estimated to be 350 000 tonnes/a (Bayer Polymers 2003).

2.1.2 Processing and Use

Adipic acid is the most important aliphatic dicarboxylic acid produced on an industrial scale (Davis 1985). The total production volume of Bayer Polymers is processed at 2 Bayer sites (Uerdingen and Dormagen) (Bayer Polymers 2003).

Adipic acid is a basic chemical but is also used in consumer products. The German GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA 1994) estimated the major uses of adipic acid (Table 3).

Table 3 Adipic acid uses (estimates, BUA 1994)

Uses	Use by Bayer 1990 (%)	Use by BASF 1990 (%)
Monomer for polyester and polyester polyurethanes	80	20
Monomer for polyamides		60
Synthetic intermediate in manufacturing of 1,6-hexanediol	15	
Synthetic intermediate in manufacturing of plasticizers, dyes, pharmaceuticals, insecticides, adhesives	5	7
Preparation of leather treatment formulations		2
Micellaneous uses (e.g. perfume fixative and foodstuff additive)		

On a global scale, the most important product manufactured from adipic acid is Nylon 66. Up to 70 % of the production of adipic acid were used in fibre manufacturing in 1996 (e.g. 68 % in the USA, 46 % in Western Europe and 33 % in Japan; Weissermel and Arpe 1998). In foodstuffs adipic acid is used as a dietetic food additive, as acidulating agent for gelatine and jams, and as a neutralizing agent and buffer for other foodstuffs (Weissermel and Arpe 1998). In the EU, adipic acid (E-No. 355) additions to several food products are permitted in concentrations of up to 10 000 mg/kg depending on the food product (EU Commission 1991; ZZulV 1998).

Adipic acid is contained in products listed in the Danish, Finnish, Norwegian and Swedish Product Registers (SPIN Database 2003). Product types are e.g. process regulators, adhesives and binding agents, paint, lacquers and varnishes, cleaning agents. In the Norwegian and Swedish product register also products intended for consumer use are registered that contain adipic acid. In the Swiss product register 300 products are registered, among them 42 consumer products with concentrations of adipic acid up to 50 %. Product types are e.g. cleaning agents (Swiss Product Register 2003). Although Kennedy (2002) reports that adipic acid is also widely used in lubricating oil additives, it is assumed that adipic acid is not used in this application. Monohydric alcohol esters of adipic acid and selected adipate polyesters are used as synthetic lubricants.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Releases of adipic acid into the environment may occur during manufacturing, processing and use.

Information on exposure from manufacturing and processing of the chemical is available for the Bayer adipic acid manufacturing and processing plants in Uerdingen, Germany (Bayer Polymers 2003).

The manufacturing and processing plants consist of dedicated systems in which only adipic acid is manufactured, separated, stored and processed (Bayer Polymers 2003).

Manufacturing and processing of adipic acid are executed in closed systems (e.g. sampling without dead volume, gas-shuttle pipe for filling processes). Cleaning of the reactors takes place only in the case of maintenance (c/f Chapter 2.3). From the manufacturing plant to the Bayer processing plants, adipic acid is transported in bulk transporters. It is introduced into the processing plant via closed pneumatic systems, thus preventing any emissions under normal operating conditions (Bayer Polymers 2003).

The exhausts from manufacturing of adipic acid contain nitrous oxide (N_2O) as the major reduction products of nitric acid. Adipic acid production also leads to the release of non-methane volatile organic compounds (NMVOC), carbon monoxide (CO) and nitrogen oxides (NO_x) (Mainhardt and Kruger 2001). To remove the organic and carbon monoxide emissions and to reduce the nitrous oxide and the other nitrogen oxides to nitrogen (N_2), the exhaust gases are led to a thermal exhaust purification plant. Exhausts from the manufacturing and processing areas, where particulate adipic acid might occur, are led to air filters (Bayer Polymers 2003).

Following the Official Emission Declaration of the year 2002, the plants manufacturing and processing adipic acid at the Bayer Uerdingen and Dormagen sites released less than 7 tonnes/a of adipic acid (total, in the form of dust) into the atmosphere (Bayer Polymers 2003).

Waste from the manufacturing and processing of adipic acid is incinerated in an incinerator for hazardous wastes (Bayer Polymers 2003).

At the Bayer adipic acid plant in Uerdingen, wastewater with significant organic load is separated from wastewater with minor load. Wastewater from the Dormagen and Uerdingen processing plants – which in general contains only minor amounts of adipic acid – is led to the respective industrial wastewater treatment plants. The significantly loaded wastewater is used to recover adipic acid. The extracted wastewater is stripped and the remainder is led to the Uerdingen industrial wastewater treatment plant, together with the wastewater with minor load (Bayer Polymers 2003).

Due to its content in some other compounds, the concentrated sewage sludge is incinerated in a hazardous waste incinerator (Bayer Polymers 2003).

24 h/d, 365 d/a, the air and water emissions of the integrated production sites at Uerdingen and Dormagen are monitored by Environmental Surveillance Groups which operate independently of any manufacturing unit. These groups are equipped with mobile detectors for various potential emissions. They also operate stations with measuring and sampling devices for air and water (Bayer Polymers 2003).

In 2002, in the effluent of the Uerdingen and Dormagen wastewater treatment plants, adipic acid was not detectable by the daily monitoring with a determination limit of 20 µg/l (Bayer Polymers 2003).

The effluent of the Bayer Uerdingen plant passes into the Rhine. Taking into account the 10 percentile of the river flow (1050 m^3/s), the max. dilution factor (1000) and the detection limit of 20 µg/l (Bayer Polymers 2003) for the receiving river a

Predicted Environmental Concentration (PEC_{local}) of < 0.02 µg/l

is calculated. The same result is obtained for the Dormagen site.

Exposure information from other production and processing sites is not available.

Further environmental releases are expected from downstream life-cycle stages like processing and consumer use of foodstuffs and formulation and consumer use of leather treatment products and perfumes. No information about releases from these life-cycle steps is available.

According to information from BUA (1994) adipic acid is not detectable in polyamide 66. No detection limit is given. From this is can be concluded that unreacted adipic acid contained as possible residue in end-products is not expected to contribute significantly to total environmental releases.

2.2.2 Photodegradation

The calculated half-life of adipic acid in air due to indirect photodegradation is 2.9 days, considering a reaction rate constant of 5.59×10^{-12} cm^3 $molecule^{-1}$ s^{-1} and a daily mean OH-radicals concentration of 500 000 radicals cm^{-3} (Bayer AG 2003).

The ozonolysis of several dicarboxylic acids including adipic acid was measured in liquid phase to elucidate the fate of these acids in aerosols. In one series of experiments, ozone was produced in an ozone generator, in another series it was produced in the liquid phase by UV irradiation. Adipic acid concentrations ranged from 0.001 to 0.1 mol/l. Kinetics were determined by measuring ozone decay and carboxylic acid decay. The measured ozonolysis rate constant (k) for the adipic acid in 0.1 mol/l aqueous solutions was 1.7×10^{-3} l mol^{-1} s^{-1}. The photoassisted ozonolysis rate constant was 2.8×10^{-3} l mol^{-1} s^{-1}. The results indicate that ozonolysis and photoassisted ozonolysis are no significant removal pathways for adipic acid. The authors estimated the ozone-dependent life-time of adipic acid in air to be about 13 000 years, assuming an ozone mixing ratio of 100 ppbv, which is an upper limit for its summer time mid-latitude continental northern hemisphere values. For ozonolysis related conversion times are expected (Nepotchatykh and Ariya 2002).

Matsumoto and Kozai (1995) examined the decomposition products and pathways of irradiated adipic acid in water. They estimated the half-life to be 62 min during ozone treatment with concomitant UV irradiation. Unfortunately, of this study only an English abstract is available, therefore the reliability of this paper cannot be established unequivocally.

The photodegradation data are compiled in Table 4.

Table 4 Photodegradation of adipic acid (IUCLID 3.1.1)

Parameter	Method	Result	Reference
Indirect photodegradation in air	Calculation for 24 h-day, 500 000 OH/cm^3	$t_{1/2}$ = 2.9 d	Bayer AG 2003*
Photodegradation	Ozonolysis photoassisted ozonolysis	ca. 13 000 years	Nepotchatykh and Ariya 2002
Photodegradation	UV and Ozone	$t_{1/2}$ = 62 min	Matsumoto and Kozai 1995

2.2.3 Stability in Water

Adipic acid is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups (Harris 1990).

2.2.4 Transport between Environmental Compartments

According to the Mackay Fugacity Model Level I (calculated via SRC-PCKOWWIN v. 1.66), the main target compartment for adipic acid (uncharged molecule) is water with 97 % (Table 5, Bayer AG 2003).

Table 5 Input parameters and results of the Mackay Fugacity Model Level I

Input Parameters	Value
Temperature	25 °C
Vapour Pressure	13.9 Pa
Water Solubility	23 g/l
Log Kow	0.093
Results **Compartment**	**Calculated distribution**
Air	2.96 %
Water	97.0 %
Soil	0.0095 %
Sediment	0.0096 %
Suspended Sediment	0.006 %
Fish	< 0.001 %
Aerosol	< 0.001 %

The distribution of adipic acid between aqueous solutions and air was calculated using the Bond-Method. A Henry´s law constant of 9.7 x 10^{-7} Pa m^3 mol^{-1} at 25 °C was obtained (Bayer AG 2003). From the ratio of vapour pressure to solubility at 25 °C (input parameter see Table 1 and 5, results see Table 6), a Henry´s law constant of 8.8 x 10^{-2} Pa m^3 mol^{-1} is obtained (Bayer AG 2003).

These data indicate that adipic acid is essentially non-volatile from waters according to the scheme of Thomas (1990).

It has to be considered, that at very low concentrations of adipic acid expected in the environment, the substance is mostly present as anion (i.e. deprotonated). As anions are neither subject to volatilization nor to adsorption, the hydrosphere is also the target compartment for the deprotonated molecule.

Table 6 Distribution in the environment (IUCLID 3.3.2)

Parameter	Method	Result	Source
Distribution throughout environmental compartments	Calculated according to Mackay Fugacity Model Level I at 25 °C	Air 2.96 % Water 97.0 %	Bayer AG 2003
Fugacity Water – air Henry´s law constant	Bond-Method (calculated)	9.7×10^{-7} Pa m^3 mol^{-1}	Bayer AG 2003
Henry´s law constant	Calculated from vapor pressure/solubility	8.8×10^{-2} Pa m^3 mol^{-1}	Bayer AG 2003

2.2.5 Biodegradation

Several experimental data proof that adipic acid is readily biodegradable.

An aerobic ready test was performed according to the national Japanese standard method comparable to the OECD TG 301C guideline. After a period of 14 days 68 - 90 % biodegradation was observed (MITI 1992).

In a ring test with 10 participating laboratories, the reliability of the OECD TG 301 E ready biodegradability test was elucidated in 16 studies using several compounds of widely differing biodegradability including adipic acid. All laboratories observed a ready biodegradability of this dicarboxylic acid with a degradation of at least 86 % and an average degradation of 96.6 +/- 4.6 % after 19 d (Haltrich et al. 1980).

Gerike and Fischer (1979) studied the biodegradation of a group of substances in several different tests. A test according to the Japanese MITI (similar to OECD TG 301 C), 92 % biodegradation related to BOD was achieved after 14 days. In an aerobic modified Sturm test (CO_2 evolution) according to OECD TG 301 B guideline, adipic acid was degraded by 91 % in terms of CO_2 evolution after a period of 28 days. In a closed bottle (OECD TG 301 D) 83 % of the substance was degraded after 30 days. In a test according to the modified OECD screening test (OECD TG 301 E) 96 % (related to DOC) was degraded after a period of 19 days.

An 84 % conversion of adipic acid carbon content to carbon dioxide was found after 30 days aerobic incubation in soil (Sharabi and Bartha 1993).

In addition, a waste water treatment simulation test (OECD TG 303 A) was performed with adipic acid.. This test is characterised to work under steady state conditions, as a continuous flow system and to employ an organic base medium maintaining nutrient competition at all times. In only one day a DOC removal of 99 % was achieved (Gerike and Fischer 1979).

In the Bayer industrial wastewater treatment plant of the Uerdingen site the comparison of influent and effluent concentrations shows that adipic acid is eliminated completely. In 2002, the maximum concentration in the influent of the wastewater treatment plant (24 h sample) was 11.1 mg/l adipic acid. In the effluent no adipic acid was detected in 365 samples with a determination limit of 20 µg/l (Bayer Polymers 2003). From these data it can be concluded that the elimination of the Uerdingen industrial wastewater treatment plant exceeds at least 99 %.

The key data of the biodegradation studies are listed in Table 7.

Table 7 Tests on biodegradation of adipic acid (IUCLID 3.5)

Inoculum	Procedure	Result	Reference
Aerobic activated sludge	MITI (comparable to OECD TG 301C)	68 - 90 % after 14 d	MITI 1992*
Aerobic domestic sludge	OECD TG 301E	97 % after 19 d	Haltrich et al. 1980
Aerobic domestic sludge	OECD TG 301B	91 % after 28 d	Gerike and Fischer 1979
Aerobic domestic sludge	OECD TG 301D	83 % after 30 d	Gerike and Fischer 1979
Aerobic domestic sludge	OECD TG 301E	96 % after 19 d	Gerike and Fischer 1979
Aerobic activated sludge	MITI (comparable to OECD TG 301C)	92 % after 14 d	Gerike and Fischer 1979
Soil	Conversion of C content of adipic acid into CO_2	84 % after 30 d	Sharabi and Bartha 1993
Activated sludge	OECD TG 303A	99 % after 1 d	Gerike and Fischer 1979

2.2.6 Bioaccumulation

Measured bioconcentration factors (BCF) for adipic acid are not available (Table 8). However, from the octanol-water partition coefficient a bioconcentration factor (BCF) can be calculated with the BCF Program (v2.14). Using log K_{ow} = 0.093, the calculated BCF was 3 (log BCF 0.5, Bayer AG 2003). Kennedy (2002) reports that the BCF estimated from Kow, is 0.68, but does not report how this estimate was obtained. However, the calculated BCF indicate that there is only a low potential for bioaccumulation of adipic acid in aquatic organisms.

Table 8 Bioaccumulative properties of adipic acid (IUCLID 3.7)

Parameter	Method	Result	Source
Bioconcentration factor	Calculated	BCF = 3	Bayer AG 2003
Bioconcentration factor	Estimated	BCF = 0.68	Kennedy 2002

2.2.7 Geoaccumulation

The distribution between the organic phase of soil or sediments and the porewater was calculated using QSAR. With the PCKOC program (v1.60), a K_{OC} value of 22 was calculated (Bayer AG 2003). Similarly, in a hardly documented study a K_{OC} of 26 was reported (Kennedy 2002). Since the deprotonation of the carboxylic groups might affect the adsorption on the organic phase, the K_{OC} may to be sensitive to pH. Thus, if released to soil, adipic acid is expected to have a very high mobility. According to the scheme of Litz (1990) adipic acid can be regarded as a substance with no geoaccumulation potential. Results of calculated and measured K_{OC} values can be found in Table 9.

Table 9 Geoaccumulative properties of adipic acid (IUCLID 3.3.1)

Parameter	Method	Result	Reference
Soil organic carbon-water distribution coefficient	Calculated with PCKOCWIN, V1.60	K_{OC} = 22	Bayer AG 2003
Soil organic carbon-water distribution coefficient	Reversed phase HPLC	K_{OC} = 26	Kennedy 2002

2.2.8 Environmental Monitoring

No information is available on the occurrence of adipic acid in the hydrosphere (BUA 1994).

Adipic acid occurs in the atmosphere (Table 10). It is formed in the atmosphere (Calvert et al. 2002) presumably from cycloalkenes (e.g. cyclohexene) and other precursors by photooxidation (Cronn et al. 1977; Hatakeyama et al. 1987). Kawamura and Kaplan (1987) examined motor exhausts of passenger cars and found 1.1 and 4.7 µg/m^3 adipic acid suggesting that adipic acid found in the atmosphere is also a combustion product.

In samples of soil from Los Angeles and in bog sediments from the Sierra Nevada Mountains, 215 - 568 and 2050 µg adipic acid/kg, respectively, were detected by Kawamura and Kaplan (1987). These authors concluded that adipic acid detected in the soil and sediment samples is of predominantly atmospheric origin.

Table 10 Atmospheric concentrations of adipic acid

Location	Medium	Content	Reference
Antarctica	background	0.9 ng/m³	Limbeck and Puxbaum 1999
Gent	urban aerosols	1.1 – 1.3 ng/m³	Kubatova et al. 2002
Heraklion	urban aerosols	0.27 and 1.07 ng/m^3 (free acid), 1.61 ng/m^3 (adipic acid salts)	Stephanou and Stratigakis 1993
Las Vegas, University of Nevada	urban aerosol	0 – 42 ng/m^3.	Tran, Steinberg and Johnson 2000
Los Angeles	smog	1500 – 8900 ng/m³	Cronn et al. 1977
Los Angeles	4 rain water samples	0.0073 - 0.18 mg/l	Kawamura, Steinberg and Kaplan 1985
Los Angeles	2 fog samples	0.38-0.52 mg/l	Kawamura, Steinberg and Kaplan 1985
Los Angeles	aerosol	12 – 484 ng/m³	Kawamura and Kaplan 1987
Los Angeles	dust	5.9 - 11.4 µg/g	Kawamura and Kaplan 1987
Los Angeles (greenhouse)	urban enriched with plant emissions	ND*-32 ng/m^3	Kawamura and Kaplan 1987
Los Angeles (1993)	aerosol	0.0 – 24.1 ng/m^3 (average: 7.5 ng/m^3),	Fraser, Cass and Simoneit 2003
Los Angeles	urban	14 ng/m³	Limbeck and Puxbaum 1999
San Nicolas Island (vicinity of Los Angeles, 1993)	aerosol	0.37 – 6.00 ng/m^3 (average: 3.43 ng/m^3)	Fraser, Cass and Simoneit 2003
South Africa	background	7.9 ng/m³	Limbeck and Puxbaum 1999
Sonnblick Observatory close to Salzburg, Austria	background	4.4 ng/m³	Limbeck and Puxbaum 1999
Tokyo	urban	31 ng/m³	Limbeck and Puxbaum 1999
Tokyo	urban aerosol	31 – 79 ng/m³	Sempere and Kawamura 1994
Tokyo	urban snow	0.94 – 3.07 µg/l	Sempere and Kawamura 1994
Tokyo	urban rain water	0.18 – 7.78 µg/l	Sempere and Kawamura 1994
Vienna	urban	117 ng/m³	Limbeck and Puxbaum 1999
Western Pacific Ocean between Japan and New Zealand	background rain water	1.75 – 10.8 µg/l (average: 5.20 µg/l)	Sempere and Kawamura 1996

*Not detectable

Adipic acid is a component of tobacco smoke (Graedel 1978, cited according to BUA 1994). Adipic acid was detected in particle emissions from the fireplace combustion of several woods (Rogge et al. 1998; Fine, Cass and Simoneit 2002) and from foliage fuel combustion (Hays et al. 2002).

Adipic acid is detectable in the ventilation system above cooking appliances (Schauer et al. 2002). Adipic acid occurs in beet juice (Merck 2001), ripe fruits of Morinda citrifolia (Indian Mulberry, Noni) (Farine et al. 1996) and rice straw (Pramanik et al. 2001), indicating biotic formation. Honey obained from the New Zealand Rewarewa tree (Knightea excelsa) contained adipic acid concentrations of 0.2 - 0.6 mg/kg (Wilkins, Lu and Tan 1995).

2.3 Human Exposure

2.3.1 Occupational Exposure

During manufacturing and processing of adipic acid workers may be exposed through the inhalational and dermal routes.

Du Pont (2001) compiled occupational exposure data of personnel including construction personnel, contractors and plant employees at several sites handling dicarboxylic acids presumably in the USA. The maximum TWA (time weighted average) of 14 samples taken for a group of 16 persons occurred during loading operations and was 15 mg/m^3, with an average TWA of 2.3 mg/m^3. All other results with other groups were below the ACGIH Threshold Limit Value (8 h-TWA) and the Workplace Environmental Exposure Level, both for adipic acid at 5 mg/m^3. The exposure level of other plant staff, e.g. manufacturing personnel, was 1 - 2 orders of magnitude less. Du Pont characterized the results by "LOGAN" (Lognormal Analysis program) which predicts exposure for an entire group in a given workplace based on a limited number of samples. LOGAN maintained that employee risk of overexposure is less than 5 % (Du Pont 2001).

In Uerdingen at the Bayer site, adipic acid is manufactured in a closed system (c/f Chapter 2.2.1.1) by oxidation of KA-oil with nitric acid, phase separation and distillation (Bayer Polymers 2003).

Leakage in the manufacturing unit would be recognized due to the odour of its precursors (e.g. cyclohexanone), its oxidative agent (nitric acid), or its byproduct nitrogen oxide and due to the high visibility of nitrogen oxides (Bayer Polymers 2003).

Regular surveys in the working area for any possible exposure to a dangerous substance at different work situations and appropriate control measures are performed. However, since adipic acid is not classified as a dangerous substance and the exposure to adipic acid is very low (see below), no specific workplace measurements were performed during the last years (Bayer Polymers 2003).

To protect workers from exposure several precautionary and protective measures are taken. These measures include technical equipment like suction devices at filling and sampling stations as well as appropriate personal protection equipment which is prescribed in detail for different work situations e.g. during sampling, maintenance and repair work. For sampling, devices without dead volume are used and the persons involved have to wear goggles and gloves (DIN EN 374-3). In case of dust formation, particles filters, e.g. DIN 3181 P2, have to be used. Depending on the work to be done during maintenance, a gas filter mask or a respirator with independent air supply has to be used as well as full protective clothing. Occupational exposure is therefore not expected to occur (Bayer Polymers 2003).

Downstream users of adipic acid are informed also by way of a material safety data sheet on the recommended safety measures (see above). The workplace situation is equally controlled at the Bayer processing sites (Bayer Polymers 2003).

There is no experience with biomonitoring of adipic acid in the Sponsor company.

2.3.2 Consumer Exposure

The major use of adipic acid is processing to polymers which leads to the incorporation of adipic acid into the polymer chain. Following processing to polyamide 66, adipic acid is not detectable in the end product. There is no information available on the biotic or abiotic cleavage back to adipic acid (BUA 1994).

Adipic acid is a secondary plant product which occurs in edible plant parts (BUA 1994) and in rice straw (Pramanik et al. 2001). It is also an additive to foodstuffs and may be ingested with food products (Kennedy 2002). In the EU, adipic acid (E-No. 355) additions to several food products are permitted in concentrations of up to 10,000 mg/kg depending on the food product (EU Commission 1991, ZZulV 1998). It is assumed that the ADI (acceptable daily intake, 0 - 5 mg/kg bw) is easily exceeded (ZZulV 1998).

On the other hand, the Joint FAO/WHO Expert Committee on Food Additives (WHO 2000) examined the use of adipic acid and 46 other aliphatic primary alcohols, aldehydes, carboxylic aids, acetals and esters containing additional oxygenated functional groups. The committee reported that adipic acid is also used as a flavoring agent in food in Europe and in the USA. The daily uptake of adipic acid was estimated to be 12 µg/capita in Europe and 18 000 µg/capita in the USA (WHO 2000), which equals to a daily intake less than 0.0002 mg/kg bw and 0.3 mg/kg bw in Europe and in the USA, respectively.

Based on the ready biodegradability and the low bioaccumulation potential of adipic acid, a significant indirect exposure of the general public via the environment is not expected. However, an intentional human exposure may occur due to its application as a food additive.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

Due to its acidic character local irritation as was demonstrated for the eye in experimental animals (BASF 1978a) is the main toxicological characteristic of adipic acid.

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

After oral administration by gavage of radioactive adipic acid to fasted rats up to 70 % of the dose was exhaled as CO_2. In the urine the parent compound adipic acid and metabolic products identified as urea, glutamic acid, lactic acid, beta-ketoadipic acid and citric acid were found (percentages not specified). Adipic acid was metabolized by beta-oxidation in a similar fashion as fatty acids and acetate was a metabolite of adipic acid. Radioactive glycogen was isolated in experiments where glycogen formation in the liver was encouraged by oral administration of glucose together with radioactive adipic acid (Rusoff et al. 1960).

When adipic acid or its sodium salt was administered to non fasted rats, rabbits and one dog 18 – 71 % of the doses were excreted in the urine. Breath was not analyzed in these studies (Mori 1918; Bernhard and Andreae 1937; Enders 1941). In an oral 28-day subacute study in rats excretion of adipic acid was similar from day 1 to 28, indicating that adipic acid did not accumulate during the treatment. Breath was not analyzed, (Enders 1941). It is unclear whether the methods of detection in these early studies were reliable.

Studies in Humans

Adipic acid was orally administered to humans to investigate compound excretion. The highest dose administered in one volunteer was 70 g over 10 days. 3 other persons took 19 to 23.4 g over up to 9

days. 15 - 75 % of the adipic acid dose was found unchanged in the urine after oral administration of up to 7 g of adipic acid over up to 10 days to 7 volunteers. Breath was not analyzed, and it is unclear whether the methods of detection used were reliable (Weitzel 1942 and 1947).

Conclusion

In limited studies in animals and humans it was shown that adipic acid is absorbed after oral administration, partially metabolized to various metabolites and CO_2 which are excreted via urine and breath, resp. None of the studies was conducted according to GLP.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

In a study similar to OECD TG 403, neither mortality, toxic symptoms nor macroscopic pathological changes were observed in 20 rats exposed for 4 hours (nose only) to the maximal attainable concentration of 7700 mg/m^3 of adipic acid (99.8 %) dust. 50 % of the particles had a MMAD below 3.5 µm (BASF 1981).

Dermal

No lethality was reported in rabbits following occlusive dermal administration of 5010 (n = 1) and 7940 mg/kg bw (n = 2) of 40 % adipic acid in corn oil for 24 hours. Animals showed reduced appetite and activity and the viscera were normal at necropsy after 14 days observation (Solutia Inc. 1975). Due to the low animal number the study is of limited reliability, however the result is consistent with the low acute oral toxicity.

Oral

In rats, an LD_{50} value of 5560 mg/kg bw was established in a study similar to OECD TG 401 performed with single doses up to 10 000 mg/kg bw of adipic acid (99.8 %) administered as 50 % suspension in carboxymethyl cellulose vehicle. Mortality was seen during the first 48 hours. Lethal doses caused acute dilatation of the heart and acute congestive hyperaemia, ulceration of glandular stomach (bleeding-corrosive gastritis), pale liver, intestinal atony and reddening of intestinal mucosa (BASF 1978c). Animals that survived to termination at 14 days showed no gross pathological changes. The doses used in this test were in excess of the currently accepted limit dose.

No signs of toxicity were observed following administration of a single dose of 5000 mg/kg bw of adipic acid (suspended in saline) to ten male rats (Litton Bionetics Inc. 1974).

In mice, an LD_{50} value of 1900 mg/kg bw was established after the administration of adipic acid (6 % solution in 0.5 % methyl cellulose) to groups of 13 male animals. Autopsy of animals that died during the experiment showed distention of the stomach and irritation and hemorrhage of the intestines as well as spastic contraction of the caecum. Initial mortality developed overnight and deaths continued throughout the first week, survivors appeared normal (Horn et al. 1957).

Studies in Humans

There are no acute toxicity studies in humans reported. No overt toxic symptoms were reported after oral administration of up to 7 g of adipic acid per day, for 10 days to one volunteer (100 mg/kg bw. per day) to investigate compound excretion (see chapter 3.1.1: Toxicokinetics, Metabolism and Distribution, Weitzel, 1942 and 1947).

Conclusion

Adipic acid is of very low acute toxicity. The oral LD_{50} in rats in a study similar to OECD TG 401 is approximately 5560 mg/kg bw. Clinical signs at lethal doses included acute dilatation of the heart and acute congestive hyperaemia, ulceration of glandular stomach (bleeding-corrosive gastritis), intestinal atony, pale liver and reddening of intestinal mucosa. The LD_{50} for mice was reported to be 1900 mg/kg bw. In an inhalation test similar to OECD TG 403 in rats neither mortality nor symptoms were observed during and after 4 hour exposure to 7700 mg/m^3 of adipic acid. Reduced appetite and activity were the only effects reported following occlusive dermal administration of 7940 mg/kg bw of adipic acid to 2 rabbits for 24 hours.

3.1.3 Irritation

Skin Irritation

Studies in Animals

500 mg of a 50 % aqueous suspension of adipic acid (99.8 %) was tested on intact and scarified skin of six rabbits, respectively. The compound was applied to an area of 5 x 5 cm, covered and held in contact for 24 hours. Responses were scored immediately after dosing (24 hours), 3 and 8 days. Reversible reddening was observed at the intact skin (scored 2-3 on a scale up to a maximum of 4) which disappeared after three days. Mild to severe reddening and edema was observed at the scarified skin (scores 24 h: 2, 3 days: 0 - 2). These effects were reversible after 1 week (all scores 0) and scale formation was observed (BASF 1978d). In similar experiments rabbits were exposed semi-occlusively to doses of 500 mg of a 50 % paste of adipic acid (99.9 %) in propylene glycol and held in contact for up to 24 hours. Responses were scored immediately after dosing. Slight to mild irritation was found in 3/6 rabbits (Haskell 1974). Adipic acid produced mild to no skin irritation when tested on the shaved intact skin of guinea pigs at a concentration of 50 % in propylene glycol (Haskell 1974).

In another study 99.8 % adipic acid or 80 % aqueous paste were applied occlusively on intact skin of the back and the ear of 2 rabbits, respectively, for 20 hours. Responses were scored at 24, 72 hours and 8 days No irritation was observed at the back, and reversible reddening was seen at the ear at 24 hours (each was scored 2 on a scale up to a maximum of 4) had disappeared at 72 hours (score of 0) (BASF 1978b).

Eye Irritation

Studies in Animals

0.1 ml of adipic acid (99.8 %) was highly irritating to the eye in a well performed study with 6 rabbits where the animals were scored at 24, 48, 72 hours and 8 days. Irritated conjunctiva (reddening, swelling, secretion) and scar formation, increasing opacity of cornea and inflammation of the iris were observed. The symptoms were not reversible within the 8 days' observation period. Primary irritation index was 41.5 on a scale with a maximum of 110 (BASF 1978a).

Severe irritation was observed in a recent study according to OECD TG 405, conducted in compliance with GLP after the application of 100 mg adipic acid. To determine reversibility of effects, the animals were observed normally for up to 21 days post administration of the test substance. If reversibility is seen before 21 days, the experiment is terminated at that time. Corneal opacity and irritation of the iris was observed in all animals up to grade 3 and grade 2, respectively. The observed effects were reversible within 16 days (LPT 2004)

Studies in Humans

7 of 12 workers exposed (for an average of 9.2 years) to various glycols, glycerine, other compounds and adipic acid dust particles (8 h average concentration 0.47 - 0.79 mg/m^3 [0.08 - 0.13 ppm]) complained of eye irritation (details see below) (Cummings and Roseman 1985).

Respiratory Tract Irritation

Studies in Animals

Evidence of respiratory tract irritation was reported neither in an acute inhalation study where 20 rats were exposed to up to 7700 mg/m^3 of adipic acid dust (MMAD 3.5 µm) for 4 hours (BASF 1981) nor in an subacute study with limited documentation where four rats were exposed to 126 mg/m^3 of adipic acid dust for 6 hours per day for 15 days. The reliability of the subacute study is limited because only four animals were investigated, the MMAD was not determined and histopathology was only performed on a maximum of nine organs, including the lung (Gage 1970). Both of these studies are however not suited to fully assess the local irritation potential of adipic acid, as the nose was not examined histopathologically. Additionally, cytotoxicity to rat nasal explants has been shown *in vitro* for adipic acid at 3.7 g/l (Trela and Bogdanffy 1991).

Studies in Humans

7 of 12 workers exposed (for an average of 9.2 years) to various glycols, glycerine, other compounds and adipic acid dust particles (8 h average concentration 0.47 - 0.79 mg/m^3 [0.08 - 0.13 ppm]) complained of mucosal irritation (eye, nose, throat). There was no local exhaust ventilation and the workers did not wear respiratory protection. They reported that clouds of adipic acid and other materials were routinely generated during charging of reaction vessels. The investigators suggested that, since the glycol level was kept below 1 ppm, adipic acid was more likely to be the cause of these complaints (Cummings and Roseman 1985). This report is difficult to evaluate, because of the mixed exposure of the workers to a series of different compounds, including adipic acid. Due to the acidic character of adipic acid, a local irritation potential is plausible.

Conclusion

In rabbits, 50 % adipic acid suspensions were slightly irritating to the intact skin and moderately irritating to scarified skin. The neat material was a severe eye irritant in rabbits, with symptoms being reversible within 16 days. Respiratory irritation in animals is not sufficiently examined. Workers exposed over an extensive period (av. 9.2 years) complained of respiratory irritation at adipic acid concentrations of 0.47 - 0.79 mg/m^3. Due to the acidic character of the substance, a local irritation potential is plausible.

3.1.4 Sensitisation

Studies in Animals

Skin

There is only one sensitisation study available and it produced no evidence of a sensitising action but its reliability can not be fully assigned. Groups of 10 guinea pigs were given series of four sacral intradermal injections, one each week over a three-week period, which consisted of 0.1 ml of a 1.0 % solution of adipic acid (99.99 %) in water. Following a two-week rest period, the test animals were challenged for sensitisation by applying, and lightly rubbing in, approximately 0.05 ml of a 50 % and 25 % suspension of the test material in propylene glycol on the shaved intact

shoulder skin. A group of 10 previously unexposed animals received similar applications at the time of challenge to provide direct comparison of the challenge reactions on the skin of similar age. The compound produced very mild to no skin irritation to previously unexposed guinea pigs and did not cause sensitisation (Haskell 1974). The study design does not accord to modern guidelines because the number of animals per group was low, no data were presented to justify the induction concentration used, no adjuvant was used, and no positive control or historical data were presented.

Respiratory Tract

No data available

Studies in Humans

Despite the wide use of adipic acid, only very few cases of skin or respiratory tract reactions are reported:

A positive patch test reaction to adipic acid (probably 1 % in alcoholic solution) was reported in a 51-year-old machine repairman with a 3- to 4-year history of work-related dermatitis of the hands and other exposed sites when working with powders in the synthesis of polyesters (Guin 2001).

Delayed cutaneous hypersensitivity to adipic acid was reported in a patch test (100 %) with a laboratory worker in a factory producing polyester resins. No further details are available in this case (Malten and Zielhuis 1964).

Two cases of bronchial asthma were reported in workers of a pharmaceutical factory coming into contact with spiramycin adipate powder. One of the workers developed an immediate asthmatic reaction also after inhalation of an aerosolized solution (10 mg/ml) of adipic acid. The reaction was reproducible and inhibited by previous administration of sodium cromoglycate. These findings suggested a hypersensitivity reaction to adipic acid by this patient (Moscato et al. 1984).

Conclusion

Despite the wide dispersive use of adipic acid, only very few cases of skin or respiratory tract sensitisation reactions are reported in humans. A sensitisation study in animals according to validated guidelines is not available. Overall, sensitisation is not expected for adipic acid.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

There is no study with histopathological examination of the nose, the probable target organ after inhalation, available. Systemic effects after repeated inhalation have not been investigated in fully valid studies. In a limited study with repeated inhalation (see 3.1.3, Gage 1970) no effects were seen, but the reliability of the study cannot be fully assigned.

Dermal

No data available

Oral

In a limited three-weeks feeding study aimed at investigating peroxisome proliferation four male rats were dosed with food containing 2 % adipic acid dissolved in alcohol (approximately 2000 mg/kg bw/day) no differences were observed compared to control animals in general behavior, liver

size, peroxisome proliferation, hepatic activities of catalase and carnitine acetyltransferase, and no hypolipidemia was seen (Moody and Reddy 1978).

Groups of 8 to 10 male rats received sodium adipate (0, 50, 100, 200 and 400 mg/day, approximately 0, 420, 840, 1700 and 3400 mg/kg bw/day) in a protein deficient diet for 19 weeks. After 7 weeks and (probably) at the end of the experiment, rats were killed and examined grossly. Weight gain and general behaviour were recorded and histopathology of liver, kidneys and intestine was performed. Rats fed with 400 mg/day showed reduced weight gain and lower weight after 19 weeks. No obvious symptoms were observed. Several unexplained intercurrent deaths in control and dose groups occurred, and only 5 - 7 animals in each group survived 19 weeks. Only at 400 mg/day slight effects were seen on liver and irritation of intestine. The NOAEL is 3333 mg/kg bw (Lang and Bartsch 1953). The study is very limited in its reliability because no details are provided on the distribution of intercurrent deaths amongst the treatment/control groups, only kidneys, liver and intestine have been examined histopathologically.

Groups of 13 - 15 male and female rats received adipic acid (neutralized with NaOH) in a standard diet (0, 400, 800 mg/day, approximately 0, 1600 and 3200 mg/kg bw/day) for 33 weeks. Weight gain and general behavior were recorded. After 8, 23 and 25 weeks, rats were killed and histopathology of liver, kidneys and intestine was performed. The administration of 400 mg/day of adipic acid had no effect on weight gain and general behavior of the animals. Ten out of 14 rats fed with 800 mg/day died during the first 4 weeks. The surviving animals showed retarded weight gain, appeared unkempt and apathetic and suffered from heavy diarrhea during the first three weeks. They recovered by the fifth week, and after 33 weeks, the weights of the high-dose rats were the same as that of the 400 mg/day group. The authors did not record the body weight of control animals at the end of the experiment, i.e. at 33 weeks. Histopathology: slight effects were seen on liver and inflammation of intestine at 400 mg/day. No NOAEL was obtained in this study (Lang and Bartsch 1953). The study is very limited in its reliability because only kidneys, liver and intestine have been examined histopathologically.

In a two-year study, groups of 20 male rats were given 0, 0.1, 1, 3 and 5 % of adipic acid in the diet (equivalent to doses of 0, approximately 75, 750, 2250 and 3750 mg/kg bw/day). Groups of 10 or 19 female rats received food containing 0 or 1 % adipic acid (0 and approx. 750 mg/kg bw/day, respectively). Body weights, food consumption and general appearance were recorded weekly throughout the experimental period. After 2 years, surviving rats were weighed, killed, and examined grossly. The brain, thyroid, lung, heart, liver, spleen, kidneys, adrenals and stomach of the animals were weighed. Microscopic examination of thyroid, lung, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, bone marrow, large and small intestine uterus, ovaries and testes on a representative number of animals (no further information) was performed. The percent survival for each test group was higher than for the control group. There were no body weight differences during the test period in female and male rats treated with 0, 0.1 and 1 % adipic acid. The weight gains of the male rats receiving 3 and 5 % adipic acid were significantly less than the control groups. At necropsy there was no treatment related effect observed. Results of microscopic examination of the organs revealed no compound related effect. The NOAEL was 1 % for male and female rats (approx. 750 mg/kg bw/day) (Horn et al. 1957). The study does not fully comply with the guidelines for chronic studies because microscopic examination of 15 tissues was done on a representative number of animals for each group, females received only one concentration, the MTD was reached only for males, and the purity of adipic acid is not indicated.

Studies in Humans

Inhalation

7 of 12 workers exposed (for an average of 9.2 years) to various glycols and adipic acid dust particles (concentration 0.47 - 0.79 mg/m^3 [0.08 - 0.13 ppm], 8 h average value) complained of mucosal irritation (eye, nose, throat). There was no local exhaust ventilation and the workers did not wear respiratory protection. They reported that clouds of adipic acid and other materials were routinely generated during charging of reaction vessels. The investigators suggested that, since the glycol level was kept below 1 ppm, adipic acid was more likely to be the cause of these complaints (Cummings and Roseman 1985). Due to the acidic character of the substance, a local irritation potential is plausible.

Oral

No overt toxic symptoms were reported after oral administration of 7 g of adipic acid per day, for 10 days to one volunteer (100 mg/kg bw per day). 3 other persons took 19 to 23,4 g over up to 9 days without showing toxic symptoms (see chapter 3.1.1: Toxicokinetics, Metabolism and Distribution, Weitzel 1942 and 1947).

Conclusion

There is no repeated inhalation toxicity study with histopathological examination of the nose available. Systemic effects after repeated inhalation have not been investigated in fully valid studies. There are no studies on repeated dermal application available. In a limited 2-year oral study adipic acid was of low repeated dose toxicity, however it was not tested according to modern standards. The NOAEL was 1 % for male rats (approx. 750 mg/kg bw/day) and higher doses (3 and 5 %) caused body weight retardation with no indication of specific target organ toxicity. The NOAEL for female rats was 1 % (approx. 750 mg/kg bw/day), the highest dose tested in females. In one volunteer no overt toxic symptoms were seen after oral administration of 7 g adipic acid per day for 10 days.

3.1.6 Mutagenicity

In vitro Studies

Adipic acid was neither mutagenic nor cytotoxic in studies similar to OECD TG 471 in bacteria such as *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 or *Escherichia coli* WP2 up to concentrations of 10 mg/plate with or without metabolic activator S9. Negative and positive controls were functional in all experiments (Mortelmans and Griffin 1982; Prival et al. 1991, Shimizu et al. 1985).

Adipic acid was negative in a yeast gene mutation assay using *Saccharomyces cerevisiae* D3 as a reporter strain without S9-mix and adipic acid concentrations up to 200 mg/l. Cytotoxicity was not mentioned. The positive and negative controls were functional (Litton Bionetics, Inc. 1974).

Adipic acid was also inactive in a cytogenetic assay using human embryonic lung fibroblast cells (WI-38) and compound concentrations up to 200 mg/l. Cytotoxicity was observed at 400 mg/l. No metabolic activation system was used in these experiments and the positive and negative controls were functional (Litton Bionetics, Inc. 1974).

In vivo Studies

Adipic acid was investigated in a host mediated assay with *Salmonella typhimurium* TA-1530 and G-46 or *Saccharomyces cerevisiae* D3 as indicator strains. In an acute and subacute study groups of 10 male mice were gavaged with 3.75, 37.5 and 375 mg/kg bw/day for one and 5 days, respectively. Adipic acid produced no significant increase in mutation frequencies in any experiment, except when using *Saccharomyces cerevisiae* D3 in the acute study. In this case an increased frequency of mutations as well as dose response was observed. In further experiments in the same study animals were gavaged with 5000 mg/kg bw once and with 2500 mg/kg bw/day for 5 days, respectively. In these studies the results were negative for all three indicator strains TA-1530, G-46 and *Saccharomyces cerevisiae* D3 in both, the acute and subacute, experiments. The positive control groups, employed only during the acute studies, were functional (Litton Bionetics, Inc. 1974).

Adipic acid was not mutagenic in *in vivo* cytogenetic studies where groups of five male rats were gavaged with adipic acid doses up to 5000 mg/kg bw (acute studies) and with doses up to 2500 mg/kg bw/day (five-days subacute studies). 200 to 500 metaphase chromosomes of bone marrow cells per dose were scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with greater than ten aberrations, polyploidy, pulverization and other chromosomal aberrations. The mitotic indices for all dose groups were considered to be within the normal limits of the controls and there was no evidence of chromosomal damage. The positive control groups, performed only during the acute studies, were functional (Litton Bionetics, Inc. 1974).

Adipic acid was administered by gavage to groups of 10 male rats in a dominant lethal assay. Each treated male rat was mated with two virgin female rats each week for seven (subacute study) or eight (acute study) weeks. Two weeks after mating, female rats were sacrificed and the fertility index, preimplantation loss and lethal effects on the embryos were determined and compared with those same parameters calculated from control animals. In an acute study (3.75, 37.5 and 375 mg/kg bw) a decrease in average implantations at week 1 and 4, and corpora lutea at week 4 and 7 were seen only in the intermediate dose level. Increase in preimplantation losses were shown at week 1 for both the low and intermediate dose groups with no changes at any other week and parameter. In a five days subacute study with the same doses significant differences between the negative control and experimental groups were shown in a few instances, no clear indications of a dose-response or time trend were seen. In a second test (acute single dose of 5000 mg/kg bw and subacute five doses of 2500 mg/kg bw/day) the values from those animals dosed with adipic acid did not significantly vary from those obtained from the negative control. Positive control groups, performed during the acute studies, gave the expected results. In summary, adipic acid does not induce dominant lethal mutations in doses up to 5000 mg/kg bw (Litton Bionetics, Inc. 1974).

Drosophila melanogaster received adipic acid via feed at a concentration of 4000 ppm. Genetically marked X and Y chromosomes were used to test simultaneously nondisjunction, chromosome loss and induced recombination or translocation involving the Y-chromosome, in offspring. No mutagenic effects were found. The positive controls were functional (Ramel and Magnusson 1979).

Conclusion

A variety of mutagenicity tests in vitro and in vivo have failed to demonstrate that adipic acid possesses genotoxic potential. A number of good quality Ames tests in Salmonella typhimurium similar to OECD TG 471 and an examination of chromosome damage in human lung cells in culture produced negative results. In gavage studies in male rats it did not induce chromosome damage in the bone marrow or dominant lethal mutations in a dose-response or time-trend pattern.

3.1.7 Carcinogenicity

In vivo Studies in Animals

Oral

Adipic acid was not carcinogenic in the previously described two-years feeding study (see chapter 3.1.5: Repeated Dose Toxicity) where groups of twenty male rats were dosed with food containing 0, 0.1, 1, 3 and 5 % adipic acid (approx. 0, 75, 750, 2250, 3750 mg/kg bw/day), and female rats were dosed with 0 (n = 10) and 1 % (n = 19) adipic acid (approx. 0, 750 mg/kg bw/day), respectively. Animals that died during the study and survivors were analyzed for incidences of tumor growth and lung pathology. The incidences of tumors observed in the adipic acid treated groups were as frequent as in the control groups (Horn et al. 1957). The study does not comply with the current guidelines for carcinogenicity studies because the number of animals used was low, microscopic examination of only 15 tissues was done only on a representative number of animals for each group, only one concentration was tested for females, the MTD for females was not reached, and the purity of adipic acid is not indicated.

Conclusion

Adipic acid was not carcinogenic in a limited two-years feeding study where male rats were fed with up to 5 % (3750 mg/kg bw/day) adipic acid and female rats with 1 % (750 mg/kg bw/day).

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

Studies on fertility are not available. In the previously described two-years feeding study in rats (see chapter 3.1.5. Repeated Dose Toxicity) histopathological examination of testes, ovaries and uterus revealed no evidence of an adverse effect on the reproductive organs up to the highest tested doses (3750 mg/kg bw/day in males, 750 mg/kg bw/day in females). Soft edematous testes were observed at least as frequent in the controls as in the adipic acid dosed animals. Two of the surviving control female animals and one of the experimental females had ovarian tumors, ovarian cysts were noted in both control and experimental rats (Horn et al. 1957).

Developmental Toxicity

The administration of up to 288 mg/kg bw/day adipic acid by gavage to groups of 20 to 24 pregnant rats from gestation days (gd) 6 – 15 (10 consecutive days) did neither result in embryo- or feto-toxicity nor in teratogenicity. No adverse effects were seen in similar experiments after administration of adipic acid to groups of 20 - 24 pregnant mice (gd 6 - 15, up to 263 mg/kg bw/day) and groups of 10 to 14 pregnant rabbits (gd 6-18, up to 250 mg/kg bw/day) (Food and Drug Res Labs, Inc. 1972 and 1974). These studies are limited to some extent by the fact that no signs of maternal toxicity have been observed and the highest doses tested were well below the limit dose of 1000 mg/kg bw which would be a precondition for a fully valid negative study.

Conclusion

No specific studies on fertility have been conducted. In an two-years feeding study in rats histopathological examination of testes, ovaries and uterus revealed no evidence of an adverse effect on the reproductive organs up to the highest doses tested (males approx. 3750 mg/kg bw/day,

females approx. 750 mg/kg bw/day). Based on the available data there is no reason to expect specific reproductive toxicity of adipic acid.

Adipic acid was not embryo- or fetotoxic and not teratogenic up to the highest tested doses of 288, 263 and 250 mg/kg bw/day via oral administration to rats, mice and rabbits, respectively. In none of these studies signs of maternal toxicity have been observed and the highest dose was well below the limit dose of 1000 mg/kg bw which would be a precondition for a valid negative study. In view of the low systemic toxicity of the compound, however, this endpoint seems to be adequately covered despite the limitations of the studies.

3.2 Initial Assessment for Human Health

In limited studies in animals and humans it was shown that adipic acid is absorbed after oral administration, partially metabolized to various metabolites and CO_2 which are excreted via urine and breath, resp. None of the studies was conducted according to GLP.

Adipic acid is of very low acute toxicity. The oral LD_{50} in rats in a study similar to OECD TG 401 is approximately 5560 mg/kg bw. Clinical signs at lethal doses included acute dilatation of the heart and acute congestive hyperaemia, ulceration of glandular stomach (bleeding-corrosive gastritis), intestinal atony, pale liver and reddening of intestinal mucosa. The LD_{50} for mice was reported to be 1900 mg/kg bw. In an inhalation test similar to OECD TG 403 in rats neither mortality nor symptoms were observed during and after 4 hour exposure to 7700 mg/m^3 of adipic acid. Reduced appetite and activity were the only effects reported following occlusive dermal administration of 7940 mg/kg bw of adipic acid to 2 rabbits for 24 hours.

In rabbits, 50 % adipic acid suspensions were slightly irritating to the intact skin and moderately irritating to scarified skin. The neat material was a severe eye irritant in rabbits, with symptoms being reversible within 16 days. Respiratory irritation in animals is not sufficiently examined. Workers exposed over an extensive period (av. 9.2 years) complained of respiratory irritation at adipic acid concentrations of 0.47 - 0.79 mg/m^3. Due to the acidic character of the substance, a local irritation potential is plausible.

Despite the wide dispersive use of adipic acid, only very few cases of skin or respiratory tract sensitisation reactions are reported in humans. A sensitisation study in animals according to validated guidelines is not available. Overall, sensitisation is not expected for adipic acid.

There is no repeated inhalation toxicity study with histopathological examination of the nose available. Systemic effects after repeated inhalation have not been investigated in fully valid studies. There are no studies on repeated dermal application available. In a limited 2-year oral study adipic acid was of low repeated dose toxicity, however it was not tested according to modern standards. The NOAEL was 1 % for male rats (approx. 750 mg/kg bw/day) and higher doses (3 and 5 %) caused body weight retardation with no indication of specific target organ toxicity. The NOAEL for female rats was 1 % (approx. 750 mg/kg bw/day), the highest dose tested in females. In one volunteer no overt toxic symptoms were seen after oral administration of 7 g adipic acid per day for 10 days.

A variety of mutagenicity tests *in vitro* and *in vivo* have failed to demonstrate that adipic acid possesses genotoxic potential. A number of good quality Ames tests in *Salmonella typhimurium* similar to OECD TG 471 and an examination of chromosome damage in human lung cells in culture produced negative results. In gavage studies in male rats it did not induce chromosome damage in the bone marrow or dominant lethal mutations in a dose-response or time-trend pattern.

Adipic acid was not carcinogenic in a limited two-years feeding study where male rats were fed with up to 5 % (3750 mg/kg bw/day) adipic acid and female rats with 1 % (750 mg/kg bw/day).

No specific studies on fertility have been conducted. In a two-year feeding study in rats histopathological examination of testes, ovaries and uterus revealed no evidence of an adverse effect on the reproductive organs up to the highest doses tested (males approx. 3750 mg/kg bw/day, females approx. 750 mg/kg bw/day). Based on the available data there is no reason to expect specific reproductive toxicity of adipic acid.

Adipic acid was not embryo- or fetotoxic and not teratogenic up to the highest tested doses of 288, 263 and 250 mg/kg bw/day via oral administration to rats, mice and rabbits, respectively. In none of these studies signs of maternal toxicity have been observed and the highest dose was well below the limit dose of 1000 mg/kg bw which would be a precondition for a fully valid negative study. In view of the low systemic toxicity of the compound, however, this endpoint seems to be adequately covered despite the limitations of the studies.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Three representative tests of the acute toxicity of adipic acid towards fish are available (Table 11).

The lowest ecotoxicological effect concentration towards fish was a 96 h-LC_{50} of 97 mg/l for *Pimephales promelas*. The study was conducted according to US-EPA Method 660/3-75-009. The same effect concentration was observed after a period of 72 h (Mattson, Arthur and Walbridge 1976). The authors note that the pH was < 5.9 during the test. In addition, there is no exact information on oxygen content of the test solutions. It is only reported that the oxygen content was not < 4 mg/l. Therefore, it cannot be excluded that the toxicity observed was due to pH effects and possibly oxygen limitations and the study should not be used for the hazard assessment of adipic acid. As adipic acid is not a strong acid, pH effects are not likely to occur in the environment.

In an acute test performed with *Leuciscus idus* according to the German national standard method DIN 38412 Part 15 a 96 h-LC_{50} of 230 mg/l was obtained (BASF AG 1980). Also in this study the pH of the test solutions was in the range of 3.8 to 7. For the concentration 215 mg/l that is in the same order of magnitude with the LC50 the pH was between 4.3 and 4.7 and therefore pH related effects cannot be excluded. For this reason also this study should not be used for the hazard assessment.

With the species *Danio rerio* a 96 h-LC_{50} higher than 1000 mg/l was obtained in a static test in accordance to the guideline proposal of the German Federal Environmental Agency (UBA). An analytical monitoring was conducted and the recovery was around 97 % (Bayer AG 1991). The pH of the test solution was in the range of 7.4 to 7.7.

With the invertebrate *Daphnia magna* one acute test according to the European guideline 79/831/EEC, method C.2 is available. For a test period of 24 hours an EC_{50} value of 85.6 mg/l was obtained. The same effect concentration was reported after a test period of 48 hours (BASF AG 1988b). pH values in the test solutions ranged from 4 (500 mg/l) to 7.7 (15.6 mg/l) and pH related effects on the daphnids cannot be excluded.

Concerning the algal toxicity, a test with *Desmodesmus subspicatus* in the presence of adipic acid was performed. According to the German standard method for water, wastewater and sludge DIN 38412 Part 9 from 1988 a growth inhibition test was performed and a 96h-E_bC_{50} of 26.6 mg/l was determined (BASF AG 1996). For a test period of 72 h the E_bC_{50} is given as 31.3 mg/l. pH values determined at test start and test end for each concentration were in the range of 3.8 to 10.2. The pH for the concentration of the E_bC_{50} (31.3 mg/l) was 6.0 at test begin and 8.2 after 96 h. Therefore, it can be concluded that the effects found in this study are likely not due to pH effects.

Table 11 Tests on acute toxicity of adipic acid to fish, *Daphnia* and algae

Species	Test type	Parameter	Effects	Reference	IUCLID
Pimephales promelas	Static	96 h-LC_{50}	97 mg/l (n)	Mattson, Arthur and Walbridge 1976*	4.1
Leuciscus idus	Static	96 h-LC_{50} NOEC	230 mg/l (n) 147 mg/l (n)	BASF AG 1980*	4.1
Danio rerio	Static	96 h-LC_{50}	>1000 mg/l (n)	Bayer AG 1991*	4.1
Daphnia magna	Static	48 h-EC_{50}	85.6 mg/l (n)	BASF AG 1988b*	4.2
Desmodesmus subspicatus	Static	96 h-EC_{50} 72 h-EC_{50}	26.6 mg/l (n) 31.3 mg/l (n)	BASF AG 1996*	4.3

(n): nominal concentration

*studies flagged as robust summary studies

Although in the above described studies the occurrence of pH related effects on the test organisms cannot be excluded, such pH effects are not likely to occur in environmental surface waters.

Chronic Toxicity Test Results

No tests to the chronic toxicity of adipic acid are available.

Determination of $PNEC_{aqua}$

Since there are acute test results available for adipic acid from three trophic levels, an assessment factor of 1000 was applied for the derivation of the $PNEC_{aqua}$ according to the EU Technical Guidance Document. The lowest acute effect concentration was found for the alga species *Desmodesmus subspicatus* with a 96h-EC_{50} = 27 mg/l (BASF AG 1996), which results in a

$PNEC_{aqua}$ = 27 µg/l.

Toxicity to Microorganisms

A test with activated sludge with a duration of 3 hours was performed according to the OECD TG 209 (Activated Sludge, Respiration Inhibition Test). The test substance was a residue from adipic acid manufacturing containing 60 % adipic acid. An EC_{50} of 4747 mg/l related to the concentration of adipic acid was observed (Bayer AG 1988).

In a 17 hours test with *Pseudomonas putida* according to the German standard method DIN-38412 Part 8 (Cell Multiplication Inhibition Test), an EC_{50} of 91.9 mg/l was observed (BASF AG

1987). pH values in the test solutions ranged from 4.65 (125 mg/l) to 7.89 (0 mg/l) and pH related effects cannot be excluded.

The toxicity of adipic acid to *Tetrahymena pyriformis* was tested in a 40 hours test. The test was performed according to the method described by Schultz (1997). An EC_{50} of 35.9 mg/l was observed after 40 hours (Seward and Schultz 1999). Microbial toxicities of adipic acid are listed in Table 12.

Table 12 Tests on acute toxicity of adipic acid to microorganisms (IUCLID 4.4)

Species	Endpoint	Parameter	Effects	Reference
Activated Sludge	Respiration inhibition	3 h-EC_{50}	4747 mg/l (n)	Bayer AG 1988*
Pseudomonas putida	Cell multiplication	17 h-EC_{50}	91.9 mg/l (n)	BASF AG 1987*
Tetrahymena pyriformis	Growth impairment	40 h-EC_{50}	35.9 mg/l	Seward and Schultz 1999*

(n): nominal concentration

*studies flagged as robust summary studies

4.2 Terrestrial Effects

Several studies of the toxicity of adipic acid towards terrestrial plants were found in the literature. Although none of these tests was performed according to guideline, the obtained effect values indicate that adipic acid is of low toxicity to terrestrial plants (Table 13).

Pramanik et al. (2001) analysed aqueous extracts from rice-straw by gas-chromatography coupled with mass spectrometry to identify allelopathic compounds, and to evaluate their phytotoxicity. The root length of Chinese milk vetch (*Astragalus sinicus*) seedlings after 5 days incubation in adipic acid solutions was measured. The authors observed a slight increase in growth rate at 7 mg/l adipic acid and an EC_0 of about 10 mg/l. They concluded that adipic acid significantly inhibits plant growth at concentrations higher than ca. 30 mg/l.

Prill, Barton and Solt (1949) measured the effects of some organic acids on the growth of the primary wheat roots. The EC_{50} was determined to be about 170 mg/l.

Kim et al. (2001) measured the toxicity of adipic acid in a seed germination test with *Raphanus sativus*. These authors found an EC_0 of ca. 134 mg/l.

Reynolds (1975) examined pH restraints on lettuce (*Lactuca sativa)* fruit germination. The EC_{50} of adipic acid was 6722 mg/l at pH 3.25.

Table 13 Effects of adipic acid on terrestrial plants

Plant	Parameter	Results	Reference
Astragalus sinicus	Root length	EC_0 = ca. 10 mg/l (measured)	Pramanik et al. 2001
Raphanus sativus	Seed germination	EC_0 = ca. 134 mg/l (measured)	Kim et al. 2001
Triticum aestivum	Primary root growth	EC_{50} = ca. 170 mg/l (measured)	Prill, Barton and Solt 1949
Lactuca sativa	Seed germination	EC_{50} = 6722 mg/l at pH 3.25 (measured)	Reynolds 1975

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

Adipic acid is an odourless, white crystalline solid with a melting point of 152 °C and a boiling point of 337.5 °C. The density of the solid is 1.36 g/ml at 25 °C. The vapour density in relation to air is 5.04. The vapour pressure is 9.7 Pa at 18.5 °C. The log K_{OW} is 0.093. The solubility in water is 23 g/l at 25 °C. The flash point is 196 °C, the auto flammability (ignition temperature) 420 °C. Decomposition starts at 230 °C.

With regard to its chemical structure adipic acid is not expected to hydrolyse under environmental conditions. According to a Mackay calculation level I the favourite target compartment of the substance (uncharged molecule) is water with 97 %. It has to be considered, that at very low concentrations of adipic acid expected in the environment, the substance is mostly present as anion (i.e. deprotonated). As anions are neither subjects to volatilization nor to adsorption, the hydrosphere is also the target compartment for the deprotonated molecule. The Henry's law constant of 9.7×10^{-7} Pa m^3 mol^{-1} (Bond method) and of 8.8×10^{-2} Pa m^3 mol^{-1} (ratio of vapour pressure versus solubility) at 25 °C indicates that the compound has a low potential for volatilization from surface waters. The calculated half-life of adipic acid in air due to indirect photodegradation is $t_{1/2}$ = 2.9 days.

Adipic acid is readily biodegradable (MITI, comparable to OECD TG 301C: biodegradation 68 - 90 % after 14 days, OECD TG 301B: 91 % after 28 days, closed bottle test OECD TG 301D: 83 % after 30 days).

The bioconcentration factor BCF = 3 for adipic acid calculated from the octanol-water partition coefficient indicates that there is only a low potential for bioaccumulation of adipic acid in aquatic organisms. With a calculated K_{oc} value of 22 adipic acid can be regarded as a substance without geoaccumulation potential.

Concerning the toxicity of adipic acid to aquatic species reliable experimental results of tests with fish, *Daphnia* and algae are available. The lowest valid effect data on acute fish toxicity was > 1000 mg/l for *Danio rerio* (96 h-LC_{50}). With *Daphnia magna* a 48 h-EC_{50}-value of 85.6 mg/l was observed. In an algae growth inhibition test with *Desmodesmus subspicatus* the 96 h-EC_{50} was 26.6 mg/l.

No tests are available on chronic toxicity of adipic acid.

Based on the acute aquatic toxicity data on three trophic levels (fish, *Daphnia*, algae), a Predicted No Effect Concentration ($PNEC_{aqua}$) can be calculated with an assessment factor of 1000. Using the lowest acute effect concentration, the 96 h-EC_{50} of 26.6 mg/l of *Desmodesmus subspicatus*, a

$PNEC_{aqua}$ of 27 µg/l

was determined.

5 RECOMMENDATIONS

Environment:

The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for the environment. Although these hazards do not warrant further work (as they are related to acute toxicity which may become evident only at very high exposure level), they should nevertheless be noted by chemical safety professionals and users.

Human Health:

The chemical is currently of low priority for further work. The chemical possesses properties (eye and respiratory tract irritation) indicating a hazard for human health. Although these hazards do not warrant further work, they should nevertheless be noted by chemical safety professionals and users, especially at the workplace.

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I U C L I D

Data Set

Existing Chemical	:	ID: 124-04-9
CAS No.	:	124-04-9
EINECS Name	:	adipic acid
EC No.	:	204-673-3
TSCA Name	:	Hexanedioic acid
Molecular Formula	:	C6H10O4

Producer related part

Company	:	Bayer AG
Creation date	:	31.07.1992

Substance related part

Company	:	Bayer AG
Creation date	:	31.07.1992
Status	:	
Memo	:	X AKTUELL / ICCA EEC (Update 1996)
Printing date	:	15.02.2006
Revision date	:	02.06.1994
Date of last update	:	13.02.2006
Number of pages	:	118
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, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : Hexanedioic Acid
Smiles Code : O=C(O)CCCCC(=O)O
Molecular formula : HOOC-CH2-CH2-CH2-CH2-COOH
Molecular weight : 146.14
Petrol class :

Flag : Critical study for SIDS endpoint
28.09.2003 (1)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity : > 99.6 % w/w
Colour : white
Odour : odourless

Remark : Purity for food-grade product
Flag : Critical study for SIDS endpoint
02.10.2003 (2)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

1,4-BUTANEDICARBOXYLIC ACID

1,6-HEXANEDIOIC ACID

ADIPIC ACID

Remark : IUPAC name
07.10.2003 (3)

ADIPINIC ACID

26.11.2003

ADIPINSAEURE

HEXANEDIOIC ACID

Remark : CAS name
07.10.2003 (3)

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Result : Commercial adipic acid is one of the purest chemicals produced on a large scale (99.8 %) because of the extreme sensitivity of polyamide synthesis to impurities. Typical impurities include other acids (monobasic acids and lower dibasic acids) (60 ppm), nitrogenous materials, trace metals such as iron (2 ppm) and other heavy metals (10 ppm), arsenic (3 ppm) and hydrocarbon oil (10 ppm)
Flag : Critical study for SIDS endpoint
26.11.2003 (4) (5)

Purity : typical for marketed substance
CAS-No : 124-04-9
EC-No : 204-673-3
EINECS-Name : adipic acid
Molecular formula : C6H10O4
Value : 95 % w/w

Flag : Critical study for SIDS endpoint
26.11.2003 (3)

Purity : other: typical for industrial intermediate
CAS-No : 110-94-1
EC-No : 203-817-2
EINECS-Name : glutaric acid
Molecular formula : C5H8O4
Value : 3 % w/w

Flag : Critical study for SIDS endpoint
26.11.2003 (3)

Purity : other: typical for industrial intermediate
CAS-No : 110-15-6
EC-No : 203-740-4
EINECS-Name : succinic acid
Molecular formula : C4H6O4
Value : 2 % w/w

Flag : Critical study for SIDS endpoint
26.11.2003 (3)

Purity : typical for marketed substance
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water, distilled, conductivity or of similar purity
Molecular formula : H2O
Value : < .2 % w/w

Flag : Critical study for SIDS endpoint
09.10.2003 (2)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : ca. 2300000 - tonnes produced in 1996

Remark : World wide manufacturing capacity of adipic acid is reported (not manufacturing volume)
Flag : Critical study for SIDS endpoint
08.09.2005 (6)

Quantity : ca. 2700000 - tonnes produced in 2000

Remark : Estimate for the global production volume is 2.7 million tonnes in 2000, compared to 1.8 million tonnes in 1995. Worldwide, there are 20 adipic acid plants (Brazil 1, Canada 1, China 3, France 1 [Mainhardt and Kruger 2001], Germany 3 [Personal Communication 2003], Italy 1, Japan 2, Korea 1, Singapore 1, Ukraine 1, United Kingdom 1, USA 4
Flag : Critical study for SIDS endpoint
26.05.2004 (7)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : Xi, , ,
Nota : , ,
R-Phrases : (36) Irritating to eyes
S-Phrases :

17.01.2006 (8)

Labelling : provisionally by manufacturer/importer
Specific limits :
Nota : , ,
R-Phrases : (37) Irritating to respiratory system
S-Phrases :

07.02.2006

Labelling : provisionally by manufacturer/importer
Specific limits :
Nota : , ,
R-Phrases : (41) Risk of serious damage to eyes
S-Phrases :

07.02.2006

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (36) Irritating to eyes
Specific limits :

17.01.2006 (8)

Classified : provisionally by manufacturer/importer
Class of danger :
R-Phrases : (37) Irritating to respiratory system
Specific limits :

07.02.2006

Classified : provisionally by manufacturer/importer
Class of danger :
R-Phrases : (41) Risk of serious damage to eyes
Specific limits :

07.02.2006

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category : Intermediates

Remark : Used for synthesis of other chemicals: monomer
02.10.2003 (2)

Type of use : industrial
Category : Chemical industry: used in synthesis

01.10.2003 (2)

Type of use : type
Category : Non dispersive use

Remark : Use as an industrial intermediate

01.10.2003 (2)

Type of use : type
Category : Wide dispersive use

Remark : Used as a food additive
01.10.2003 (2)

Type of use : industrial
Category : Fuel industry

Remark : Although Kennedy (2002) reports that adipic acid is also widely used in lubricating oil additives, it is assumed that adipic acid is not used in this application (see e.g. Weissermel and Arpe 1998). Monohydric alcohol esters of adipic acid and selected adipate polyesters are used as synthetic lubricants.
28.11.2003 (1) (6)

Type of use : use
Category : Food/foodstuff additives

01.10.2003 (2)

Type of use : use
Category : Food/foodstuff additives

Remark : In the EU, adipic acid (E-No. 355) additions to several food products are permitted in concentrations of up to 10,000 mg/kg depending on the food product. Kennedy (2002) reports that adipic acid is used in baking powder, however, this application is not permitted in the EU.
Flag : Critical study for SIDS endpoint
28.11.2003 (9) (1) (10)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

Proposed residues level : 0-5 mg/kg
Maximum residue level : 5 mg/kg

26.11.2003 (10)

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)

Remark : Official German Classification with identification number (Kenn-Nr.) 474 (VwVwS addendum 2)

31.01.2006 (11)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation :
Substance listed : no
No. in Seveso directive :

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number :
Class of danger :

Remark : no labelling

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

Memo : Origin of name

Result : Name adipic acid is derived from Latin "adeps" (fat) since adipic acid was originally obtained from oxidised fats

02.10.2003 (12)

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 1
Date of search : 02.01.2003

Remark : Search by Sponsor Company
26.11.2003

Type of search : Internal and External
Chapters covered : 2
Date of search : 02.01.2003

Remark : Search by Sponsor Company
26.11.2003

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 02.01.2003

Remark : Search by Sponsor Company
26.11.2003

Type of search : Internal and External
Chapters covered : 5
Date of search : 01.02.2003

Remark : Search by Sponsor Company
01.12.2003

Type of search : External
Chapters covered : 2
Date of search : 30.09.2003

Remark : Search by BUA-Büro Essen
26.11.2003

Type of search : External
Chapters covered : 3, 4
Date of search : 30.09.2003

Remark : Search by BUA-Büro Essen
26.11.2003

Type of search : External
Chapters covered : 2
Date of search : 15.10.2003

Remark : Search by BUA-Büro Dresden
26.11.2003

Type of search : External
Chapters covered : 3, 4
Date of search : 15.10.2003

Remark : Search by BUA-Büro Dresden
26.11.2003

Type of search : External
Chapters covered : 5
Date of search : 30.10.2003

Remark : Search by BUA-Büro Weihenstephan
01.12.2003

1.13 REVIEWS

Memo : BUA Report
28.09.2003 (3)

Memo : Toxicity of adipic acid
28.09.2003 (1)

2.1 MELTING POINT

Value : 152 °C
Sublimation :
Method :
Year : 1976
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
25.11.2003 (13)

Value : 152.1 °C
Sublimation :
Method :
Year : 1985
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
02.10.2003 (2)

Value : 152.1 °C
Sublimation :
Method :
Year : 1991
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
02.10.2003 (5)

Value : 150 - 153 °C
Sublimation :
Method :
Year : 1992
GLP :
Test substance :

Reliability : (2) valid with restrictions
Reliable source
21.08.2003 (14)

Value : 145 - 155 °C
Sublimation :
Method :
Year : 2003
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.11.2003 (15)

Value : 153 °C
Sublimation :
Method :
Year : 1996
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.05.2004 (16)

Value : 152 °C
Sublimation :
Method : other: no data
Year : 2002
GLP : no data
Test substance : no data

Reliability : (4) not assignable
Secondary literature
21.08.2003 (1)

Value : 151 - 153 °C
Sublimation :
Method :
Year : 1996
GLP :
Test substance :

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
25.05.2004 (17)

2.2 BOILING POINT

Value : 337.5 °C at 1013 hPa

Result : Other data in Davis (1985):

p (hPa)	bp (°C)
133	265
26.7	222
6.7	191
1.33	159.5

Other data in the Merck Index (electronic version) (2001):

p (hPa)	bp (°C)
133	265
52.6	240.5
26.7	222
13.3	205.5
6.7	191
1.33	159.5

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
07.10.2003 (2) (13)

Value : 265 °C at 133 hPa

Remark : Data also published in: Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals (3. ed). Van Nostrand Reinhold, New York, 137-138
Reliability : (2) valid with restrictions
Data from handbook or collection of data
14.08.2003 (2) (13) (14) (16)

Value : ca. 330 °C at
Decomposition :
Method : other: no data
Year : 2002
GLP : no data
Test substance : no data

Reliability : (4) not assignable
Secondary literature
14.08.2003 (1)

Value : 338 °C at 1013 hPa

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
25.05.2004 (17)

Value : 330.5 °C at 1013 hPa

Result : The following boiling points are reported (°C):
330.5 (1013 hPa)
265.1 (133 hPa)
216.5 (20 hPa)
205.5 (13 hPa)
Reliability : (2) valid with restrictions
Data from handbook or collection of data
02.10.2003 (12)

2.3 DENSITY

Type : density
Value : 1.36 g/cm³ at 25 °C

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
02.10.2003 (15)

Type : density
Value : 1.085 g/cm³ at 170 °C

Remark : Molten adipic acid
Reliability : (2) valid with restrictions
Data from handbook or collection of data
07.10.2003 (2)

Type : bulk density
Value : 600 - 700 kg/m3 at °C

Remark : Loose bulk density reported. Bulk density of crystalline solid depends on

particle size
Reliability : (2) valid with restrictions
Data from handbook or collection of data
07.10.2003 (2)

Type : density
Value : 1.344 g/cm³ at 18 °C

Result : Density of the molten liquid: 1.07 kg/l at 170 °C
Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.11.2003 (5)

Type : density
Value : 1.36 at °C

Reliability : (4) not assignable
Secondary literature
30.09.2003 (1)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .097 hPa at 18.5 °C

Remark : Sublimation;
value isw also published in: Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals (3. ed). Van Nostrand Reinhold, New York, 137-138
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
25.05.2004 (5)

Value : .097 hPa at 18.5 °C

Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.05.2004 (12)

Value : 1.33 hPa at 159.5 °C

Reliability : (2) valid with restrictions
Data from handbook or collection of data
07.10.2003 (2)

Value : .103 hPa at 20 °C

Result : Another result reported: 0.175 hPa at 30 °C.
The vapor pressure of 0.139 Pa is the average value of the vapour pressures at 20°C an 30°C. Estimations of physico-chemical parameters like Henry law constant will be performed with this vapor pressure as the value selected as critical is for a temperature of 18.5 °C. As the water solubility is measured at 25 °C, is it more proper to use a vapor pressure for the same temperature range. This will not have any significant influence

on the estimation of the environmental behaviour of the substance.

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
25.05.2004 (18)

Value : .000000424 hPa at 25 °C

Reliability : (4) not assignable
Reference not available
26.11.2003 (19)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = .093 at 25 °C
pH value : 3.3
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1988
GLP : no
Test substance : other TS: Purity 99.8%

Remark : The log Kow is very much dependent on the pH value, since a protolytic equilibrium is established.
At pH 7 (NaOH addition) the log Kow was < -3.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
25.11.2003 (20)

Partition coefficient : octanol-water
Log pow : = .081 at 25 °C
pH value :
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1988
GLP : no data
Test substance : other TS: 30% adipic acid

Result : The partition coefficient of 3 decarboxylic acids was measured.
The mean value of 2 measurements of log Kow for each compound was as follows:
Adipic acid 0.081
Glutaric acid -0.256
Succinic acid -0.575
Test substance : Test substance consisted of a mixture containing:
Adipic acid: 27.5 %
Glutaric acid: 45 %
Succinic acid: 27.5 %
Reliability : (2) valid with restrictions
Basic data given
30.09.2003 (21)

Partition coefficient : octanol-water
Log pow : .08 at °C
pH value :
Method : other (measured)
Year : 1995

GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
10.10.2003 (22)

Partition coefficient : octanol-water
Log pow : .23 at 25 °C
pH value :
Method : other (calculated): with KOWWIN v. 1.66, 2000
Year : 2003
GLP :
Test substance :

Reliability : (2) valid with restrictions
Accepted calculation method
01.10.2003 (23)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : 23 g/l at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: measured at the Chemicals Inspection and Testing Institute, Japan
Year : 1992
GLP :
Test substance :

Reliability : (2) valid with restrictions
Reliable source
Flag : Critical study for SIDS endpoint
01.10.2003 (14)

Solubility in : Water
Value : 14.1 g/l at 15 °C
pH value : 3.2
concentration : .1 other: % at 25 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1985
GLP :
Test substance :

Result : Other solubilities reported:
temperature (°C) solubility (g/100 g of H2O)

40 4.5
60 18.2
80 73
100 290
This corresponds to
temperature (°C) solubility (g/l)
40 43.6
60 161
80 475
100 925
pH reported for saturated solution at 25 °C is pH = 2.7

Reliability : (2) valid with restrictions
Data from handbook or collection of data

26.11.2003 (2)

Solubility in : Water
Value : = 24 g/l at 25 °C
pH value : = 2.5
concentration : 150 g/l at 70 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1991
GLP : no data
Test substance :

Reliability : (4) not assignable
Reference not available

30.09.2003 (24)

Solubility in : Water
Value : 19 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 2002
GLP :
Test substance : other TS: Purity 100 %

Result : Other reported solubility:
830 g/l at 90 °C
Reliability : (4) not assignable
Manufacturer data without proof

09.10.2003 (25)

Solubility in : Organic Solvents
Value : at °C
pH value :
concentration : at °C
Temperature effects :

Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1985
GLP :
Test substance :

Result : Very soluble in methanol and ethanol; soluble in acetone and ethyl acetate; very slightly soluble in cyclohexane and benzene
Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.05.2004 (2) (5)

Solubility in : Water
Value : 30.8 g/l at 34 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
26.05.2004 (26)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : ca. 196 °C
Type : closed cup
Method :
Year : 1985
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
26.11.2003 (2)

Value : 210 °C
Type : other: Cleveland open cup
Method :
Year : 1985
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint

07.10.2003 (2)

2.8 AUTO FLAMMABILITY

Value : 420 °C at
Method :
Year : 1985
GLP :
Test substance :

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
07.10.2003 (2)

Value : 405 °C at
Method : other: DIN 51 794
Year : 1991
GLP :
Test substance :

Remark : Ignition temperature
Reliability : (4) not assignable
Reference not available
25.09.2003 (24)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : Ionization constants in water at 25 °C
Method : other: no data
Year : 1985
GLP : no data
Test substance : no data

Result : Ka1 = 4.6 x 10E-5: pKal = 4.34
Ka2 = 3.6 x 10E-6: pKa2 = 5.44
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
25.11.2003 (2)

Acid-base constant : Ionization constants in water at 25°C
Method : other: measured
Year : 1995
GLP : no data
Test substance : other TS: no purity given

Method : 5 mM aliphatic mono- and dicarboxylic acids in 0.05 M phosphate buffer (pH 7) were treated with ozone+UV and their degradation pathways were investigated by analysing their decomposition products.
Remark : Summary available in English.
Result : pKa1 = 4.43
pKa2 = 5.277
Reliability : (4) not assignable
Original reference in Japanese
25.11.2003 (27)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo : Conversion factors at 25 °C (calculated)

Result : 1 ppm = 5.96 mg/m3
1 mg/m3 = 0.168 ppm
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
09.10.2003 (4)

Memo : Decarboxylation temperature = 230 °C

Reliability : (4) not assignable
Data from non-peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
25.05.2004 (17)

Memo : Dust cloud ignition temperature = 550 °C

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
30.09.2003 (2)

Memo : Lower flammability (explosive) limit: 35 g/m3

Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
26.11.2003 (2) (5)

Memo : Sublimation

Result : At a pressure of 0.097 hPa, the substance has a sublimation temperature of 18.5°C.
Reliability : (2) valid with restrictions
Data from handbook or collection of data
25.11.2003 (12)

Memo : Vapour density in relation to air = 5.04

Remark : Data also published in: Verschueren K (1996). Handbook of Environmental

Data on Organic Chemicals (3. ed). Van Nostrand Reinhold, New York, 137-138

Reliability : (2) valid with restrictions
Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
30.09.2003 (5)

Memo : pH value

Result : Weak acid. 2.7 (saturated solution at 25 °C)
3.2 (0.1% solution)

Reliability : (2) valid with restrictions
Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
09.10.2003 (2)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.00000000000559 cm³/(molecule*sec)
Degradation	:	50 % after 2.9 day(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWIN v.1.90 (2000)
Year	:	2003
GLP	:	
Test substance	:	
Remark	:	In deviation from the U.S. EPA AOPWIN (calculation program) the calculated half-life is based on a mean OH radical concentration of 5E+05 OH radicals/cm3 as a 24 h average
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

25.11.2003 (23)

Type	:	air
Light source	:	other: 100 W Hg arc lamp
Light spectrum	:	> 250 nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	.1 mol/l at °C
Deg. product	:	
Method	:	other (measured)
Year	:	2002
GLP	:	no data
Test substance	:	other TS: Purity 99%
Method	:	A liquid phase kinetic study on the ozonolysis and on the UV-induced ozonolysis of selected dicarboxylic acids was performed. - Decay of ozone in excess dicarboxylic acid solution was measured with an UV spectrophotometer (Varian Cary 50-Bio UV-vis spectrophotometer). - The adipic acid decay was monitored using a flow-cell coupled with FT-IR spectometer at constant ozone concentration. - A 20 ml Pyrex reactor equipped with four quartz windows, forming two perpendicular optical pathways through the reaction mixture at 25 °C was used. The reactor was placed in the UV-VIS spectrophotometer chamber and was aligned to directly measure ozone concentration. In selected experiments, the reactor content was irrigated with UV light (lambda >= 250 nm) using a 100 W Hg arc lamp (Oriel 6281) through high-grade quartz fibre optic bundle (Oriel 77578), which was equipped with a quartz collimating beam probe (77640 Oriel). - Adipic acid concentrations ranged from 0.001 to 0.1 mol/l Ozone produced by an ozone reactor was introduced into the reactor through a capillary tube. Decay of ozone concentrations in selected experiments was measured in the reaction solution according to UV adsorption of dissolved ozone in the region of 240 < lambda < 310 nm.

To determine dicarboxylic acid concentration the peak in the area of 2550-2650 cmE-1 was used, which corresponds to the characteristic overtone frequency of the COOH group.

Result : The results of both methods (ozone decay versus carboxylic acid decay) agreed within +/- 5%.
The measured ozonolysis rate constant for adipic acid in 0.1 mol/l aqueous solution is:
1.7 +/- 0.1 E-3 l/mol/sec
The photoassisted ozonolysis rate constant is:
2.8 +/- 0.2 E-3 l/mol/sec
(The rate constants had been corrected for the ozone-self-decomposition reactions)
The results obtained indicate that ozonolysis and photoinduced photolysis are not significant removal pathways for adipic acid.
The authors estimated the dicarboxylic acid aerosols "lifetime" in air, assuming an ozone mixing ratio of 100 ppbv, which is an upper limit for its summertime mid-latitude continental Northern Hemisphere values. For adipic acid ozonolysis a half-life of about 13,000 years is estimated

Reliability : (2) valid with restrictions
Study well documented and meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

08.09.2005 (28)

Type : water
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant : $cm^3/(molecule*sec)$
Degradation : ca. 50 % after 62 minute(s)
Deg. product :
Method : other (measured)
Year : 1995
GLP : no data
Test substance : other TS: no purity given

Method : 5 mM aliphatic mono- and dicarboxylic acids in 0.05 M phosphate buffer (pH 7) were treated with ozone+UV and their degradation pathways were investigated by analysing their decomposition products.

Remark : Summary available in English.

Result : Compared to the treatment of ozone alone, the treatment with ozone and UV decreased the TOC (total organic carbon) of adipic acids very efficiently. The authors assumed that adipic acid decomposed to inorganic carbon dioxide.
Degradation products after 3 h: formic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, formaldehyd, glutaraldehydic acid.
A t1/2 of 62 min and a 90 % reduction time of 158 min are given for adipic acid.

Reliability : (4) not assignable
Original reference in Japanese

Flag : Critical study for SIDS endpoint

01.10.2003 (27)

Type : other: aerosol
Light source :

Light spectrum : nm
Relative intensity : based on intensity of sunlight

Result : The aerosol and gas phase photooxidation products of cyclohexene-ozone system were investigated. Several dicarbonic acids, hydroxydicarbonic acids, oxodicarbonic acids and aldehydes were formed, pentanal being the predominant cyclohexen degradation product.
Adipic acid was identified in the aerosol as well as in the gas phase:
gas phase molar yield: 1.46 % +/- 0.82
aerosol molar yield: 0.74 % +/- 1.08

Test condition : - Experiments were performed in the dark in two outdoor Teflon chambers of about 22 m3 volume each (25 +/- 2 °C).
- Before the reactants were introduced into the chambers, (NH4)2SO4 seed aerosol (mean diameter 100 nm) was injected at a number concentration of 10000 ml-1.
- Particle number and size were measured with a differential mobility analyser and a condensation nucleus counter.
- To prevent OH oxidation by OH generated in alkene-ozone reactions, Carbon monoxide was added as an OH scavenger.
- All experiments were carried out under dry conditions (relative humidity < 5 %).
- Samples for gas- and particle-phase analysis were taken after the hydrocarbon was essential consumed. Since many reaction products are present in both gas and particle phases, the sampling system consisted of a series of two annular denuders to remove the gaseous reaction products, followed by a teflon-coated quartz fiber filter to collect all particles.

Reliability : (2) valid with restrictions
Basic data given

25.11.2003 (29)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product : no
Method : other: Deduction from chemical structure
Year : 1990
GLP :
Test substance :

Remark : Adipic acid is not expected to undergo hydrolysis in the environment due to the lack of hydrolysable functional groups

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

30.09.2003 (30)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product : yes

Method	:	other: see Method
Year	:	1997
GLP	:	no
Test substance	:	other TS: no purity given
Method	:	Oxidation of aqueous solutions of organics (0.5% or 5 g/l) were performed in a 250 ml Hastealloy C22 autoclave, connected to an air reserve and equipped with a magnetically driven turbine. The reactor was loaded with 150 ml of solution and 1 g catalyst (5 % ruthenium on carbon). After flushing with argon, the temperature of the mixture was raised to 190°C under stirring. Air was then admitted until a pressure of 1.5 MPa was attained and the reaction was started. The total run time was approximately 6 h. All samples were analysed for pH, TOC (Total organic carbon) and by HPLC for reaction intermediates formed during the reaction.
Remark	:	Method was designed for industrial wastewater treatment at 200 °C using Ru catalyst. Formation of chlorinated organics and other byproducts not examined.
Result	:	The intermediate products of adipic acid degradation were glutaric acid, succinic acid, acrylic acid, and acetic acid. Final degradation products are water and carbon dioxide. All reaction products were completely oxidized, resulting in a TOC abatement of more than 99.5 % after 6 h. The limiting reaction was the oxidation of acetic acid formed.
Reliability	:	(2) valid with restrictions Study well documented and meets generally accepted scientific principles
30.09.2003		(31)

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	other: see Method
Year	:	1999
GLP	:	no data
Test substance	:	other TS: no purity given
Method	:	Reactions were carried out with a 270 ml or 1 l autoclave equipped with a sample injector and a valve for sampling. A model wastewater and nitrogen (3 MPa at room temperature) were charged in the autoclave and this was heated to a prescribed temperature. Then, 3 MPa of oxygen was introduced to start the reaction while stirring the solution with a magnetic agitator. The reaction was followed by the decrease in total organic carbon (TOC).
Result	:	Adipic acid TOC was decreased by 13 % after 2 h at 220 °C.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
30.09.2003		(32) (33)

3.1.3 STABILITY IN SOIL

Type	:	laboratory
Radiolabel	:	no
Concentration	:	1000 mg/kg

Soil temperature	:	27 °C
Soil humidity	:	60 other: % of water holding capacity
Soil classification	:	
Year	:	
Content of clay	:	%
Content of silt	:	21 %
Content of sand	:	50 %
Organic carbon	:	5 %
pH	:	5.5 - 6
Cation exch. capacity	:	
Microbial biomass	:	
Dissipation time		
DT50	:	
DT90	:	
Dissipation	:	84 % after 30 day(s)
Deg. product	:	yes
Method	:	other: US Food and Drug Administration (FDA) Environmental Assessment Technical Assistance Handbook
Year	:	1993
GLP	:	no data
Test substance	:	other TS: adipic acid, purity > 99 %
Deg. products	:	124-38-9 204-696-9 carbon dioxide

Method : 1) Biometer flasks contained the equivalent of 25 g of dry soil each. To optimize biodegradation, 5 days prior to test start, the original pH was rised to pH 7.5 by addition of 10 mg CaCO3/g soil. Nutrition solution (0.6 ml of 1% solution (NH4)2HPO4) plus distilled water to bring the soil moisture level to 60% water holding capacity were added to each flask. The test substances were dissolved in this water. Control: soil, treated like the test samples, but received no test compound. Titrations for CO2 and aeration of the flasks through the Ascarite filters were performed initially daily and at 2- to 3-day intervals later in the experiment.

2) A further experiment was carried out to investigate the influence of test solution concentration on the CO2 evolution. Same soil samples were treated as described, but test concentrations of adipic acid were 250, 500, 1000 and 2000 mg/kg.

Result : 1) Cumulative net CO2-evolution during incubation in soil (1000 mg/kg soil; average of three replicates) as percent conversion of calculated carbon content:

day 9: 63%
day 20: 76%
day 30: 84%

2) Cumulative net CO2 evolution (average of triplicate flasks) as percent conversion of calculated carbon content at day 22:

250 mg/kg dw soil: 78.8%
500 mg/kg dw soil: 79.1%
1000 mg/kg dw soil: 91.5%
2000 mg/kg dw soil: 94.1%

60 % degradation was reached in 1 to 6 d.

Adipic acid is readily biodegradable in soil.

Reliability : (2) valid with restrictions
26.05.2004 (34)

Type	:	laboratory
Radiolabel	:	
Concentration	:	
Soil temperature	:	°C
Soil humidity	:	13.3 g water/100g soil dry weight
Soil classification	:	
Year	:	1999
Content of clay	:	%
Content of silt	:	%
Content of sand	:	%
Organic carbon	:	4 %
pH	:	7.2
Cation exch. capacity	:	
Microbial biomass	:	
Dissipation time		
DT50	:	
DT90	:	
Dissipation	:	ca. 60 % after 33 day(s)
Deg. product	:	yes
Method	:	other: Modified Sturm test according to ASTM D 5209-91
Year	:	2001
GLP	:	no data
Test substance	:	other TS: Adipic acid commercial grade
Deg. products	:	124-38-9 204-696-9 carbon dioxide
Method	:	Mixture of forest soil and agricultural soil (1.5 : 1 w/w) has the following properties: pH 7.15; water content 13.3 %; organic substance: 6.79 %; carbon content 3.98 %; nitrogen content: 0.25 %; C:N ratio adjusted to 10 : 1 using (NH4)2HPO4 Sources of soils collected in 1999: - Forest soil from Bukhan Mountain Seoul, Korea; pH 6.84; C-content 4.61 %; N-content 0.29 % - Agricultural soil from Kyunggi-do, Korea; pH 7.32; C-content 1.97 %; N-content 0.13 %
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

26.05.2004 (35)

3.2.1 MONITORING DATA

Type of measurement	:	background concentration
Media	:	air
Concentration	:	
Method	:	
Remark	:	Although the mechanism of formation is not elucidated, it is clear that adipic acid is a secondary photodegradation product formed in the atmosphere.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data
Flag	:	Critical study for SIDS endpoint

24.11.2003 (36)

Type of measurement	:	background concentration
Media	:	air
Concentration	:	.0015 - .0089 µg/l
Method	:	MS

Remark : Among other substances adipic acid was found in concentrations between 1.5 and 8.9 µg/m³ as secondary particles in the atmosphere during a smog period in Los Angeles in 1973.
Concentrations given as µg/m³

Result : Concentration of adipic acid in atmospheric aerosol, Los Angeles:

Sampling times	adipic acid (µg/m³)
21.21-01.20	2.0
01.23-06.21	1.5
06.24-08.20	2.3
08.22-10.20	5.7
10.23-12.20	5.6
12.22-14.20	8.3
14.20-16.20	8.9
16.23-18.23	7.6
18.25-21.21	3.1

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint
26.11.2003 (37)

Type of measurement : background concentration
Media : air
Concentration :
Method :

Remark : Adipic acid is a secondary smog compound which is assumed to be a degradation product of cycloalkenes in the atmosphere. Formation of adipic acid takes place via dialdehyde and omega-oxo carboxylic acid

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint
12.01.2004 (38)

Type of measurement :
Media : other: motor exhaust gases
Concentration : .0011 - .0047 µg/l
Method : GC/MS of butyl esters

Result : Motor exhausts of passenger cars (models of 1971 and 1981) contained 1.1 and 4.7 µg/m3 adipic acid suggesting that adipic acid found in the atmosphere is also a combustion product

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint
13.01.2004 (39)

Type of measurement : background concentration
Media : sediment
Concentration :
Method : GC/MS of butyl esters

Result : Two samples of bog sediments from Nevada contained each 2,050 µg adipic acid/kg. Original data were given as 14 nmol/g. Kawamura and Kaplan (1987) concluded that adipic acid detected in the sediment samples is of predominantly atmospheric origin (presumably from the oxidation of cyclohexene)

Reliability : (2) valid with restrictions

Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
26.05.2004 (39)

Type of measurement : background concentration
Media : soil
Concentration :
Method : GC/MS of butyl esters

Result : In samples of soil from Los Angeles 215-568 µg adipic acid/kg were detected. Original data were given as 1.47 and 3.89 nmol/g. Kawamura and Kaplan (1987) concluded that adipic acid detected in the soil and sediment samples is of predominantly atmospheric origin.
Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles
Flag : Critical study for SIDS endpoint
13.01.2004 (39)

Type of measurement : background concentration
Media : air
Concentration : .000001 - .000012 µg/l
Method : GC/FID/MS

Method : Sampling with Quartz fiber filter (Pallflex TIS-SUQUARTZ 2500QAT-UP), first extraction step with diethylether, second extraction step with 33 % methanol, third extraction step with pure water. The extracts were combined. Pure water was added to achieve a total methanol concentration of 4 %. Sample-separation into different classes of organic compounds using a C-18 solid phase extraction (SPE) cartridge. The aqueous solution passing the SPE-tube contains the not adsorbed dicarboxylic acids (DCAs). The solution was spiked with 2-Bromo-dodecanoic acid and evaporated to dryness. Residue was dissolved in 1-propanol and treated with BF3-propanol-complex to obtain the propyl-ester. DCA-esters were extracted with cyclohexane and analyzed by GC-FID-MS.
Result :

	South Africa	SBO	Vienna	Tokyo	Los Angeles
	ng/m³	ng/m³	ng/m³	ng/m³	ng/m³
Adipic acid	7.9	4.4	117	31	14

SBO: Sonnblick Observatory close to Salzburg, Austria
Data for Tokyo and Los Angeles taken from literature, for Antarctica a background level of 0.9 ng/m³ is cited.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (40)

Type of measurement : concentration at contaminated site
Media : air
Concentration : .000001 µg/l
Method :

Result : About 3 km south of the city center of Gent, samples of atmospheric aerosols were collected during two periods: 12 January - 11 March 1998 (winter) and 10 June - 21 August 1998 (summer).
Average concentrations for both sampling periods were reported:
Winter: 1.1 ± 0.8 ng/m3, summer: 1.3± 2.0 ng/m3.
Reliability : (2) valid with restrictions

Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (41)

Type of measurement : concentration at contaminated site
Media : air
Concentration : 0 - .000002 µg/l
Method : GC-FID and GC-MS
Method : Sampling on glass fiber filters with a collection efficiency of > 99 % for particles over 0.3 µm radius or on a Millipore filter. Analyses of the methyl ester were done by GC-FID and GC-MS (no further details reported, only reference to an earlier paper).
Result : Aerosols in the centre of Heraklion, town on the northern coast of the island of Crete
Concentrations of adipic acid in 1991:
April: 0.27 ng/m3 (free acid)
August: 1.07 ng/m3 (free acid), 1.61 ng/m3 (adipic acid salts).
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (42)

Type of measurement : concentration at contaminated site
Media : air
Concentration : 0 - .000042 µg/l
Method : GC/MS

Method : Sampling on neutral quartz filters (i. e. without KOH impregnation), extraction of the filter with pure water, evaporation to dryness, and conversion into the butyl esters, analysis by capillary-GC-MS for identification and capillary-GC with an integrator. Triplicate analyses showed a variation of about 5-11 %.
Result : Aerosol on the University of Nevada, Las Vegas, in April and May 1997
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (43)

Type of measurement : background concentration
Media : other: Rain and fog
Concentration : .007 - .52 mg/l
Method : GC/MS

Method : Samples were taken in 1983
Rainwater samples from University of California, Los Angeles:
- preserved with HgCl2 and stored at 4 °C
- 50 ml in vacuum concentrated to 2 ml
- pH 8-9 with KOH, dried
Fog from San Gabriel Mountains, north of Pasadena:
- collected with fog water sampler and stored at -20 °C
- 1 or 2 ml samples pH adjusted, dried
Esterification:
- BF3/butanol added and esterification at 100 °C for 30 min
- treatment with TFAA, washing with water, addition of 5 ml hexane
- organic (hexane) phase dreid, repetition of TFAA treatment
- dried and esters dissolved in CH2Cl2, washed and volume adjusted to 50
- 100 µl in hexane
Final analysis:
- GC/MS
Result : Adipic acid concentration was 0.0073-0.18 mg/l in 4 rain water samples

and 0.38-0.52 mg/l in 2 fog samples

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

14.01.2004 (44)

Type of measurement : concentration at contaminated site
Media : air
Concentration :
Method : GC/MS of butyl esters

Result : Adipic acid concentration in air over Los Angeles were 0.08-3.31 nmol/m3 which equals 12-483 ng/m3.
In one air sample of a greenhouse (urban air enriched with plant emissions) in Los Angeles no adipic acid was detectable, in the other sample, 0.22 nmol/m3 were detected.
Los Angeles dust contained 5.9 - 11.4 µg adipic acid per gram of dust

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

07.09.2005 (39)

Type of measurement : concentration at contaminated site
Media : other: Aerosols in Southern California in September 1993
Concentration : 0 - .000024 µg/l
Method : GC/MS

Method : Sampling with quartz fiber filters followed by polyurethane foam or with Teflon particle prefilters followed by a potassium hydroxide impregnated glass fiber filter, extraction, concentration and analysis by GC-MS as methyl ester (derivatization with diazomethane) after addition of perdeuterated standards. Recovery was 61 % on average for the Quartz filters (no more details reported, only reference to earlier papers).

Result : Sampling at 4 urban sites in Los Angeles (Long Beach, Central Los Angeles, Azusa, Claremont) and on San Nicolas Island (in the Pacific Ocean south-west of Los Angeles) on September 8 - 9, 1993, gave the following concentrations of adipic acid in fine particulate matter:
Los Angeles: 0.0 - 24.1 ng/m3 (average: 7.5 ng/m3),
San Nicolas Island: 0.37 - 6.00 ng/m3 (average: 3.43 ng/m3).

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

13.01.2004 (45)

Type of measurement : concentration at contaminated site
Media : air
Concentration : .000031 - .000079 µg/l
Method : capillary-GC-FID and GC/MS

Method : Precipitation samples were collected in brown glass bottles, and mercuric chloride was added as bactericide. The samples were evaporated to dryness, converted to the butyl esters by reacting with borontrifluoride in butanol and analyzed by capillary-GC-FID. Identification took place by GC-MS of the samples and authentic standards.
Aerosol samples were collected on a quartz fiber filter. Total aerosol mass was determined by weighing the filter before and after sampling. Filters were extracted with pure water. The extracts were analyzed as described above for the precipitation samples.
Recovery for adipic acid was 90 %.

Result : Aerosol samples (n = 4), February and July 1992: 31 - 79 ng/m3
Snow samples (n = 3), March 1992: 0.94 - 3.07 µg/l
Rain samples (n = 6), June and August 1992: 0.18 - 7.78 µg/l
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (46)

Type of measurement : background concentration
Media : other: rain water
Concentration : 1.75 µg/l
Method : capillary-GC-FID and GC/MS

Method : Rainwater samples were collected in brown glass bottles, and mercuric chloride was added as bactericide. The samples were evaporated to dryness, converted to the butyl esters by reacting with borontrifluoride in butanol and analyzed by capillary-GC-FID. Identification took place by GC-MS of the samples and authentic standards.
Recovery for adipic acid was 90 %.
Result : Rain water in the Western Pacific Ocean between Japan and New Zealand in September and October 1992
Concentrations of adipic acid in 14 rain water samples: 1.75 - 10.8 µg/l, average: 5.20 µg/l.
For Comparison: Tokyo rain samples (n = 6), June and August 1992: 0.18 - 7.78 µg/l (Sempere and Kawamura 1994)
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (47)

Type of measurement :
Media : other: tobacco smoke
Concentration :
Method :

Remark : Original reference (Graedel 1978) is cited according to BUA Report 1994
Result : Adipic acid is a component of tobacco smoke
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
13.01.2004 (3)

Type of measurement :
Media : other: combustion gases
Concentration :
Method : capillary-GC-MS

Method : Wood samples (6 - 13 kg) were burnt in a traditional fireplace. Smoke samples were withdrawn from the chimney. Particulate emissions were analyzed by extraction, methylation (diazomethane) and capillary-GC-MS (without further details reported, only reference to earlier papers).
Result : Smoke aerosols from burning wood logs in fire places contained (in mg adipic acid/kg wood):
Pine wood: 0.63
Oak wood: 1.75
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (48)

Type of measurement :
Media : other: combustion gases
Concentration :
Method : GC/MS

Method : Woods (5-12 kg) were burnt on residential fire places. Sampling of the smoke (diluted with particle-free air) lasted from the beginning of the wood burning until the virtual end of the burning cycle. Particle were collected in a cyclon separator and on a filter (without further details, only reference to an earlier paper). After addition of deuterated compounds as internal standards, the samples were extracted with hexane and benzene/propanol. The combined extracts were concentrated and derivatized with diazomethane to the methyl esters. Analysis took place by GC/MS.

Result : Adipic acid was quantified in smoke particles from 4 different hard woods (g fine particles/kg wood / % organic carbon of fine particles / mg adipic acid/g organic carbon / mg adipic acid/kg wood combusted):
Yellow poplar: 6.8 ± 0.8 / 84.9 ± 5.1 / 0.154 / 0.89
White ash: 3.3 ± 0.3 / 76.8 ± 5.4 / 0.257 / 0.65
Sweetgum: 3.5 ± 0.4 / 78.8 ± 6.0 / 0.304 / 0.84
Mockernut Hickory: 6.8 ± 0.9 / 74.2 ± 6.4 / 0.222 / 1.1

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint
14.01.2004 (49)

Type of measurement :
Media : other: combustion gases
Concentration :
Method : capillary-GC-MS

Method : Fuel samples (1-5 kg foliage) were burned in fireboxes to simulate burning in the field. Ambient air (20 m3/min) was blown into the box. Sampling of particles took place on Teflon membrane filters (2 µm pore size), semivolatile compounds on polyurethane foam plugs. The mass balance was determined by weighing the filters before and after sampling. The samples were spiked with perdeuterated standards and extracted with hexane/isopropanol. The extracts were concentrated, derivatized with diazomethane to the methyl ester, and analysed by capillary-GC-MS.

Result : Particles from burning of foliar fuels were analyzed. Adipic acid was found in PM2.5 from 4 of 6 foliar fuels tested (PM2.5 mass in g/kg fuel / % of PM2.5 / mg adipic acid/kg fuel):
Loblolly pine: 28.4 ± 11.6 / 0.0028 ± 0.0003 / 0.80
Western hemlock: 11.2 ± 0.7 / 0.0034 ± 0.0002 / 0.38
Mixed hardwood forest litter foliage: 10.8 ± 3.9 / 0.0027 ± 0.0014 / 0.29
Wiregrass/longleaf pine: 27.2 / 0.0059 / 1.60

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint
14.01.2004 (50)

Type of measurement :
Media : other: emissions from food cooking
Concentration :
Method : capillary-GC-MS

Method : The emissions were sampled in dilution with ambient air downstream from the filters and grease extractors in the ventilation system above the cooking appliances. Fine particles were sampled in a XAD-coated denuder / quartz

filter / polyurethane foam sampling train and a quartz filter / polyurethane foam sampling train. Grilling of vegetables in oil was conducted with 22.6 kg vegetables in 1.5 l seed oil over a period of 1 hour. The filters were extracted, and the extracts were evaporated to nearly dryness and analyzed after derivatization to the methyl esters by capillary-GC-MS together with deuterated standards.
Recovery for internal standards (n-hexanoic acid and n-decanoic acid) was 69 ± 15 % for the filter analysis and 62 ± 7 % for the denuder and polyurethane foam analysis.

Result : Vegetables were grilled together with seed oils. Off gasses were withdrawn from the kitchen and analysed for aerosol particles. Results are given as µg adipic acid / kg vegetables fried in canola oil: 33 µg/kg.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (51)

Type of measurement : background concentration
Media : food
Concentration :
Method :

Result : Adipic acid occurs in beet juice (no other information supplied, no literature cited)
Reliability : (2) valid with restrictions
Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
14.01.2004 (13)

Type of measurement : background concentration
Media : food
Concentration :
Method : capillary-GC-FID and capillary-GC-MS

Method : Adipic acid was determined in ripe fruits of Morinda citrifolia (Indian Mulberry, Noni)
Frozen fruits were crushed in deionized water and ammonium sulfate. The slurry was extracted with dichloromethane. The dextract was evaporated nearly to dryness and analyzed with capillary-GC-FID and capillary-GC-MS. Substances were identified by comparison with authentic samples
Result : Ripe fruits contained 0.03 ppm adipic acid
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (52)

Type of measurement : background concentration
Media : biota
Concentration :
Method : GC-MS

Result : Adipic acid occurs in rice straw (not quantified)
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
13.01.2004 (53)

Type of measurement : background concentration
Media : biota

Concentration :
Method : thin layer chromatography, GC-MS and GC-FID

Method : Only few details are described (reference to an earlier paper): Honey samples were extracted with diethylether. Extracts were methylated with diazomethane and separated by preparative thin layer chromatography (1.5 mm layer thickness). 12 Fractions isolated from the plates were analyzed by GC-MS and GC-FID. The quantitation limit was reported to be 0.1 mg/kg honey.
Result : Adipic acid in honey from New Zealand Rewarewa tree (Knightea excelsa) Honey samples from the period 1985-1992 contained adipic acid concentrations of 0.2 - 0.6 mg/kg.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
14.01.2004 (54)

Type of measurement : background concentration
Media : sediment
Concentration :
Method : Oxidation with copper oxide (oxidative hydrolysis)

Result : After oxidation with CuO (oxidative hydrolysis), adipic acid was identified. It was discussed to be released from biotic precursors, presumably lipids. However, it cannot be distinguished whether adipic acid or a precursor (e.g. ester, dial) was present in the sediments
Reliability : (3) invalid
Significant methodological deficiencies
13.01.2004 (55)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : volatility
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: QSAR Estimation Method: HENRYWIN v. 3.10 (2000)
Year : 2003

Result : 8.81 E-2 Pa x m3/mol (calculated with a water solubility of 23 g/l and the average value of vapour pressure according AUER of 0.139 hPa)
9.66 E-7 Pa x m3/mol (Bond method)
8.21 E-8 Pa x m3/mol (Group method)
All results at 25°C
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
01.10.2003 (23)

Type : adsorption
Media : water - soil

Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: QSAR Estimation Method: PCKOCWIN v. 1.66 (2000)
Year : 2003

Result : Koc = 21.5
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
01.10.2003 (23)

Type : adsorption
Media : water - soil
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year : 2002

Remark : Kennedy (2002) cites Swann et al. (1983), which means that the koc was obtained from Reverse phase HPLC. However, Kennedy does give any other information to assess his data.
Result : Soil organic carbon-water distribution coefficient is reported to be Koc = 26
Reliability : (4) not assignable
Documentation insufficient for assessment
09.10.2003 (1) (56)

3.3.2 DISTRIBUTION

Media : other: air - biota - sediment(s) - soil - water - aerosol
Method : Calculation according Mackay, Level I
Year : 2003

Method : Data used in the calculation:
- Temperature (°C): 25
- Molar Mass (g/mol): 146.14
- Vapour pressure (Pa): 13.9
- Water solubility (g/m3): 23 E+03
- log Pow: 0.093

Properties of the compartments:

	Volumina (m3)	Density (kg/m3)	Organic Carbon(%)
Air:	6 E+09	1.185	
Water:	7 E+06	1000	
Soil:	4.5 E+04	1500	2
Sediment:	2.1 E+04	1300	5
Susp.Sedim.:	35	1500	16.7
Aerosol:	0.12	1500	
Aquat.biota:	7	1000	5

Compartment properties were based on the parameters from the first publication of Mackay (1991) as suggested by the Federal Environmental Agency (UBA, Germany).
Result : Based on the model calculations (Mackay level I, V 2.11) the target

compartment of the environmental distribution of adipic acid (124-04-9) is the hydrosphere.
Water: 97.0 %
Air: 2.96 %
Sediment: 0.0096 %
Soil: 0.0095 %
susp. sediment: 6.17 E-05 %
Aerosols: 1.42 E-06 %
Aquatic biota: 6.01 E-06 %

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

26.11.2003 (23)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other: sludge samplings from different sewage plants, rivers, bays and a lake in Japan
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	
Degradation	:	68 - 90 (±) % after 14 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	other: Japanese Guide-line by MITI from 1974. Comparable to OECD 301C Modified MITI Test I
Year	:	1992
GLP	:	no data
Test substance	:	other TS: no purity is given

Remark : A blank control (sterile mineral medium only), positive control (aniline as reference compound at 100 mg/l) and adipic acid control (adipic acid in pure water at 100 mg/l) in 300 ml were incubated simultaneously.
Oxygen consumption resulting from biodegradation of the compounds was measured over 14-day test period using an Okura Electric Closed System Oxygen Consumption measuring apparatus (Coulometer). Percentage biodegradation was calculated based on BOD, TOC and HPLC analysis.
The test solutions were maintained in a darkened room at a temperature of 25 ±1 °C and continuously stirred by magnetic stir bars over the 14-day test period.
Percent degradation (%) was obtained from the following equations.

BOD
Degradation (%) = (BOD - B)/ThOD * 100
BOD (mg): BOD in Sludge + adipic acid system
B (mg): BOD in Sludge blank
ThOD: theoretical oxygen demand required when adipic acid was completely oxidized.

HPLC
Degradation (%) = (Sw - Ss)/Sw * 100

Sw (mg): Residual amount of adipic acid detected by HPLC in Water + adipic acid system
Ss (mg): Residual amount of adipic acid detected by HPLC in Sludge + adipic acid system

Test condition : Sludge samples were collected from the 10 sites such as sewage treatment works, industrial wastewater treatment works, rivers, lakes, and sea throughout Japan and mixed thoroughly. A filtrate (500 ml) of the supernatant of the mixed sludge was then mixed with 5 liters of the filtered supernatant of an activated sludge in the present use.
After the combined sludge solution (pH adjusted at 7.0 ± 1.0) was aerated for about 23.5 hours. 30 min after stopping aeration, the supernatant corresponding 1/3 of the whole volume was discarded. An equal volume of pure water was then added to the remaining portion and the supernatant (final concentration: 0.1 %) of the resulting sludge solution was mixed with sterile mineral medium and continuously aerated at 25 ± 2 °C to allow minimization of residual dissolved organic carbon according to the procedure outlined in the TG.
The test was conducted in triplicate with adipic acid in sterile mineral medium at 100 mg/mL and with a small volume of the activated sludge to give a final MLSS concentration of 30 mg/L

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

Flag : Critical study for SIDS endpoint

09.01.2004 (14)

Type : aerobic
Inoculum : other: effluent from sewage treatment plant
Concentration : 20 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time : 19 day(s)
Degradation : 96.6 (±4.6) % after 19 day(s)
Result :
Deg. product :
Method : OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year : 1980
GLP : no
Test substance : other TS: Purity is not specified

Method : Determination of DOC
Remark : Seven ring tests were performed according to the OECD screening test method test procedure; participants: 10 laboratories. Biodegradation was referred to DOC-elimination; n (determinations) = 16
Result : DOC-elimination (%)
min = 86
max = 100
mean value = 96.6
standard deviation 4.62
n = 16
Kinetic was not described

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

25.11.2003 (57)

Type : aerobic
Inoculum : other: effluent after acclimation
Concentration : 10 mg/l related to DOC (Dissolved Organic Carbon)
related to

Contact time	:	28 day(s)
Degradation	:	91 (±) % after 28 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO_2 evolution)"
Year	:	1979
GLP	:	no
Test substance	:	other TS: No purity is specified
Method	:	The preacclimation was modified in such a way that 20 mg/l of material, 20 mg/l of yeast extract, and 10 % of sewage treatment plant effluent rather than raw sewage were added to BOD water in order to avoid anaerobic conditions.
Remark	:	Besides the carbon dioxide production the DOC removal was followed as a further biodegradation measure. The test employed a preacclimation procedure (28 days without and 42 days including the acclimation). As kinetic values are not reported, no further information concerning the 10-day window could be given.
Result	:	Adipic acid degradation related to CO_2 evolution: 91 % Adipic acid degradation related to DOC removal: 100 %
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions

25.11.2003 (58)

Type	:	aerobic
Inoculum	:	other: 1 drop of effluent per liter
Concentration	:	2 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	83 (±) % after 30 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1979
GLP	:	no
Test substance	:	other TS: purity not specified
Remark	:	related to BOD
Result	:	BODT30 = 83 %
Test condition	:	Inoculum: 1 drop of effluent/l
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions

25.11.2003 (58)

Type	:	aerobic
Inoculum	:	other: 0.05 % STP effluent
Concentration	:	related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	96 (±) % after 19 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1979
GLP	:	no
Test substance	:	other TS: Purity is not specified

Method	:	The test was usually run with a test concentration of 20 mg C/l, later on with 10 mg C/l (no further details). In order to maintain an optimal C:N:P ratio the ammonium concentration specified in the OECD procedure was tripled. A trace metal and an essential vitamin solution were added inorder to optimize test conditions. Inoculation: 0.05 % effluent
Result	:	Result is given as DOC
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions

25.11.2003 (58)

Type	:	aerobic
Inoculum	:	other: sludge samplings from different sewage plants and environmental waters in the vicinity of the laboratory in Germany
Concentration	:	50 mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	14 day(s)
Degradation	:	92 (±) % after 14 day(s)
Result	:	readily biodegradable
Deg. product	:	
Method	:	other: ORIGINAL-MITI-Test, Biodegradability and Bioaccumulation Test of Chemical Substances (C-5/98/JAP) 1978
Year	:	1979
GLP	:	no
Test substance	:	other TS: Purity is not specified

Method	:	Inoculum: 30 mg sludge/l; the inoculum was prepared in accordance with the procedure of the Japanese MITI test with the single exception that the partial inoculum samples were not collected all over Germany but in the closer surroundings of the investigating laboratories. The sapromat used was basically a BOD determination apparatus with an electrolytic oxygen supply.
Result	:	DOC degradation: 96 %
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions

09.01.2004 (58)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	1000 mg/l related to COD (Chemical Oxygen Demand) related to
Contact time	:	
Degradation	:	> 90 (±) % after 5 day(s)
Result	:	inherently biodegradable
Control substance	:	Diethylene glycol
Kinetic	:	11 day(s) > 90 % %
Deg. product	:	
Method	:	Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn-Wellens test"
Year	:	
GLP	:	
Test substance	:	

Test condition	:	Adaptation phase: 1 day
Reliability	:	(2) valid with restrictions Basic data given

Flag : Critical study for SIDS endpoint
29.09.2003 (59)

Type : aerobic
Inoculum : other: surface water of river Main
Concentration : 997 mg/l related to COD (Chemical Oxygen Demand)
345 mg/l related to DOC (Dissolved Organic Carbon)
Contact time :
Degradation : > 95 (±) % after 8 day(s)
Result : inherently biodegradable
Kinetic of testsubst. : 1 day(s) ca. 10 %
2 day(s) ca. 25 %
3 day(s) ca. 40 %
4 day(s) ca. 65 %
7 day(s) > 90 %
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1980
GLP : no
Test substance : other TS: Purity is not specified

Method : 700 mg/L adipic acid was diluted in surface water of the river Main (inoculum); bacterial density: 0.3E5 - 1E5 /ml
Reliability : (2) valid with restrictions
Basic data given
25.11.2003 (59)

Type : aerobic
Inoculum : activated sludge
Concentration : related to DOC (Dissolved Organic Carbon)
related to
Contact time : 14 day(s)
Degradation : 97.9 (±) % after 14 day(s)
Result : inherently biodegradable
Deg. product :
Method : other: Test according to the Zahn-Wellens test adopted in 1981 as OECD 302 B for determining inherent biodegradability
Year : 1980
GLP : no
Test substance : other TS: Purity is not specified

Method : Inoculum: activated sludge (1000 mg/l dry weight substance)
Concentration of the test substance: 100-400 mg/l DOC
Determination of DOC and COD
Remark : Seven ring tests were performed according to the static Zahn Wellens test procedure participated by 10 laboratories.
Biodegradation was referred to DOC-elimination; n = 9
Result : DOC-elimination
min = 92%
max = 100%
mean value = 97.9%
standard deviation 2.57%
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions
29.09.2003 (57)

Type : aerobic
Inoculum : activated sludge
Concentration : 400 mg/l related to DOC (Dissolved Organic Carbon)

related to
Contact time : 14 day(s)
Degradation : 100 (±) % after 4 day(s)
Result : inherently biodegradable
Deg. product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1979
GLP : no
Test substance : other TS: Purity is not specified

Method : The test was started with 1 g sludge/l
The mean DOC removal is reported with its tolerant limits at a 95 % probability level.
Remark : Results refer to CO2 evolution
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions

30.09.2003 (58)

Type : aerobic
Inoculum : activated sludge, domestic
Concentration : related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : 99 (±) % after 1 day(s)
Result :
Deg. product :
Method : OECD Guide-line 303 A "Simulation Test - Aerobic Sewage Treatment: Coupled Unit Test"
Year : 1979
GLP : no
Test substance : other TS: Purity is not specified

Method : The test was started with a full load of 2.5 g/l of dry matter (sludge from a municipal sewage treatment plant); working-in time: 1 day.
The mean DOC removal is reported with its tolerant limits at a 95 % probability level.
Remark : DOC-removal 99 +/- 4 %
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions

09.01.2004 (58)

Type : aerobic
Inoculum :
Concentration : related to COD (Chemical Oxygen Demand)
related to
Contact time :
Degradation : 56 (±) % after 28 day(s)
Result :
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1988
GLP : no
Test substance : other TS: 60% adipic acid (production residue)

Remark : It is not clear how the other compounds affected the degradation of the adipic acid.
Test substance : Test substance consisted of a mixture containing:
Adipic acid: 60%

Glutaric acid: 14%
Succinic acid: 6%
Carbon: 10%
Vanadium pentoxide: 6.5%
Copper nitrate: 3%
Copper: 0.5%

Reliability : (2) valid with restrictions
Basic data given

30.09.2003 (60)

Type : aerobic
Inoculum : other: activated sludge or sewage
Deg. product :
Method : other: Manometric BOD measurements
Year : 1997
GLP : no data
Test substance : other TS: blend of 2-ethyl hexanol + adipic acid ; blend of butanol + adipic acid

Method : The study was conducted to compare four dispersal techniques: direct addition, dispersion by ultrasound, emulsification, and dosing in the form of a Freon solution. Manometric BOD determinations were performed on a biochemical analyzer on which oxygen demand is observed by means of U-tube pressure gauge placed between measuring and compensating flasks.
Remark : No specification of the blend. Method and results concerning adipic acid are poorly described. Variations in the protocol included methods of substrate dosage
Result : Biological degradation of substrate dosed by technique of weighing plus sonification (30 min.):

2-Ethyl hexanol + adipic acid

mass of substrate (mg)	BODultimate (mg/l)	BODu/ThOD (%)
3.96	1564	58.8
3.88	1473	55.3

butanol + adipic acid

mass of substrate (mg)	BODultimate (mg/l)	BODu/ThOD (%)
2.81	763	34.1
2.96	564	35.2

Reliability : (3) invalid
Documentation insufficient for assessment

30.09.2003 (61)

Type : aerobic
Inoculum : activated sludge, domestic
Contact time : 30 day(s)
Degradation : ca. 75 (±) % after 10 day(s)
Result :
Kinetic of testsubst. : 2 day(s) ca. 22 %
4 day(s) ca. 44 %
8 day(s) ca. 75 %
10 day(s) ca. 78 %
30 day(s) ca. 85 %
Deg. product :
Method : other: Modified Sturm test according to ASTM D 5209-91
Year : 2001

GLP	:	
Test substance	:	other TS: Adipic acid commercial grade
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
30.09.2003		(35)
Type	:	aerobic
Inoculum	:	other: Acinetobacter calcoaceticus LB2
Contact time	:	30 day(s)
Degradation	:	ca. 80 (±) % after 30 day(s)
Result	:	
Kinetic of testsubst.	:	2 day(s) ca. 25 % 4 day(s) ca. 40 % 10 day(s) ca. 60 % 20 day(s) ca. 70 % 30 day(s) ca. 80 %
Deg. product	:	
Method	:	other: Modified Sturm test according to ASTM D 5209-91
Year	:	2001
GLP	:	no data
Test substance	:	other TS: Adipic acid commercial grade
Method	:	Strains degrading the adipic acid were isolated from activated sludge soil of Seoul municipial sewage treatment plant by minimal agar medium containing 0.1 % of the substance as a sole carbon source at 27 °C for 15 days after incubation with 1 ml of the bacterial suspension (1E6 cells/ml). The bacterial growth rates were measured using spectrophotometer (UV-1201, Shimadzu, Japan). Strains were identified by using the fatty acid methyl esters (FAMEs) analysis according to Miller and Berger (Bacteria identification by gas chromatography of whole cell fatty acid. Hewlett-Packard application note. Hewlett Packard Co., Palo Alto, Calif: 228-238, 1985). The Sturm test was performed with A. calcoaceticus.
Remark	:	Results refer to CO2 evolution
Result	:	The four strains growing most rapidly on adipic acid are (relative degradation activity): Acinetobacter calcoaceticus LB2 (100 %) > Methylobacterium mesophilicum LB9 (91.7 %) > Ochrobactrum anthropi LB13 (70.3 %) > Rhodococcus erythropolis LB17 (60.1 %)
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
26.05.2004		(35)
Type	:	aerobic
Inoculum	:	other: mixture of forest soil / agricultural soil
Contact time	:	33 day(s)
Degradation	:	ca. 60 (±) % after 33 day(s)
Result	:	
Kinetic of testsubst.	:	4 day(s) ca. 11 % 8 day(s) ca. 28 % 14 day(s) ca. 40 % 25 day(s) ca. 52 % 30 day(s) ca. 58 %
Deg. product	:	
Method	:	other: Modified Sturm test according to ASTM D 5209-91
Year	:	2001
GLP	:	no data

Test substance : other TS: Adipic acid commercial grade

Method : Mixture of forest soil and agricultural soil (1.5 : 1 w/w) has the following properties: pH 7.15; water content 13.3 %; organic substance: 6.79 %; carbon content 3.98 %; nitrogen content: 0.25 %; C:N ratio adjusted to 10 : 1 using (NH4)2HPO4
Sources of soils:
- Forest soil from Bukhan Mountain Seoul, Korea; pH 6.84; C-content 4.61 %; N-content 0.29 %
- Agricultural soil from Kyunggi-do, Korea; pH 7.32; C-content 1.97 %; N-content 0.13 %

Remark : Results refer to CO2 evolution

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

26.05.2004 (35)

Deg. product :

Method : other: measured or calculated

Year : 1993

GLP : no data

Test substance :

Method : A Structure-biodegradation-relationship using a non-linear group contribution method and using the "neural" networking have been developed.
The experimental study was conducted using an automated continuous oxygen uptake and BOD-measuring Voith Sapromat B-12 (12 unit system).
- The nutrient solution was an OECD synthetic medium consisting of measured amounts per liter of deionized distilled water of a mineral salts solution; a trace salts solution, and a solution (150 mg/l) of yeast extract as a substitute for vitamin solution.
- The microbial inoculum was an activated sludge from the Little Miami wastewater plant in Cincinnati, Ohio, receiving municipal waste water.
- Activated sludge was aerated for 24 h before use
- The sludge biomass was added to the medium at a concentration of 30 mg/l total solids.
- Test and control compounds concentrations in the media were 100 mg/l
- Reaction vessels were incubated in the dark at 25 °C and stirred continuously throughout the run.
- The incubation period was between 28 and 50 days.

Remark : Although measuring procedure is described it is not clear which results were taken from literature and which were measured during the study.

Result : It was shown that the nonlinear group contribution method using "neural" network is able to provide superior fit to the training set data and test set data and produces a lower prediction error than the previous linear method.

Adipic acid -ln(k) values

experimental:	2.96
"neural" network:	2.93
linear method:	2.94

Reliability : (4) not assignable
Documentation insufficient for assessment

01.10.2003 (62)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : 3.16
Elimination :
Method : other: calculated with BCFWIN v. 2.14 (2000)
Year : 2003
GLP :
Test substance :

Result : calculation from Kow
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
24.11.2003 (23)

BCF : .68
Elimination :
Method :
Year : 2002
GLP :
Test substance :

Remark : Kennedy (2002) states that the BCF (= 0.68) is estimated from the data of Hansch, Leo, and Hoekman (1995) but does not specify the method.
Reliability : (4) not assignable
Secondary literature
08.10.2003 (22) (1)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC0	:	>= 1000
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: UBA-Verfahrensvorschlag: "Letale Wirkung beim Zebrabaerbling Brachydanio rerio, LC0, LC50, LC100; 48-96 h" (Mai 1984)
Year	:	1991
GLP	:	yes
Test substance	:	other TS: Purity 99.9 %
Method	:	Guideline proposal of the German Federal Environmental Agency (UBA)
Remark	:	Accepted new scientifically name for Brachydanio rerio is Danio rerio. It is assumed that the test solution was buffered because the pH remained between 7.4 and 7.7
Result	:	97 % of the test substance was recovered based on analytical monitoring
Test condition	:	- The test was conducted in a 5 l aquarium (300x135x200 mm) filled with the test medium (synthetic origin, prepared according to ISO). - 10 (3-month-old) fishes were used. Length: 2.5 to 3.5 cm - Just one nominal concentration was tested (1000 mg/l). The concentration was analytically checked every 24 h by ion chromatography. - The values of temperature (21.8 to 22.5 °C), oxygen concentration (88.8 to 102.8 % of the saturation level) and pH (7.4 to 7.7) had no significant variation during the test. - Analytical monitoring: ion chromatography
Reliability	:	(1) valid without restriction Test procedure in accordance with national standard method
Flag	:	Critical study for SIDS endpoint

26.05.2004 (63)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 97
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Method by US-EPA 1975 (EPA-660/3-75-009)
Year	:	1976
GLP	:	no
Test substance	:	other TS: Reagent grade
Method	:	"Methods for Acute Toxicity Testing with Fish, Macroinvertebrates and Amphibians", Ecological Research Series, EPA-660/3-75-009, National Environmental Research Center, Office of Research and Development, U.S.
Result	:	Only nominal concentrations are given. In Lake Superior water the following results were obtained: 24 h-LC50=172 mg/l

48 h-LC50=114 mg/l
72 h-LC50= 97 mg/l
96 h-LC50= 97 mg/l

Test condition : - Fish were previously acclimated in flowing water (from Lake Superior) for at least 48 h.
- Fish were not fed during the test.
- The test medium was Lake Superior water.
- At least five concentrations and a control were tested.
- 2 glass jars containing 2 l of test solution and 10 fish (4-8 week old), with a length of 1.1-3.1 cm per jar were used at each concentration level. Jars were covered with glass to reduce evaporation, no aeration.
- Oxygen concentration was >= 4 mg/l and the pH was < 5.9. Temperature was in the range of 18-22 °C.

Reliability : (3) invalid
Significant methodological deficiencies

Flag : Critical study for SIDS endpoint

09.01.2004 (64)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC0 : 147
LC50 : 230
Method : other: DIN-Standard 38412 Part 15 (Fish, Acute toxicity test)
Year : 1980
GLP : no
Test substance : other TS: Purity 99.8%

Method : Method of the German Standards Institution, Berlin, Germany
Result : LC50, was estimated with Probit Analysis.
Other results:
24h-LC50=320 mg/l
48h-LC50=230 mg/l
The low pH values with higher substance concentrations might be jointly responsible for the toxicity development in this fish test.
Source : BASF AG Ludwigshafen
Test condition : - The test was conducted with 10 l solution in a 300x220x240 mm aquarium.
- Dilution water with Ca hardness of 82 mg/l and Mg hardness of 12 mg/l was obtained by addition of 344 mg/l CaSO4x2H2O, 124 mg/l MgSO4x7H2O, 70 mg/l NaHCO3 and 3 mg/l KCl.
- 10 (3-month-old) fishes were used and previously adapted during 3 days. Length: 6.3 cm
- The following nominal concentrations were tested (68.1, 100, 147, 215, 316 and 464 mg/l).
- The test temperature was 20 +/- 1°C, oxygen concentration >6 mg/l and pH 7-8 at the start of the controls.
- The following pH values were measured (concentrations in mg/l):
The pH values were as follows (concentrations in mg/l):

conc.	0 h	24 h	48 h	72 h	96 h
0		7.8	7.9	8.0	8.0	7.9
68.1		5.6	5.9	6.2	6.4	6.5
100		4.9	5.2	5.4	6.4	7.0
147		4.6	4.8	4.8	5.0	6.4
215		4.3	4.5	4.5	4.5	4.7
316		4.0	4.3	4.3		
464		3.8	4.0			

The oxygen concentrations were as follows (mg/l):

conc.	0 h	24 h	48 h	72 h	96 h

		0 8.9 8.8 8.9 9.0 8.9 68.1 7.7 8.1 8.0 8.1 6.5 100 8.2 8.4 7.9 6.9 6.8 147 7.9 8.6 8.5 5.5 2.3 215 8.1 8.6 8.6 7.6 2.7 316 8.7 8.8 9.1 464 8.5 9.2
Reliability	:	(2) valid with restrictions Test procedure according to national standard methods
Flag	:	Critical study for SIDS endpoint
12.01.2004		(65)

Type	:	other: not specified
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	97
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: calculation
Year	:	2001
GLP	:	no data
Test substance	:	other TS: Purity is not specified
Result	:	Measured LC50 concentration was obtained from Aquire Database. Experimental and calculated results are given as -log LC50 (mol/l): - Measured -log LC50 = 3.18 (LC50 = 97 mg/l) - Calculated -log LC50 = 3.08 (LC50 = 122 mg/l)
Reliability	:	(4) not assignable Secondary literature
09.01.2004		(66)

Type	:	semistatic
Species	:	Salmo gairdneri (Fish, estuary, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	= 100
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: Liebmann and Stammer (1960) Handbuch der Fischwasser und Abwasser-Biologie
Year	:	1972
GLP	:	no
Test substance	:	other TS: Purity not specified
Remark	:	The main target of the study was to evaluate the toxic effect of a group of chemicals (mixture) as they are present in waste water.
Result	:	48h-LC0=100 mg/l 24h-LC100= >200 mg/l
Test condition	:	- Fish were previously acclimated with well water for at least 10 days. During the test no food was given - Test was performed in a closed circulation system - 2 year-old fish were used - Temperature during the test: 16 - 21.5 °C - The oxygen concentration was maintained at 8.4 mg/l.
Reliability	:	(2) valid with restrictions Basic data given
24.11.2003		(67)

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	>= 1000
Limit test	:	
Analytical monitoring	:	no
Method	:	other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Arbeitskreis "Fischtest" im Hauptausschuss "Detergentien" (15.10.73)
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Test solution was neutralised.
Reliability	:	(4) not assignable Documentation insufficient for assessment

08.08.2003 (68)

Type	:	
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	24 hour(s)
Unit	:	mg/l
LC50	:	< 330
Limit test	:	
Analytical monitoring	:	no
Method	:	other: The method used was outlined in Freeman L (1953) "A Standardized Method for Determining Toxicity of Pure Compounds to Fish
Year	:	1965
GLP	:	no
Test substance	:	other TS: Purity is not specified
Result	:	Results given as TLm (Median Tolerance Limit), which is defined as the concentration of a substance which is lethal to 50% of the test animals in an arbitrary time of period
Reliability	:	(4) not assignable Documentation insufficient for assessment

01.10.2003 (69)

Type	:	
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	> 100
Method	:	
Year	:	2002
GLP	:	
Test substance	:	other TS: purity 100 %
Reliability	:	(4) not assignable Manufacturer data without proof

09.10.2003 (25)

Type	:	
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	97

Method	:	
Year	:	2002
GLP	:	
Test substance	:	other TS: purity 100 %
Reliability	:	(4) not assignable Manufacturer data without proof

09.10.2003 (25)

Type	:	
Species	:	other: see below
Exposure period	:	
Unit	:	mg/l
LC50	:	97 - 172
Method	:	
Year	:	1990
GLP	:	
Test substance	:	other TS: Purity is not specified
Result	:	Measured LC50 concentrations were obtained from Aquire Database. They were compared with the predicted LC50 using QSAR-models. The duration of the test as well as other details about the test system are not given. The following results are reported: - For Fathead minnow (Pimephales promelas): - LC50 measured: 97, 97, 114, 172 mg/l - LC50 calculated: 10287 mg/l - For Rainbow trout (Oncorhynchus mykiss): - LC50 measured: not available - LC50 calculated: 11876 mg/l - For Bluegill (Lepomis macrochirus): - LC50 measured: 330 mg/l - LC50 calculated: 13251 mg/l In comparison to the available measured data, calculated values are not satisfactory.
Reliability	:	(4) not assignable Secondary literature

29.09.2003 (70) (71)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC0	:	62.5
EC50	:	85.7
EC100	:	125
Analytical monitoring	:	no
Method	:	other: EG-Richtlinie 79/831/EWG, C.2 "Akute Toxizitaet fuer Daphnien"
Year	:	1988
GLP	:	no data
Test substance	:	
Remark	:	At adipic acid concentrations of up to 215 mg/l the oxygen concentrations droped within 4 days indicating that adipic acid was biodegraded by microorganisms.

pH values in the test solutions ranged from 4 (500 mg/l) to 7.7 (15.6 mg/l) and pH related effects on the daphnids cannot be excluded.

Result : Just nominal concentration values are available. The same effect concentrations were reported after 24h.

Source : BASF AG Ludwigshafen

Test condition : The test was performed under the following conditions:
- Test organism: Daphnia magna Straus
- The test system consists of 4 parallel test vessels per concentration level and at least 4 for the control. Each vessel was filled with 2 to 24 h-old Daphnia, the total number per concentration level was 20 organisms
- Test temperature between 19-20 °C
- Dilution water: Source = Synthetic fresh water, Hardness = 2.7+/-0.5 mmol/l Ca + Mg, Ca/Mg ratio = 4:1, Na/K ratio = 10:1, pH = 7.7-8.3
- pH values and oxygen concentrations were measured during the test in one of the test-vessels per concentration level.
- The pH values were as follows (concentrations in mg/l)

conc.	0 h	48 h
0	7.94	7.95
15.62	7.14	7.73
31.2	6.68	7.55
62.5	5.77	7.2
125	4.88	5.26
250	4.36	4.48
500	3.99	4.08

- The oxygen concentrations were as follows (mg/l)

conc.	0 h	48 h
0	9.65	8.72
15.62	9.46	7.56
31.2	9.28	6.67
62.5	9.10	6.42
125	9.13	2.04
250	9.05	8.14
500	9.08	8.67

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

Flag : Critical study for SIDS endpoint

09.01.2004 (72)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Scenedesmus subspicatus (Algae)
Endpoint : biomass
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : 26.6
EC20 : 13.6
EC90 : 56.9
Limit test :
Analytical monitoring : no
Method : other: DIN-Standard 38 412 Part 9 (Alga, Growth Inhibition Test)
Year : 1988
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Method of the German Standards Institution, Berlin, Germany.
To measure biomass, algae suspension was illuminated with short light impulse at 435 nm and the fluorescence at 685 nm was

measured. Biomass was determined at 0, 24, 48 and 72 hours and the pH-value after 0 and 72 hours.
Cell concentration in the control cultures increased by a factor of at least 16 within a 3-day period (validity criteria)

Remark : Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus

Result : Results are give as effective concentrations for 20, 50 and 90 % growth inhibition (referring to nominal concentrations).

After 24, 48 and 72 h the following effect concentrations were observed:

24 h: EC20 = 42.4 mg/l EC50 = 68.1 mg/l EC90 = 125 mg/l
48 h: EC20 = 35.4 mg/l EC50 = 47.8 mg/l EC90 = 84.5 mg/l
72 h: EC20 = 15.1 mg/l EC50 = 31.3 mg/l EC90 = 59.6 mg/l

Source : BASF AG Ludwigshafen

Test condition :
- Static conditions
- Algal inoculum 10000 cells/ml initial cell density
- 10 ml reagent tubes with flat bottoms
- Temperature 23 +/- 2 °C
- Lighting 120 µE/m2s
- Culturing media, comparable to algal nutrient solution
OECD TG 201, containing (after aeration pH = 8):
15 mg/l NH4Cl, 2 mg/l MgCl2*6H2O, 18 mg/l CaCl2*2H2O, 15 mg/l MgSO4*7H2O, 1.6 mg/l KH2PO4, 0.08 mg/l FeCl3*6H2O, 0.1 mg/l Na2EDTA*2H2O, 0.185 mg/l H3BO3, 0.415 mg/l MnCl2*4H2O, 50 mg/l NaHCO3 and 0.003 mg/l ZnCl2, 0.0015 mg/l CoCl2*6H2O, 0.00001 mg/l CuCl2*2H2O and 0.007 mg/l Na2MoO4*2H2O
- pH values (* without algae, ** with algae)

conc.	0 h*	96 h**
0	8.1	10.1
1.95	7.7	10.2
3.91	7.3	10.2
7.81	6.9	10.1
15.6	6.6	9.7
31.3	6.0	8.2
62.5	5.1	5.4
125	4.5	4.7
250	4.1	4.2
500	3.8	3.9

Reliability : (2) valid with restrictions
Test procedure according to national standard methods

Flag : Critical study for SIDS endpoint

26.05.2004 (73)

Species : Scenedesmus subspicatus (Algae)
Endpoint : growth rate
Exposure period : 7 day(s)
Unit : mg/l
EC50 : 610
Limit test :
Analytical monitoring : no
Method : other: according to modified ISO 8692-1989
Year : 2000
GLP : no data
Test substance : other TS: specified as commercially available standard compounds

Remark : Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus
It is unclear whether the algae are within the exponential

growth throughout the whole exposure period of 7 days.

Result : Nominal concentrations
Endpoint biomass: EC50=890 mg/l

Test condition : - 7 day incubation with 12 hour day/night rhythm of lighting at 100 µE/m2/s
- Static conditions
- Each sample contained approx. 10000 cells/ml algal culture
- Concentrations were chosen so that 4-5 of them covered 10-90 % inhibition. Per concentration 4 samples and 4 blanks were prepared.

Reliability : (3) invalid
Documentation insufficient for assessment (long exposure duration, information missing on the exponential growth of the algae during the whole exposure period)

26.05.2004 (74)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 17 hour(s)
Unit : mg/l
EC10 : 65
EC50 : 91.9
EC90 : 118.7
Analytical monitoring : no
Method : other: DIN-Standard 38 412 Part 8 (Cell Multiplication Inhibition Test)
Year : 1987
GLP : no
Test substance : other TS: Purity is not specified

Method : Static incubation
- 100 ml test solution containing nutrient medium (all media for test and culture are described in detail in the method)
- Cell multiplication measured turbidically at 436 nm

Source : BASF AG Ludwigshafen

Test condition : Total volume = 100 ml
Test temperature = 20 °C
pH values depended on the nominal concentrations tested (mg/l):

conc.	pH
0	7.89
3.91	7.02
7.81	6.94
15.625	6.78
31.25	6.47
62.5	5.47
125	4.65

pH values in the test solutions ranged from 4.65 (125 mg/l) to 7.89 (0 mg/l) and pH related effects on the bacteria cannot be excluded.

Reliability : (2) valid with restrictions
Test procedure according to national standard methods

Flag : Critical study for SIDS endpoint

09.01.2004 (75)

Type : aquatic
Species : activated sludge
Exposure period : 3 hour(s)
Unit : mg/l
EC10 : 611
EC50 : 4747

Analytical monitoring	:	no
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1988
GLP	:	no
Test substance	:	other TS: 60 % adipic acid (production residue)
Remark	:	Results were calculated for adipic acid using the adipic acid percentage (60 %) and the reported results for the production residue: EC10 = 1018 mg/l and EC50 = 7911 mg/l
Test condition	:	- The following concentrations were tested: 1000, 1800, 3200, 5600 and 10000 mg/l - Aerated and stirred during 3 h at 20 °C - Oxygen consumption was recorded for over 10 minutes pH values were as follows (conc. in mg/l): conc. pH 1000 7.8 1800 8.0 3200 8.0 5600 7.9 10000 7.3
Test substance	:	Test substance consisted of a mixture containing: Adipic acid: 60% Glutaric acid: 14% Succinic acid: 6% Carbon: 10% Vanadium pentoxide: 6.5% Copper nitrate: 3% Copper: 0.5%
Reliability	:	(2) valid with restrictions Test procedure in accordance with guideline. Described in sufficient detail
Flag	:	Critical study for SIDS endpoint

26.05.2004 (76)

Type	:	aquatic
Species	:	Tetrahymena pyriformis (Protozoa)
Exposure period	:	40 hour(s)
Unit	:	mg/l
EC50	:	36
Analytical monitoring	:	no
Method	:	other: Growth Impairment Test
Year	:	1999
GLP	:	no data
Test substance	:	other TS: Purity > 95%
Method	:	Test was performed according to the method described by Schultz TW (1997) TETRATOX: Tetrahymena pyriformis population growth impairment endpoint. A surrogate for fish lethality. Toxicol. Methods 7, 289-309
Remark	:	The aquatic toxicity of a group of aliphatic mono- and dicarboxylic acids and sodium salt was tested in the Tetrahymena population growth assay in order to related these values with the corresponding octanol-water partition coefficients.
Result	:	Result was given as log IG50 = -0.61, IG50 in mM. IG50 = 50% growth inhibition concentration
Test condition	:	- Test was performed using the freshwater ciliate Tetrahymena pyriformis (strain GL-C) - Test conditions, non-neutralised, allow for 8-9 cell cycles in control cultures - The pH of the test media was 7.3 and was not controlled during the test

- Prior to testing in duplicate for three replicates, the compound was tested in a range finder. Test replicates consisted of 6 to 8 concentrations with duplicate flasks of each concentration.
- The endpoint population density was measured spectrophotometrically at 540 nm

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
09.01.2004 (77)

Type : aquatic
Species : Pseudomonas fluorescens (Bacteria)
Exposure period : 16 hour(s)
Unit : mg/l
EC0 : 10000
Analytical monitoring : no
Method : other: DIN-Standard 38 412 Part 8 (Cell Multiplication Inhibition Test)
Year : 1974
GLP : no
Test substance : other TS: Purity is not specified

Test condition : Adipic acid solution (10 g/l) was neutralized
Reliability : (4) not assignable
Documentation insufficient for assessment
09.01.2004 (78)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species : other terrestrial plant: Astragalus sinicus
Endpoint : growth
Exposure period :
Unit : mg/l
EC50 : ca. 20
Method : other: Petri dish bioassay
Year : 2001
GLP : no data
Test substance : other TS: Purity >98%

Remark : EC50 value was estimated from the given values of concentration (µmol/l) and the corresponding root length (%).
Result : % of root length of Chinese milk vetch seedlings incubated in adipic acid:

Concentration (µmol/l)	Concentration (mg/l)	root length (%)
0	0	100

50	7.3	112+/-3
100	14.6	80+/-11
200	29	37+/-5
400	58	42+/-2
800	117	26+/-1

Test condition : - 2 pieces of filter paper were placed in each Petri dish and 5 ml of distilled water or the relevant fractions at different level of dilution was added to moisten the filter paper. After solvents had evaporated from the hexane and the ethylacetate fractions, 5 ml of distilled water were added to each dish, followed by 10 pregerminated Chinese milk vetch seeds, and the dishes were incubated at room temperature of 28-31°C, three replicates were made. After 5 days, the lengths of shoot and the longest root were recorded.

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

02.10.2003 (53)

Species : Raphanus sativus (Dicotyledon)
Endpoint : emergence
Exposure period : 6 day(s)
Unit : mg/l
EC50 : ca. 1000
EC0 : ca. 134
Method : other: Seed germination test
Year : 2001
GLP : no data
Test substance : other TS: Adipic acid commercial grade

Method : Germination rate was observed of young radish seeds. 10 ml of 0.01 % (0.134 g/l), 0.1 % (1.34 g/l), 1 % (13.4 g/l) and 5 % (67 g/l) adipic acid test solution was added to petri dishes padded with filter paper and then 50 young radish seeds were sown on them. After culture at 20 °C for 6 days, the germination rate and health state of the roots were examined. The electric conductivity was checked prior to the test using a water quality checker (U-10, Horiba, Japan).

Result : No salinity effect on the growth of radish was assumed, because conductivity was well below 5 mS/cm.
At a concentration of 0.01 %, little difference was observed in the germination rate as well as in the growth of leaf, stem and root compared to the control experiment.
Germination rate decreased at a concentration of 0.1 % (88 %). The germination rate dropped to 47 % in the presence of 1 % adipic acid. When the concentration increased further to 5 %, the germination rate was zero.

Reliability : (2) valid with restrictions
Study meets generally accepted scientific principles

Flag : Critical study for SIDS endpoint

02.10.2003 (35)

Species : other terrestrial plant: Triticum aestivum (Monocotyledon)
Endpoint : growth
Exposure period : 3 day(s)
Unit : mg/l
EC50 : ca. 170
Method : other: see Test conditions
Year : 1949
GLP : no
Test substance : other TS: Purity is not specified; Adipic acid solutions were adjusted to pH 4.3 with KOH

Result	:	The following resuls are obtained: EC(6) = 0.05 mM = 7.3 mg/l EC(27) = 0.25 mM = 37 mg/l EC(56) = 1.25 mM = 183 mg/l EC(88) = 6.25 mM = 913 mg/l
Test condition	:	- Wheat seeds were germinated on moist filter paper in the laboratory. When the roots measured 6-7 mm, the seedlings were transferred to the beakers containing the test solutions so that the primary roots extended through cheesecloth perforations into the solutions. After 64 to 68 h growth in the dark at a constant temperature of 20 °C, the primary root length of each seedling was measured. The growth was calculated as % of the growth given by the control. Duplicate lots of 25 seedlings each were used for each solution.
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles

02.10.2003 (79)

Species	:	Lactuca sativa (Dicotyledon)
Endpoint	:	other: germination
Exposure period	:	3 day(s)
Unit	:	mg/l
EC50	:	6722
Method	:	other: inhibition of germination
Year	:	1975
GLP	:	no
Test substance	:	other TS: Purity is not specified

Result	:	The result is given as LC50 = 46 mmol/l pH at the given concentration = 3.25
Reliability	:	(4) not assignable Documentation insufficient for assessment

26.05.2004 (80)

Species	:	other terrestrial plant: Avena (Monocotyledon)
Endpoint	:	growth
Exposure period	:	0 day(s)
Unit	:	mg/l
Method	:	other: see test conditions
Year	:	1939
GLP	:	no
Test substance	:	other TS: Purity is not specified

Remark	:	Although species not mentioned, it is assumed that Avena sativa was used.
Result	:	In the concentration range tested (0.08 to 100 mg/l) greatest inhibition was observed in the range 25 to 100 mg/l.
Test condition	:	- The compounds tested were dissolved in distilled water and mixed with 3 % agar - All agar was washed in daily changes of distilled water for a period of two weeks before use - The agar solutions were then poured into molds 10.7x8x1.5 mm - The Avena test plants were cultured and tested in a laboratory maintained at 25°C, 85-90 % relative humidity and illuminated only with phototropically inactive light - 4-day-old Avena seedlings were used (ca. 20-25 mm) for obtaining decapitated coleoptiles -After 40 min the agar blocks were applied across the terminal ends of the

coleoptile stumps
-In every set of tests plain 1.5 % agar blocks were applied to 12 test plants (controls) as the basis for estimating the growth stimulating qualities of the compound tested
- 8 hours after the application of the agar blocks the measurements were made with a small millimeter rule

Reliability : (4) not assignable
Documentation insufficient for assessment

01.10.2003 (81)

Species : other terrestrial plant: Prunus persica
Endpoint : other: Injury
Exposure period : 14 day(s)
Unit :
Method : other: see test conditions
Year : 1949
GLP : no
Test substance : other TS: Purity is not specified

Result : A moderate injury at a concentration of 2 pounds per 100 gallon (ca. 2.40 kg/m³) is reported.
Mixed with lime the substance lost their phytotoxicity, but became extremely phytotoxic when mixed with nicotine-bentonite.

Test condition : -The substance was suspended in water.
-The plants were sprayed. The small limbs or small plants were completely covered with the spray.
-To consider the compatibility of the substance with adjuvants, lime or lime plus bentonite was added.

Reliability : (3) invalid
Documentation insufficient for assessment

01.10.2003 (82)

Species : other terrestrial plant: Tobacco plant (Nicotiana tabacum L. cv. samsun NN)
Endpoint : growth
Exposure period :
Unit :
Method :
Year : 2001
GLP : no data
Test substance : other TS: Purity is not specified

Remark : It isn´t excluded that the water evaporated from the solution applied on the leaf surfaces thus increasing toxicity.
Cell culture experiments have been perfomed but no results clearly presented. Although this experiment was performed in solution, no concentration is reported and milliequivalents were mixed up with concentrations

Result : Plant growth almost stopped immediately after exposure to adipic acid solution. All samples withered within a few days after exposure of the leaf surface to adipic acid.

Test condition : - pH was adjusted to 5.8+/-0.2 using a buffer solution (morpholinoethanesulfonic acid).
- Tobacco plants which had been grown on soil until 4 to 5 leaves appeared were used on the test.
- Each leaf was sprayed with 2.5 ml of the carboxylic acid (5 µeq) solution using an atomizer.
- Tests were performed in parallel with 2 monocarboxylic (formic and acetic acid) and 2 dicarboxylic acids (succinic acid and adipic acid).

Reliability : (3) invalid
Significant methodological deficiencies

01.10.2003 (83)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species	:	other: Monilinia fructicola, Glomerella cingulata
Endpoint	:	other: fungicidal effectiveness
Exposure period	:	14 day(s)
Unit	:	
Method	:	other: see test conditions
Year	:	1949
GLP	:	no
Test substance	:	other TS: Purity is not specified
Result	:	-A fungicial effectivity during 14-day test period was observed for 6 days at a concentration of 2 pounds per 100 gallons (2.40 kg/m³). -In both, mixed with lime and mixed with nicotine-bentonite the substance lost its fungicidal properties.
Test condition	:	-The test substance was suspended in water. -Deposits were prepared by centering a small droplet of the suspension of clean glass cover slips and allowed to dry out to form a residue. -The cover slips were subjected naturally to the varying environments of the tree Prunus persica (Peach) and exposed usually for 14 days. After each 2-3 days, one cover slip and its weathered residue was removed from the tree and cut into two parts. -One half was seeded, by means of a uniform platinum loop, with a standardized suspension of the conidia of Monilinia fructicola and the other half with a standardized suspension of the conidia of Glomerella cingulata. -The conidia seeded in the residues were incubated for 24 h at 21°C. -Germination or inhibition was observed under a microscope. -To check the compatibility of the substance with adjuvants, lime or lime plus bentonite was added.
Reliability	:	(3) invalid Documentation insufficient for assessment

01.10.2003 (82)

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 vivo
Type : Excretion
Species : dog
Number of animals
Males :
Females : 1
Doses
Males :
Females :
Vehicle :
Route of administration : oral feed
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1937
GLP : no
Test substance : other TS: purity not specified

Method : One dog (female, 13.4 kg, 2.5 years old) was fed a sodium adipate containing diet.
1. Experiment: 1 g compound, twice a day, 5 days (=150 mg/kg bw/day, total 10 g).
2. Experiment: 5 g compound, twice a day, 7 days (=750 mg/kg bw/day, total 70 g).
Urine was collected and the dose of adipic acid in the urine was determined (urine was strongly acidified, extracted with ether, and adipic acid was allowed to crystallize) and the purity verified by chemical analysis (melting point, carbon and hydrogen content).
Result : 18% adipic acid was recovered unchanged in the low dose experiment and 63.6% in the high dose experiment
Reliability : (2) valid with restrictions
No GLP but overall good documentation; only one dog used. Breath not analysed, purity not specified, reliability of detection method unclear
Flag : Critical study for SIDS endpoint
26.11.2003 (84)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration :
Exposure time : 2 day(s)
Product type guidance :

Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1941
GLP : no
Test substance : other TS: purity not specified

Method : Experiment 1: Four rabbits (2 to 2.5 kg bw) were dosed via gavage with 2.43 g/kg bw/day adipic acid (partially neutralized) at two successive days. (This dose was chosen, because the higher dose 4.86 g/kg bw/day was found to be lethal for the rabbits.) Urine was collected for the 2 days of administration and the consecutive 4 days.
Experiment 2: Two rabbits were dosed i.v. with 2.43 g/kg bw/day adipic acid (partially neutralized) at two successive days. Urine was collected for the 2 days of administration and the consecutive 4 days.
Adipic acid analysis in the urine: urine was acidified, extracted with ether, boiled with caustic soda, again extracted with ether, distilled, precipitated as cooper-salt, and iodometrically titrated.

Result : Experiment 1 (gavage): 53-61% (mean value 57%) of the doses were recovered unchanged in the urine during this time period with a maximum in excretion at day two.
Experiment 2 (i.v.): 59 and 71% of the doses were recovered unchanged in the urine at the first day. The excretion was complete in the first 24 h after the second administration and the percentage recovered similar to that in the feeding study (no further details).

Reliability : (2) valid with restrictions
No GLP, short documentation. Limited number of animals of unknown sex used. Breath not analysed, purity not specified, reliability of detection method unclear

Flag : Critical study for SIDS endpoint
26.11.2003 (85)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : gavage
Exposure time : 28 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :

Year : 1941
GLP : no
Test substance : other TS: purity not specified

Method : Two adult rats (300 g) were dosed via gavage with 2.43 g/kg bw/day adipic acid (partially neutralized) for 4 weeks. Urine was collected four days prior to administration, for the time of administration and the consecutive 2 days. Adipic acid analysis in the urine: urine was acidified, extracted with ether, boiled with caustic soda, again extracted with ether, distilled, precipitated as cooper-salt, and iodometrically titrated.
Result : 67% of the doses were recovered unchanged in the urine during this time period. There was no change in the excretion pattern from day 1 to 28.
Reliability : (2) valid with restrictions
No GLP, short documentation. Limited number of animals of unknown sex used. Breath not analysed, purity not specified, reliability of detection method unclear
Flag : Critical study for SIDS endpoint
26.11.2003 (85)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1960
GLP : no
Test substance : other TS: purity not specified

Method : Male albino rats (Carworth Farm), 150-250 g in weight, were fasted for approximately 24 hours and subsequently dosed.
The following experiments were performed:
1) Animals were fed by gavage a solution containing approximately 50 mg radioactive adipic acid labeled in the 1-C or 2-C position. Rats were immediately placed in individual metabolism chambers for 24 hours for collection of respiratory carbon dioxide. Urine was collected during the whole experimental procedure.
2) Animals were fed by gavage a solution containing approximately 100 mg radioactive adipic acid labeled in the C-1 position and 400 mg glucose. Animals were sacrificed after two hours and livers were analyzed for glycogen.
3) Animals were fed by gavage a solution containing approximately 50 mg radioactive adipic acid labeled in the 1-C position and then injected intraperitoneally with 2 ml of 0.5 M sodium malonate. Urine was collected for 24 hours.
4) Animals were fed by dog chow approximately 25 mg radioactive adipic acid labeled in the 1-C position and 100 mg gamma-phenyl-alpha-aminobutyric acid. Urine was collected for 48 hours.
5) Animals were dosed with radioactive sodium bicarbonate alone and in the presence of nonradioactive adipic acid. The distribution of radioactivity in the breath and urine was monitored.

Result : Experiment 1): up to 70 % of the radioactivity was exhaled as C02 in 24 h. In the urine the following radioactive metabolic products were identified: urea, glutamic acid, lactic acid, beta-ketoadipic acid, citric acid and adipic acid. The tissue showed very little radioactivity. Similar results were obtained with adipic acid labeled in the 1-C or 2-C position.

Experiment 2) When glycogen formation in the liver was increased by oral administration of glucose together with radioactive adipic acid, a high concentration of glycogen was isolated which was radioactive; no further data.

Experiment 3) Radioactive succinic acid as well as radioactive adipic acid was obtained from the urine of these rats, indicating that adipic acid undergoes b-oxidation.

Experiment 4) In order to accumulate acetate in the urine rats were fed with gamma-phenyl-alpha-aminobutyric acid. The presence of radioactive
acetyl-gamma-phenyl-alpha-aminobutyric provided evidence that acetate is a metabolite of adipic acid.

Experiment 5) In the presence of adipic acid radioactive citric acid was formed, suggesting that carbon dioxide interacts with a metabolite of adipic acid.

Reliability : (2) valid with restrictions
No GLP, short documentation. Number of animals not given, purity not specified

Flag : Critical study for SIDS endpoint
19.11.2003 (86)

In Vitro/in vivo : In vivo
Type : Excretion
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : s.c.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1918
GLP : no
Test substance : other TS: purity not specified

Method : Rabbits, 2.7-3.5 kg in weight, were dosed with adipic acid by the s.c. route.
Three rabbits were dosed by single administration of 2000

mg, one animal was dosed twice (days 1 and 5) and one animal was dosed four times (days 1, 5, 9, 13, 15). Urine was collected and adipic acid and oxalic acid concentrations were monitored.
Adipic acid analysis in the urine: urine was strongly acidified, extracted with ether, and adipic acid was allowed to crystallize. These crystals were carefully purified and weighed.

Result : In average 61 % of the adipic acid doses were recovered unchanged in the urine, and increase of the oxalic acid concentrations in the urine were observed.

Reliability : (2) valid with restrictions
No GLP, short documentation. Sex of animals not given. Breath not analysed, purity not specified, reliability of detection method unclear

Flag : Critical study for SIDS endpoint

26.11.2003 (87)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1937
GLP : no
Test substance : other TS: purity not specified

Remark : One human received orally 33mg/kg bw and day i.e. 10 g (total) sodium adipate during a five days treatment. The urine was collected for 8 days and the amount of adipic acid was determined. 676 mg of adipic acid (6.76 % of the dose) was recovered in the urine. Adipic acid analysis in the urine: urine was strongly acidified, extracted with ether, and adipic acid was allowed to crystallize.

Reliability : (4) not assignable
Short documentation, only one individual, breath not analysed, purity not specified, reliability of detection method unclear.

26.11.2003 (84)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1947
GLP : no
Test substance : other TS: purity not specified

Method : Adipic acid was orally administered to 4 different humans to investigate the excretion of this compound. Urine was
collected and the adipic acid concentration analyzed.
Adipic acid analysis in the urine: urine was acidified, extracted with ether,

derivatized, and crystallized.

Result : One Person (70 kg) received 7 g adipic acid per day (100 mg/kg bw/day) over 10 days (70 g in total) given in several portions over the day. Urine was collected for these 10 days and two additional days after end of administration. 61% of the administered dose was found in the urine.

Three further persons received 23.4, 19.0, and 23.4 g adipic acid over 6, 5, and 9 days, respectively. 53% of the administered dose was found in the urine.

No symptoms were reported during and after exposure

Reliability : (2) valid with restrictions
No GLP, short documentation, purity not specified, reliability of detection method unclear

Flag : Critical study for SIDS endpoint

05.01.2006 (88)

In Vitro/in vivo : In vivo
Type : Excretion
Species : human
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1942
GLP : no
Test substance : other TS: purity not specified

Method : Adipic acid was orally administered to 3 different humans to investigate the excretion of this compound. Urine was
collected and the adipic acid concentration analysed.
Adipic acid analysis in the urine: urine was acidified, extracted with ether, boiled with caustic soda, again extracted with ether, distilled, precipitated as cooper-salt, and iodometrically titrated.

Result : Doses of compound ranged from 1.46 - 7.3 g/day and time of administration was up to 6 days.The highest dose administered in one volunteer was 70 g over 10 days. 3 other persons took 19 to 23,4 g over up to 9 days. 15-75% of the doses were excreted with the urine. The doses excreted varied with the individuals and with the dose applied.

No symptoms were reported during and after exposure

Reliability : (2) valid with restrictions
No GLP, short documentation, purity not specified, reliability of detection method unclear

Flag : Critical study for SIDS endpoint

10.01.2005 (89)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 5560 mg/kg bw
Species : rat
Strain : Sprague-Dawley
Sex : male/female

Number of animals : 10
Vehicle : other: 14.7% - 50% suspension in 0.5% carboxymethyl-cellulose
Doses : 1470, 2150, 3160, 4540, 6810, 10000 mg/kg bw
Method :
Year : 1978
GLP : no
Test substance : other TS: purity 99.8%

Method : Test substance was administered via single dose gavage to five female rats (mean bw 173 g) and five male animals (mean bw 217 g). Animals were observed 1, 24, 48 hours, 7 and 14 days after dosing. Heart, stomach, intestine and liver were grossly examined of animals that died and survivors, sacrificed 14 days after administration. LD50 value was calculated according to the Finney equation.

Result :

Dose (mg/kg bw)	compound concentration (%)	sex	mortality (14 days)
10000	50	m	5/5
		f	5/5
6810	50	m	2/5
		f	5/5
4640	46.4	m	0/5
		f	2/5
3160	31.6	m	0/5
		f	1/5
2150	21.5	m	0/5
		f	0/5
1470	14.7	m	0/5
		f	0/5

Mortality was seen during the first 48 hours. Animals that died showed acute dilatation of the heart and acute congestive hypereamia, ulceration of glandular stomach (bleeding-corrosive gastritis), intestinal atony, reddening of intestinal mucosa and pale liver. Organs of the survivors were without findings.

Reliability : (2) valid with restrictions
No GLP but overall good documentation, similar to TG 401.
Flag : Critical study for SIDS endpoint
26.11.2003 (90) (91)

Type : LD50
Value : = 940 mg/kg bw
Species : rat
Strain : no data
Sex : male
Number of animals : 5
Vehicle : other: suspension in 0.85% saline, precise adipic acid concentration not given.
Doses : 5000 mg/kg bw (10 rats); 100, 200, 500, 1000, 2000, 3000 mg/kg bw (5 rats at each dose)
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Compound application by intubation. Animals were observed for 10 days. An autopsy was performed on animals that died. LD50 values were calculated according to

Litchfield-Wilcoxson.

Remark : In a second experiment no signs of toxicity were observed following administration of a single dose of 5000 mg/kg bw to ten rats; see next entry. The result of the study is also discrepant to other studies of the authors where doses of 2500 or 5000 mg/kg bw have been given without mortality. Also other investigators have found higher LD50 values.

Result :

Dose mg/kg	No.dead/ No.animals	day of death
5000	10/10	day 1 (5), day 2 (5)
100	0/5	none
200	0/5	none
500	1/5	day 4
1000	3/5	day 3
2000	4/5	day 1 (2), day 2 (2)
3000	5/5	day 1 (4), day 2 (1)

Animals that succumbed showed a patchy liver and blood in the intestinal mucosa.

Reliability : (4) not assignable
Only males used, only 10 days post observation period, purity not specified, see also "Remark"

19.11.2003 (92)

Type : LD0
Value : 5000 mg/kg bw
Species : rat
Strain : no data
Sex : male
Number of animals : 10
Vehicle : other: 33.3% adipic acid suspension in 0.85% saline
Doses : 5000 mg/kg bw
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Compound application by intubation. Animals were observed for 7 days. Surviving rats were killed and examined grossly.

Result : No signs of toxicity or abnormal behavior were observed. No deaths occurred. At termination all animals were killed and on necropsy no gross findings were observed.

Reliability : (2) valid with restrictions
Only one dose used, only 7 days post observation period, purity not specified, authors reported an LD50 of 940 mg/kg bw in a parallel experiment during the same study; see previous entry.

Flag : Critical study for SIDS endpoint

20.11.2003 (92)

Type : LD50
Value : > 10000 mg/kg bw
Species : rat
Strain : other: albino
Sex : no data
Number of animals :
Vehicle : no data
Doses : 10000 mg/kg bw
Method : other: no further information published

Year : 1983
GLP : no data
Test substance : other TS: purity not specified

Reliability : (4) not assignable
No further details

19.11.2003 (93)

Type : LD50
Value : ca. 3600 mg/kg bw
Species : rat
Strain : Wistar
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: The compound was applied by intubation and the animals were observed for 14 days. (No further information published)
Year : 1972
GLP : no
Test substance : other TS: purity not specified

Reliability : (4) not assignable
No further details

20.11.2003 (94)

Type : LD50
Value : = 1900 mg/kg bw
Species : mouse
Strain : no data
Sex : male
Number of animals : 13
Vehicle : other: 6% suspension in 0.5% methyl cellulose
Doses : 1500, 2000, 2500 mg/kg bw
Method :
Year : 1957
GLP : no
Test substance : other TS: purity not specified

Method : The compound was administered orally. animals were observed for 10 days. Autopsy was performed on animals that died, and survivors were sacrificed at day 10.
Result : At 1500, 2000 and 2500 mg/kg bw mortality of the animals was 3/13, 8/13 and 9/13, respectively. Autopsy of animals that died showed distention of the stomach and small intestine, with a spastic contraction of the caecum. Irritation and hemorrhage of the intestines were noted. Initial mortality developed overnight and deaths continued throughout the first week, after which survivors appeared normal.
Reliability : (2) valid with restrictions
No GLP, short documentation, only 10 days post observation period, mortality in all dose groups
Flag : Critical study for SIDS endpoint
20.11.2003 (95)

Type : LD50
Value : = 4200 mg/kg bw
Species : mouse
Strain : no data

Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information published
Year : 1983
GLP : no data
Test substance : other TS: purity not specified

Reliability : (4) not assignable
No further data
19.11.2003 (93)

Type : LD50
Value : = 4175 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information published
Year : 1981
GLP : no data
Test substance : other TS: purity not specified

Reliability : (4) not assignable
No further data
19.11.2003 (96)

Type : other: ALD50
Value :
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle : other: 20% solution, partially neutralized (25% adipic acid; 75% sodium adipate)
Doses : two doses tested: 2430 and 4860 mg/kg bw
Method : other: test substance was administered via single dose gavage.
Year : 1941
GLP : no
Test substance : other TS: purity not specified

Remark : Approximately LD50: ALD50 >2430 and <4860 mg/kg bw
Result : At 2430 mg/kg bw no mortality observed. Animals were apathic and diarrhea was observed after exposure. At lethal doses, 4860 mg/kg bw, animals died 10 - 30 hours after application. Autopsy revealed swelling of the entire intestine and the intestine was filled with masses of brown liquid.
Microscopic examination of tissue from the liver and kidneys showed marked venous obstruction.
Reliability : (4) not assignable
No GLP, short documentation, purity not specified, number and sex of rabbits not described. Only 2 doses tested
05.01.2005 (85)

Type : LD50
Value : > 11000 mg/kg bw

Species	:	other: rat and rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity not specified
Reliability	:	(4) not assignable No further data

19.11.2003 (93)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: preliminary experiment
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	12
Vehicle	:	
Doses	:	not analyzed
Exposure time	:	8 hour(s)
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	For adipic acid dust enrichment 200 l air/h were flown through an adipic-acid bed, 5 cm in high, at 20 degree Celsius. Animals were exposed for 8 hours. No more data.
Result	:	All animals survived the experiment. No further data.
Reliability	:	(3) invalid Test system not suitable for solid substances

19.11.2003 (91)

Type	:	LC0
Value	:	7.7 mg/l
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	20
Vehicle	:	other: dust
Doses	:	7.7 and 5.4 mg/l
Exposure time	:	4 hour(s)
Method	:	
Year	:	1981
GLP	:	no data
Test substance	:	other TS: purity 99.8%
Method	:	Similar to TG 403. Two independent experiments were performed with 7.7 and 5.4 mg/l adipic acid, with 20 animals per concentration. Head/nose-only exposure was the technique used (system INA 20, BASF; animals were sitting in tubes and the mouth protruded into the inhalation chamber). It is unclear whether the eyes of the animals were exposed also.

A dust atmosphere with a particle-size mass distribution (MMAD50) of 3.5 µm (i.e. 50% of the particles had a MMAD < 3.5 µm) and a geometric standard deviation (GSD) of 2.6 was used throughout the experiment. The maximal attainable concentration in this test was 7.7 mg/l. Animals were exposed for 4 hours. Body weights and general appearance were recorded daily throughout the experimental period. After 14 days animals were killed and gross autopsy was performed.

Result : Neither mortality nor symptoms were observed during and after exposure. No pathological changes were reported at necropsy.

Reliability : (2) valid with restrictions
No GLP, short documentation, no data on humidity during the exposure

Flag : Critical study for SIDS endpoint

19.11.2003 (97)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD0
Value	:	7940 ml/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	2
Vehicle	:	
Doses	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	other TS: purity not specified

Method : Adipic acid was tested as a 40% solution in corn oil. Minimum lethal dose was determined using 1-2 rabbits per group (5010 mg/kg bw one animal, 7940 mg/kg bw two animals). A 24- hour dermal exposure under occluded conditions was conducted. Necropsy was conducted after a 14-day observation period.

Result : No deaths occurred at 5010 mg/kg bw (0/1) or 7940 mg/kg bw (0/2). Observations included reduced appetite and activity. The viscera were normal at necropsy.

Reliability : (2) valid with restrictions
Number of animals low, purity not specified. However, in view of the low oral acute toxicity, the results are plausible

Flag : Critical study for SIDS endpoint

01.12.2003 (98)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 275 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	7
Vehicle	:	other: 3% aqueous solution
Doses	:	200, 300, 350 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	

Method	:	
Year	:	1957
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Animals were observed for one week. Autopsy was performed on animals that died, and on survivors, sacrificed after one week.
Result	:	Mortality occurred during the first 5 days (200 mg/kg bw = 1/7, 300 mg/kg bw = 4/7, 350 mg/kg bw = 6/7). Animals that succumbed showed hemorrhagic lungs and irritation of the intestines. The survivors showed extensive irritation and adhesions of the visceral organs.
Reliability	:	(2) valid with restrictions No GLP, short documentation, purity not specified, only 7 days post observation period, statistics used not specified
19.11.2003		(95)
Type	:	LD50
Value	:	ca. 170 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: 0.681 - 50% suspension in 0.5% carboxymethylcellulose
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: purity: 99.8%
Result	:	Excitation and laboured breathing was observed shortly after application, mortality was observed after 3 - 4 days.
Reliability	:	(4) not assignable No further experimental data described
19.11.2003		(91)
Type	:	LD100
Value	:	600 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	water
Doses	:	600 and 900 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1957
GLP	:	no
Test substance	:	other TS: purity not specified
Remark	:	A few mice were given lethal doses (600 and 900 mg/kg bw) of a 3% aqueous solution of adipic acid intraperitoneally. These mice showed depression immediately and, at autopsy, the intestines appeared irritated and the lungs appeared hemorrhagic. No further data.

Reliability	:	(2) valid with restrictions No further experimental data described, purity not specified, number of animals not given but result can be used qualitatively
19.11.2003		(95)
Type	:	LD50
Value	:	= 4000 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1965
GLP	:	no
Test substance	:	other TS: purity not specified
Reliability	:	(4) not assignable Unpublished data, original reference not available
19.11.2003		(99)
Type	:	LD50
Value	:	= 680 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	13
Vehicle	:	other: 2% solution of adipic acid
Doses	:	650, 675, 700 mg/kg bw
Route of admin.	:	i.v.
Exposure time	:	
Method	:	Intravenous injection to mice at a rate of 0.01 ml/second
Year	:	1957
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Statistical analysis was done by the method of Litchfield and Wilcoxon
Result	:	Mortality: 650 mg/kg bw (4/13), 675 mg/kg bw (7/13), 700 mg/kg bw (8/13). Adipic acid caused immediate, convulsive deaths, probably due to acute acidosis as the pH of the solution was 3.08. Autopsy showed hemorrhagic lungs but no other gross pathology. In survivors, recovery was apparently complete and there were no latent deaths.
Reliability	:	(2) valid with restrictions No GLP, short documentation, purity not specified
19.11.2003		(95)
Type	:	LD0
Value	:	2430 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: 20% solution, partially neutralized
Doses	:	2430 mg/kg
Route of admin.	:	i.v.
Exposure time	:	

Method :
Year : 1941
GLP : no
Test substance : other TS: purity not specified

Result : No effects observed, except polyurie and bodyweight loss of up to 20% within eight hours.
Reliability : (2) valid with restrictions
No GLP but overall good documentation, number and sex of rabbits not described

19.11.2003 (85)

Type : other
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Route of admin. : other: i.t.
Exposure time :
Method :
Year : 2002
GLP : no data
Test substance : other TS: purity not specified

Remark : Single intratracheal installation of either 2.5, 5 or 7 mg of adipic acid in rats produced acute pulmonary cytotoxicity and inflammation. One day after installation, lavage protein, LDH and inflammatory cells were markedly increased. Histopathology confirmed acute pulmonary inflammation. Four weeks after exposure, pulmonary alterations persisted and were most pronounced in the rats receiving 7 mg. Significant changes induced hydroxy-proline increases, histologic foci of pulmonary fibrosis and persistent tachypnea. Neutralization of the pH ameliorated the toxicity. No more data.
Reliability : (4) not assignable
No further data

20.11.2003 (1)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : 500 mg
Exposure : Semiocclusive
Exposure time : 24 hour(s)
Number of animals : 6
Vehicle : other: 50% aqueous suspension
PDII : 2.21
Result : slightly irritating
Classification :
Method : other: §1500.41; Federal Register Vol. 38, No. 187, pp 26019 dated 27.09.1973
Year : 1978
GLP : no
Test substance : other TS: purity 99.8%

Method : The fur was removed by clipping the dorsal area of the trunk of the rabbits (mean bw 3.1 kg). On one site the skin was left intact and on the other site the skin was scarified. The compound was applied for 24 hours to an area of 5x5 cm and covered with a gauze patch. During the application the animals were fixed. Responses were scored at three time points immediately after exposure (24 hours), 3 and 8 days.

Result : Reversible reddening was observed at the intact skin which disappeared after three days. Mild to severe reddening and edema was observed at the scarified skin. These effects were reversible after 1 week and scale formation was observed.

Observation scores:

Intact skin:

Reddening:

time	score animal 1/2/3/4/5/6
24 h	2/2/2/3/2/2
3 days	0/0/0/0/0/0
8 days	0/0/0/0/0/0

Oedema observation:

24 h	0/0/0/0/0/0
3 days	0/0/0/0/0/0
8 days	0/0/0/0/0/0

Scarified skin

Reddening:

24 h	2/3/3/3/2/2
3 days	2/1/2/1/1/1
8 days	0/0/0/0/0/0 scale formation in every case

Oedema observation:

24 h	2/2/2/2/2/2
3 days	2/0/2/0/1/0
8 days	0/0/0/0/0/0

Reliability : (2) valid with restrictions
No GLP, short documentation, 24 h exposure time, purity not specified

26.11.2003 (100)

Species : rabbit
Concentration : other: pure compound and 80% aqueous paste
Exposure : Occlusive
Exposure time : 20 hour(s)
Number of animals : 2
Vehicle : water
PDII :
Result : not irritating
Classification :
Method :
Year : 1978
GLP : no
Test substance : other TS: purity 99.8%

Method : Pure substance and 80 % aqueous paste was administered to the shaved intact skin. The application sites were wiped with Lutrol 9 and 50% Lutrol 9 solution after the end of the short time exposure periods (1, 5, 15 min; back), not after

20 hour exposure (back, ear). Responses were scored at 24, 72 hours and 8 days after exposure.

Result : No irritation was observed at the back. A reversible clear reddening was seen at the ear after 20 hours (scores 2 and 2) which disappeared at 72 hours (scores 0 and 0).

Reliability : (2) valid with restrictions
No GLP, short documentation, 20 h occlusive exposure

19.11.2003 (101)

Species : rabbit
Concentration : other: 500 mg
Exposure : Semiocclusive
Exposure time : 24 hour(s)
Number of animals : 6
Vehicle : other: 50% paste of adipic acid in propylene glycol was applied for 24 hours and in a second experiment 500 mg of pure compound was applied for 4 hours.
PDII :
Result : slightly irritating
Classification :
Method : other: according to Federal Register section 1500.41 (1973)
Year : 1974
GLP : no
Test substance : other TS: 99.99 %

Method : The compound was applied to the clipped, intact skin, covered and held in contact for 4 and 24 hours. Animals were observed for 48 hours.

Result : Two experiments were performed in this study.

1) semi-occlusive exposure for 24 hours. Scoring immediately after dosing (24 h). 3/6 rabbits showed slight to mild irritation.

2) semi-occlusive exposure for 4 hours. Scoring immediately after dosing (4 hours). 0/6 rabbits showed skin corrosion.

Reliability : (2) valid with restrictions
No GLP, short documentation, 24 h semi-occlusive exposure

05.01.2005 (102)

Species : rabbit
Concentration :
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals :
Vehicle : no data
PDII :
Result : not irritating
Classification :
Method :
Year : 1972
GLP : no
Test substance : other TS: purity not specified

Remark : The fur was depilated and 500 mg of the compound was applied. Subsequently, the site of application was covered with a gauze patch for 24 hours. Animals were examined for 14 days.

Result : No irritation observed; score: 0

Reliability : (4) not assignable
No further data

19.11.2003 (94)

Species	:	guinea pig
Concentration	:	other: 50, 25 %
Exposure	:	no data
Exposure time	:	
Number of animals	:	10
Vehicle	:	other: 50% suspension of adipic acid in propylene glycol
PDII	:	
Result	:	
Classification	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: 99.99%

Method : Adipic acid suspension was lightly rubbed in the shaved intact skin. Animals were observed for 48 hours. Evaluation after 24 and 48 h. No more data.
Result : Very mild to no skin irritation observed.
Reliability : (2) valid with restrictions
No GLP, short documentation, unusual species

05.01.2005 (102)

Species	:	other: rabbit, rat
Concentration	:	
Exposure	:	no data
Exposure time	:	no data
Number of animals	:	
Vehicle	:	no data
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other: no data
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity not specified

Reliability : (4) not assignable
No experimental details described

02.09.2003 (93)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	100 mg
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	3
Vehicle	:	none
Result	:	highly irritating
Classification	:	risk of serious damage to eyes
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	2004
GLP	:	yes
Test substance	:	other TS: purity >99.8%

Method : To determine reversibility of effects, the animals were observed normally for up to 21 days post administration of the test substance. If reversibility is seen before 21 days, the experiment is terminated at that time.

Result : Under the present test conditions, a single application of 100 mg Adipinsaure per animal into the conjunctival sac of the right eye of three rabbits caused the following changes:
Corneal opacity was observed in all animals:
- animal no. 1: 1 hour to 72 hours (grade 3), 4 to 6 days (grade 2) and 7 to 15 days (grade 1) after instillation;
- animal no. 2: 1 hour to 72 hours (grade 2) and 4 to 12 days (grade 1) after instillation;
- animal no. 3: 1 hour (grade 3), 24 to 72 hours (grade 2) and 4 to 12 days (grade 1) after instillation.

The fluorescein test performed 24 hours after instillation revealed comeal staining in animal nos. 1 and 3 (3/4 of the surface) and animal no. 2 (1/2 of the surface). The fluorescein test performed 7 days after instiltation revealed corneal staining in animal nos. 1 and 3 (1/2 of the surface) and animal no. 2 (1/4 of the surface). The fluorescein test performed 14 days after instillation revealed corneal staining in animal no. 1 (1/4 of the surface).

Irritation of the iris was observed in all animals:
- animal no. 1: 1 hour to 4 days (grade 2) and 5 to 8 days (grade 1) after instillation;
- animal no. 2: 1 hour and 24 hours (grade 2) and 48 hours to 6 days (grade 1) after instillation;
- animal no. 3: 1 hour to 72 hours (grade 2) and 4 to 8 days (grade 1) after instillation.

Conjunctival redness (grade 1) was observed in animal no. one 1 hour to 12 days, in animal nos. two and three 1 hour to 72 hours after instillation.

Conjunctival chemosis (grade 1) was observed in animal nos. one and two 1 hour to 6 days, in animal no. three 1 hour to 11 days after instillation.

There were no systemic intolerance reactions.

Reliability : (1) valid without restriction
13.02.2006 (103)

Species : rabbit
Concentration : 99.8 % active substance
Dose : .1 ml
Exposure time :
Comment : not rinsed
Number of animals : 6
Vehicle :
Result : highly irritating
Classification :
Method : other: Federal Register, Vol. 38, No. 187, paragraph 1500.42 and Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, FDA, Austin 1959, p. 51
Year : 1978
GLP : no
Test substance : other TS: purity 99.8%

Result : The eyelids were closed for one second and the eyes were not washed. The eyes were examined 24, 48, 72 hours and 8 days after exposure. Irritated conjunctiva (reddening, swelling, secretion) and scar formation, increasing opacity of cornea and

inflammation of the iris were observed. The symptoms were not reversible within 8 days. Primary irritation index: 41,5
Scores:

Cornea:

Animal no.	1	2	3	4	5	6
24 hours	1	1	1	1	2	2
48 hours	1	1	1	1	2	2
72 hours	1	1	1	1	2	2
8 days	2	2	2	1	2	2

mean value 24, 48 and 72 hours: 1.33
Area: 4 (maximum value) in every case and timepoint

Iris:

Animal no.	1	2	3	4	5	6
24 hours	1	0	0	1	1	1
48 hours	1	0	1	1	1	1
72 hours	1	1	1	1	1	1
8 days	1	1	1	1	1	1

mean value 24, 48 and 72 hours: 0.83

conjunctivae:

Animal no.	1	2	3	4	5	6
24 hours	2	2*	2	2	2	2
48 hours	2*	2*	2*	2	2*	2*
72 hours	2*	2*	2*	2*	2*	2*
8 days	2*	2*	2*	2*	2*	2*

* = scar formation observed
mean value 24, 48 and 72 hours: 2

chemosis:

Animal no.	1	2	3	4	5	6
24 hours	2	2	2	2	3	3
48 hours	2	2	2	1	2	2
72 hours	2	2	2	1	2	2
8 days	1	1	1	1	1	2

mean value 24, 48 and 72 hours: 2

Reliability : (2) valid with restrictions
No GLP but overall good documentation; observation time 8 days

05.01.2005 (104)

Species : rabbit
Concentration : 99.8 % active substance
Dose : 50 other: mg
Exposure time :
Comment : not rinsed
Number of animals : 2
Vehicle : none
Result : highly irritating
Classification :
Method : other: Pure substance was placed in the conjunctival sac. The eyelids were closed for one second and the eyes were not washed. Responses were scored at 24, 48 h and 8 days after exposure
Year : 1978
GLP : no
Test substance : other TS: purity 99.8%

Result : A clear irritation and opacity of cornea was observed which persisted over the whole observation time of 8 days, and a reversible iris affection was seen.

Scores:

Cornea:

Animal no.	1	2
24 hours	1	2
48 hours	1	2
8 days	1	1

Iris:

Animal no.	1	2
24 hours	0	1
48 hours	1	1
8 days	0	0

conjunctivae:

Animal no.	1	2
24 hours	1	2
48 hours	1	2
8 days	1*	1

* = scar formation observed

chemosis:

Animal no.	1	2
24 hours	2	2
48 hours	2	2
8 days	0	1

Reliability : (2) valid with restrictions
Only 2 animals per dose, no 72 hours value, observation time only 8 days, no GLP but overall good documentation

05.01.2005 (101)

Species : rabbit
Concentration :
Dose : 57.1 other: mg
Exposure time :
Comment :
Number of animals : 1
Vehicle : none
Result :
Classification :
Method :
Year : 1974
GLP : no
Test substance : other TS: 99.99 %

Method : 10 mg compound was placed into the right conjunctival sac of each of 2 albino rabbits. Twenty seconds after contact one eye of one rabbit was washed with tap water for one minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made at 1 and 4 hours, and at 1, 2, 3, 7, and 14 days.

In a 2nd procedure, 0.1 ml (57.1 mg) of the lightly compacted powder was placed into the right conjunctival sac of each of 2 albino rabbits. Twenty seconds after contact one eye of one rabbit was washed with tap water for one minute. The treated eye of the other rabbit was not washed. Observations were made at 1 and 4 hours, and at 1, 2, 3, 7 days.

Result : 10 mg Experiment: The washed eye had mild irritation with no corneal or iritic effect and was normal within 3 days. The unwashed eye had mild conjunctival irritation, minimal iritic effect and no corneal effect. At seven days there was minimal conjunctival irritation and at 14 days the eye was normal.

57.1 mg experiment: Compound produced mild opacity of the cornea with minimal iritic effect and moderate to mild conjunctival irritation in the unwashed eye. The eye was normal at day seven. In the washed eye, adipic acid produced a transient, mild opacity with no iritic effect and a moderate to mild conjunctival irritation. The eye was normal within three days

Reliability : (2) valid with restrictions
No GLP but overall good documentation, only one animal used.

05.01.2005 (102)

Species : rabbit
Concentration :
Dose :
Exposure time :
Comment :
Number of animals : 1
Vehicle : no data
Result : irritating
Classification :
Method : other: no data
Year : 1972
GLP : no
Test substance : other TS: purity not specified

Method : 50 to 500 mg compound was placed into the conjunctival sac of one rabbit and the eyelid was closed for one minute. After contact the treated eye was not washed. Observations of the cornea, iris, and conjunctiva were made 18-24 hours after application and a fluorescein stain was used at examination.

Result : Score 5, irritant effect; no more data
Reliability : (4) not assignable

05.01.2005 (94)

Species : other: rabbit, rat
Concentration : other: 1 - 10% solution
Dose :
Exposure time :
Comment :
Number of animals :
Vehicle : no data
Result :
Classification :
Method : other: no data

Year : 1983
GLP : no data
Test substance : other TS: purity not specified

Remark : redness of the conjunctivae was observed, which was normal within three days.
Reliability : (3) invalid
Concentration too low, no experimental details given.

05.01.2005 (93)

5.3 SENSITIZATION

Type : other
Species : guinea pig
Number of animals : 10
Vehicle :
Result : not sensitizing
Classification :
Method :
Year : 1974
GLP : no
Test substance : other TS: 99.99 %

Method : A series of four sacral intradermal injections was given, one each week over a 3-week period, which consisted of 0.1 ml of a 1.0% solution of test material in water. Following a 2-week rest period, the test animals were challenged for sensitization by applying, and lightly rubbing in, approximately 0.05 ml of a 50% and 25% suspension of the test material in propylene glycol on the shaved intact shoulder skin. A group of 10 previously unexposed animals received similar applications at the time of challenge to provide direct comparison of the challenge reactions on the skin of similar age.
Remark : The compound produced very mild to no skin irritation when tested in a dose-finding study by applying, and lightly rubbing in, approximately 0.05 ml of a 50% suspension of the test material in propylene glycol on the shaved intact shoulder skin of 10 male guinea pigs.
Result : The compound did not cause skin sensitization.
Reliability : (4) not assignable
Limited documentation, no positive control group, no historical data, study design does not accord to modern guidelines, the number of animals per group was low, no data were presented to justify the induction concentration used (no range-finding study for induction dose), no adjuvant used.

26.11.2003 (102)

Type : other: case report
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method :
Year : 2001
GLP : no
Test substance : other TS: purity not specified

Result	:	A 51-year-old machine repairman with a 3- to 4-year history of work-related dermatitis of the hands and other exposed sites when working with powders in the synthesis of polyesters. Patch testing (buffered 1% alcoholic solution pH 6) demonstrated a ++ reaction to adipic acid at D2 and a less prominent ++ reaction at D5, while controls (number not given) were negative.
Reliability	:	(2) valid with restrictions Purity not specified, human case report

19.11.2003 (105)

Type	:	other: case report
Species	:	human
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1984
GLP	:	no
Test substance	:	other TS: purity not specified

Remark	:	Two cases of bronchial asthma due to spiramycin in workers of a pharmaceutical factory are reported. The subjects complained of cough, breathlessness and symptoms of asthma at work when coming into contact with spiramycin adipate powder. The symptoms cleared when away from work for more than 3 to 4 days. Inhalation challenge tests by aerosolization of solutions of spiramycin reproduced asthmatic reactions dual in type in both patients. Both patients were tested with 0.1, 1 and 10 mg adipic acid/ml in saline solution. One of the patients developed an immediate asthmatic reaction at a concentration of 10 mg/ml adipic acid. The reaction was reproducible after several months and inhibited by previous administration of sodium cromoglycate. These findings and the failure to elicit the reaction in the other patient prompted the authors to suggest a hypersensitivity type I reaction to adipic acid.
Reliability	:	(2) valid with restrictions Purity not specified, human case report

19.11.2003 (106)

Type	:	other: case report
Species	:	human
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1964
GLP	:	no
Test substance	:	other TS: purity not specified

Result	:	Delayed cutaneous hypersensitivity to a patch test with adipic acid was reported in a laboratory worker in a factory producing polyester resins. Test concentration 100%. No more data.
Reliability	:	(2) valid with restrictions Human case report, purity not specified.

19.11.2003 (107)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	oral unspecified
Exposure period	:	5 d
Frequency of treatm.	:	daily
Post exposure period	:	14 d
Doses	:	3600, 4000, 4500, 5000, 5600 mg/kg bw/day
Control group	:	no data specified
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: purity not specified

Method : The test substance was administered to groups of six animals (average body weight 248 g). After an observation period period of 14 days surviving animals were killed and gross necropsies was performed.

Result : The subacute oral LD50 was estimated to be 3615 mg/kg bw/day using the Finnley probit analysis method. The signs of toxicity consisted of depression, labored respiration, ataxia and convulsions which appeared on the second day and persisted through the fifth day.
Mortality: 3600 mg/kg bw/day (3/6), 4000 mg/kg bw/day (5/6), all other doses (4500 - 5600 mg/kg bw/day) (6/6).
No abnormal findings at gross necropsies of the surviving animals after the period of observation.

Test substance : Adipic acid was prepared as an 18.6-24.9% suspension in saline

Reliability : (3) invalid
No GLP, limited documentation. Only limited number of parameters examined, high mortality, no histopathology, examination after 14 days post exposure period, purity not specified

19.11.2003 (92)

Type	:	Sub-acute
Species	:	rat
Sex	:	male
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	3 w
Frequency of treatm.	:	
Post exposure period	:	no data
Doses	:	2 % (approx. 2000 mg/kg bw/day)
Control group	:	yes
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: purity not specified

Method : The compound (dissolved in alcohol) was administered as a 2% mixture in Purina rat chow along with water ad libitum to rats weighting 150-180g. The rats were killed after they had been on the diet for three weeks. Blood was

drawn from the abdominal aorta, and the serum was used for measurement of cholesterol and triglycides. Sections of liver were taken for electron microscopy. Liver carnitine acetyltransferase, medium-chain carnitine acetyltransferase activity and hepatic catalase activity was measured
spectrophotometrically. Test group: 4 rats, control group: 13 rats

Remark : Study was aimed at investigating peroxisome proliferation by plasticizers.
Result : no hepatic peroxisome proliferation, no increase in liver size, in hepatic activities of catalase and carnitine acetyltransferase and no hypolipidemia were observed.
Reliability : (2) valid with restrictions
No GLP but overall good documentation, only limited number of parameters investigated, low animal number, purity not specified.
Flag : Critical study for SIDS endpoint
10.01.2005 (108)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : 4 w
Frequency of treatm. : once a day
Post exposure period : no data
Doses : 5 young rats (75 - 80 g at start) 243 mg/day; ca. 3000 mg/kg bw/day
Control group : other: water-treated control, 5 young rats
Method : other: no more data
Year : 1941
GLP : no
Test substance : other TS: purity not specified

Result : Animals showed no symptoms compared to the control animals. Slightly decreased body weight gain without indication of significance.
Test substance : A 20% adipic acid solution was used which was neutralized with sodium carbonate.
Reliability : (3) invalid
Only bodyweight and behaviour examined, no histopathology, purity not specified
19.11.2003 (85)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : 4 w
Frequency of treatm. : once a day
Post exposure period : no data
Doses : Adult rats (ca. 300 g) 730 mg/day; ca. 2400 mg/kg bw/day
Control group : no data specified
Method : other: no more data
Year : 1941
GLP : no
Test substance : other TS: purity not specified

Remark : adult rats (3 animals ca. 300 g bw)
Result : constant body weight, no behavioural abnormalities, no dysfunction of the kidney, normal level of blood residual nitrogen at the end of the study.
Reliability : (3) invalid

Sex of rats not described, only 3 animals used. Only limited number of parameters examined, no control group, no histopathology, purity not specified.

19.11.2003 (85)

Type	:	Sub-acute
Species	:	rat
Sex	:	female
Strain	:	no data
Route of admin.	:	other: oral feed, ad libitum
Exposure period	:	4 w
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 10, 20, 40 mg/day (max. 435 mg/kg bw/day)
Control group	:	yes
Method	:	
Year	:	1953
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Groups of 17-20 animals with an average weight of 92 g received adipic acid in a standard diet (80% bruised wheat, 20% milk powder). Weight gain and general behavior were recorded.
Remark	:	NOAEL: > 40 mg/d (435 mg/kg bw/day)
Result	:	no effects reported
Reliability	:	(3) invalid No GLP, short documentation, only limited number of parameters investigated, no histopathology, purity not specified

19.11.2003 (109)

Type	:	Sub-acute
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	5 w
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 200, 400, 800 mg/day (0, 3 333, 6 666, 13 333 mg/kg bw/day)
Control group	:	yes
Method	:	
Year	:	1953
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Groups of 15-18 animals with a weight of 40-60 g received adipic acid in a standard diet (80% bruised wheat, 20% milk powder). Weight gain and general behaviour were recorded.
Result	:	The administration of 200 and 400 mg/day of the compound had no effect on weight gain and general behaviour. Rats feat with 800 mg/day showed retarded weight gain, appeared unkempt and apathetic and suffered from heavy diarrhea during the first three weeks.

Compound mg/day	No. of rats	Avarage body weight initial/final, g
0	18	49/154

	200	18	52/152
	400	18	44/139
	800	15	47/100

Test substance : Adipic acid neutralized with sodium hydroxide
Reliability : (3) invalid
No GLP, limited documentation, only limited number of parameters investigated, purity not specified. No histopathology

21.11.2003 (109)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 5 w
Frequency of treatm. : 5 days/week
Post exposure period : no data
Doses :
Control group : yes
Method : other: Groups of four rats were fed 100 or 200 mg/day, five days/week for five weeks as a 20% solution in ethanol. These doses correspond to 310-386 mg/kg bw/day at the 100 mg dose and 610-922 mg/kg bw/day at the 200 mg dose.
Year : 1943
GLP : no
Test substance : other TS: purity not specified

Result : Animals showed no adverse pathology attributable to adipic acid. Rate of weight gain closely paralleled that of the controls. One rat died from pneumonia. Animals became sleepy after treatment. This was attributed to the ingested alcohol.
Reliability : (4) not assignable
No experimental details described, unclear whether histopathology has been performed, purity not specified

19.11.2003 (110)

Type : Sub-chronic
Species : rat
Sex : male/female
Strain : other: Albino rats
Route of admin. : oral feed
Exposure period : 90 d
Frequency of treatm. :
Post exposure period : 8 w
Doses : 0, 0.1, 1,5 % (approx. 3750 mg/kg bw/day) males, 0, 1 % females
Control group : yes
Method :
Year : 1943
GLP : no
Test substance : other TS: purity not specified

Result : Retardation of growth during the feeding of adipic acid at 5 %, no such effects at the lower doses.
Reliability : (3) invalid
No histopathology, purity not specified

19.11.2003 (111)

Type : Sub-chronic
Species : rat

Sex	:	male
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	19 w
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 50, 100, 200, 400 mg/day (0, 420, 840, 1700, and 3400 mg/kg bw/day)
Control group	:	yes
Method	:	
Year	:	1953
GLP	:	no
Test substance	:	other TS: purity not specified, neutralized with NaOH
Method	:	Groups of 8-10 animals with a weight of 40-60 g received adipic acid in a protein deficient diet (crushed wheat supplemented with cod liver oil and protein concentration of 11%). Weight gain and general behavior were recorded. After 7 weeks and (probably) at the end of the experiment, rats were killed and examined grossly. Weight gain and general behavior were recorded and histopathology of liver, kidneys and intestine was performed. Body weight at start of experiment approx. 53-54 g, after 6 weeks approx. 79-104 g, and at end of experiment (19 weeks) approx. 144 - 200 g.
Remark	:	NOAEL: 200 mg/day (approx. 1700 mg/kg bw/day)
Result	:	The administration of 50, 100 and 200 mg/day of the compound had no effect on weight gain and general behavior. Rats fed wit 400 mg/day showed retarded weight gain. These animals did not recover, and after 19 weeks, the weights of the high-dose rats were still retarded. No obvious symptoms observed. Several unexplained intercurrent deaths in control and dose groups, only 5-7 animals survived 19 weeks. Histopathology: no effects observed in animals dosed with =< 200 mg. At higher doses (=> 400 mg) slight effects were seen on liver and irritation of intestine.
Reliability	:	(2) valid with restrictions No GLP, short documentation, only limited number of parameters investigated. Histopathological data only mentioned very briefly, purity not specified
Flag	:	Critical study for SIDS endpoint

10.01.2005 (109)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	33 w
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 400, 800 mg/day (0, 1600 and 3200 mg/kg bw/day)
Control group	:	yes
Method	:	
Year	:	1953
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Groups of 13-15 animals with a weight of 60-80 g received adipic acid in a standard diet (80% bruised wheat, 20% milk powder). Weight gain and general behavior were recorded. After 8, 23 and 25 weeks, rats were killed and histopathology of liver,

kidneys and intestine was performed.

Result : The administration of 400 mg/day of the compound had no effect on weight gain and general behavior of the animals. Of 14 rats fed with 800 mg/day mortality was as follows: first week: 1 animal, second week: 3 animals, third week: 5 animals, fourth week: 1 animal. The surviving animals showed retarded weight gain, appeared unkempt and apathetic and suffered from heavy diarrhea during the first three weeks. They recovered by the fifth week, and after 33 weeks, the weights of the high-dose rats were the same as that of the 400 mg/day group. The authors did not record the body weight of control animals at the end of the experiment, i.e. at 33 weeks.

Compound mg/day	No. of rats initial/final	Avarage body weight initial/ 8 weeks/ 33 weeks
0	15/11	74/207/-
400	13/9	74/183/325
800	14/4	73/154/320

Histopathology:
Kidney: no specific findings. (Strong regeneration in the joint with a high number of mitoses was quoted "minor" effect.)
Liver: no strong effects. Enlargement of nuclei and increased number of cells with two and more nuclei; no structural alteration of the nuclei. Sometimes, increase in cell-volume was observed. Number and volume of Kupffer-cells increased.
Intestine: chronically inflamed

Reliability : (2) valid with restrictions
No GLP, short documentation, only limited number of parameters investigated. Body weight of control animals after 33 weeks not documented. Histopathological data only mentioned very briefly, purity not specified

Flag : Critical study for SIDS endpoint
13.02.2006 (109)

Type : Chronic
Species : rat
Sex : male/female
Strain : other: Carworth Farm strain
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatm. :
Post exposure period :
Doses : 0.1, 1, 3 and 5 % (approx. 75, 750, 2250, 3750 mg/kg bw)
Control group : other: basal laboratory diet
Method :
Year : 1957
GLP : no
Test substance : other TS: purity not specified

Method : Rats were fed either the basal laboratory diet, or the basal diet to which adipic acid was added. Body weights, food consumption, and general appearance were recorded weekly throughout the experimental period. Whenever possible, gross autopsy was performed on those animals that died during the course of the experiment. After two years, surviving rat were weighed, killed, and examined grossly. The brain, thyroid, lung, heart, liver, spleen, kidneys and adrenals, stomach of approximately half of each group of males were

weighed. The kidneys, spleen, liver and heart of each female were weighed. Microscopic examination of thyroid, lung, heart, liver, spleen, kidneys, adrenals, stomach, pancreas, bone marrow, large and small intestine and testis or ovaries and uterus on a representative number of animals was performed.

Remark : NOAEL: 1% adipic acid (approx. 750 mg/kg bw/day)

Result : Males: The percent survival for each test group was higher than for the control group. During the rapid growth of the 2-year feeding studies, weight gains for the male rats receiving 3 or 5% adipic acid was significantly less than the male controls.
Growth for other groups, 0.1, 1% male and 1% female, was comparable to that of the respective controls.
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%.

Compound %	Sex m/f	No. of rats start/finish	Average body weight initial/final, g
0	m	20/8	59/440
0	f	10/8	49/321
0.1	m	20/13	61/417
1	m	20/15	63/437
1	f	19/17	48/304
3	m	20/16	61/400
5	m	20/15	57/360

There was no evidence of gross pathology associated with the feeding of adipic acid. There was no significant difference in survival among the various groups from the controls. The results of microscopic examination appeared to be within normal limits.

The following signs were observed among all male groups, including the controls, especially during the final six months: wheezing, blood-tinged crust about the noses and eyes, and body sores. These findings were not significantly different among the groups although a lower incidence of signs indicative of respiratory infection and body sores occurred in the 5% adipic acid group. Autopsy data for the male animals that died during the course of the two-year feeding program and for the sacrificed rats were analyzed for incidence of tumors and/or lung pathology. The incidence of lung pathology, tumors, soft testes observed in the adipic acid treated groups was as frequent as in the control group.

Female animals, dosed with 1% adipic acid and controls, exhibited signs normally associated with advancing senility in rats in the last six months. There was an equal incidence of blood-tinged crust about the eyes and noses, unthriftiness, and body scores in both groups. A few control and experimental animals had alopecia, and one experimental rat appeared to develop a middle ear infection during the 102nd week. One experimental and two control animals died during the final six months. All three exhibited diarrhea, respiratory infection and loss of body weight prior to

death. Upon autopsy, one control rat and one experimental rat were found to have tumors, while the other control animal had a granular liver and dark red apexes on both lungs. When surviving animals were sacrificed at the end of the two-year period, there was no significant gross pathology that could be related to ingestion of the compound. There was an equal incidence of mottled, granular livers with peripheral thickening in both the control and experimental animals. Two of the surviving control animals and one of the experimental animals had ovarian tumors, ovarian cysts were noted in both control and experimental rats.

Reliability : (2) valid with restrictions
No GLP, short description of the results, low number of animals, few organs examined, unclear number of animals examined, only one dose for females, purity not specified.

Flag : Critical study for SIDS endpoint

21.11.2003 (95)

Type : Sub-acute
Species : guinea pig
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 5 w
Frequency of treatm. : 5 d/w
Post exposure period : no data
Doses : 400 mg/day (682-942 mg/kg bw/day) and 600 mg/day (1032-1739 mg/kg bw/day)
Control group : no data specified
Method :
Year : 1943
GLP : no
Test substance : other TS: purity not specified

Method : Groups of five guinea pigs were fed 400 mg/day for five days followed by 600 mg/day, five days/week for five weeks. The adipic acid was given in capsules. These doses correspond to 682-942 mg/kg bw and day at the 400 mg dose and 1032-1739 mg/kg bw/day at the 600 mg/day dose.

Remark : 5 guinea pigs/dose group

Result : no signs of toxicity, one animal died from pneumonia, no adverse pathology.

Reliability : (4) not assignable
No experimental details described, unclear whether histopathology has been performed, purity not specified

19.11.2003 (110)

Type : Sub-acute
Species : pig
Sex :
Strain : other: Nursery
Route of admin. : oral feed
Exposure period : 7 d
Frequency of treatm. :
Post exposure period :
Doses :
Control group :
Method :
Year : 2001

GLP	:	no data
Test substance	:	other TS: purity not specified
Remark	:	The objectives of this research were to determine whether adipic acid improves the efficiency of lysine utilization in pigs. 14 Nursery pigs were fed for a period of seven days either a standard nursery diet or the same diet supplemented with 1% adipic acid. No signs of toxicity were observed. No further data.
Reliability	:	(2) valid with restrictions No standard toxicological study, purity not specified

19.11.2003 (112)

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	other: Alderley Park
Route of admin.	:	inhalation
Exposure period	:	6 h
Frequency of treatm.	:	15 applications
Post exposure period	:	no data
Doses	:	dust 126 mg/m3
Control group	:	no data specified
Method	:	
Year	:	1970
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Two female and two male rats (average bw 200 g) were maintained in the exposure chamber for 6 hours, and between repeated daily exposure they were returned to their cages where food and water were freely available. Rats were weighed each morning, and their conditions and behaviours were recorded throughout the exposure period. Urine was collected overnight after the last exposure day for biochemical testing. On the following day rats were anaesthetized, partially exsanguinated by heart puncture for hematological tests and organs were grossly examined. Histopathology: lung, liver, kidneys, spleen, adrenals, and occasionally heart, jejunum, ileum, and thymus. Test atmosphere was generated by injecting the powdered solid into a metered air stream, MMAD not specified.
Result	:	No signs of toxicity were observed. Blood tests were normal and no pathological changes were reported at necropsy.
Reliability	:	(4) not assignable Study is poorly documented, low number of animals, limited histopathology, nose as target organ not examined, MMAD not specified, purity not specified
Flag	:	Critical study for SIDS endpoint

21.11.2003 (113)

Type	:	Sub-acute
Species	:	rabbit
Sex	:	male
Strain	:	no data
Route of admin.	:	s.c.
Exposure period	:	4 d
Frequency of treatm.	:	once a day for 2 consecutive days, third appl. on the 4th day
Post exposure period	:	2 d
Doses	:	2000 mg/day (1. u. 2. appl.), 4000 mg/day (3. appl.)

Control group	:	no
Method	:	
Year	:	1925
GLP	:	no
Test substance	:	other TS: purity not specified
Result	:	The authors called adipic acid a mildly nephropathic agent due to the examined blood parameters (e.g. non-protein nitrogen, urea-N, creatinine, sugar, NaCl). No statistics given because data for only one rabbit published.
Test substance	:	neutralized sodium salt
Reliability	:	(4) not assignable Data for only one animal published.

26.11.2003 (114)

Type	:	Sub-acute
Species	:	mouse
Sex	:	
Strain	:	
Route of admin.	:	inhalation: dust
Exposure period	:	1.5 to 4 months
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	13 and 129 mg/m3 (4 months exposure), 460 mg/m3 (1.5 months exposure)
Control group	:	other: no data
Method	:	
Year	:	1981
GLP	:	no data
Test substance	:	other TS: purity not specified
Remark	:	The following organs were affected: upper respiratory tract, liver, kidney and central nervous system. Additionally the following effects were observed: reduced weight gain, alteration of the oxidase activity.
Reliability	:	(4) not assignable

19.11.2003 (96)

Type	:	Sub-acute
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	9 w
Frequency of treatm.	:	5 days/week
Post exposure period	:	no data
Doses	:	
Control group	:	other: yes, equimolar sodium as sodium acetate
Method	:	other: Groups of ten immature rats were fed 199 mg/day, five days/week for nine weeks as a aqueous solution. These doses correspond to 638-1332 mg/kg bw/day.
Year	:	1943
GLP	:	no
Test substance	:	other TS: sodium adipate, purity not specified
Result	:	Animals showed no adverse pathology attributable to sodium adipate. Significantly greater incidence of weight loss in animals treated with sodium adipate than in controls, both during weekly period of treatment and during week-end rest. All deaths (4/10) were due to infection.
Reliability	:	(4) not assignable

No experimental details described, unclear whether histopathology has been performed, purity not specified

26.11.2003 (110)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium TA 1535, TA 1537, TA 1538, TA 98, TA 100, and Escherichia coli WP2
Test concentration	:	0.033, 0.10, 0.33, 1.0, 3.3 and 10 mg/plate
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1982
GLP	:	no data
Test substance	:	other TS: purity not specified

Method : The standard S. typhimurium plate-incorporation assay was performed. The S9 mix used as an in vitro metabolic activator system contained 10% Aroclor 1254-induced liver S9 from male Sprague-Dawley rats. Each substance was tested in the presence and in the absence of S9 mix. In addition the tryptophan requiring E. coli strain WP2 was tested for reversion to tryptophan independance. This test was performed by the same procedure as the S. typhimurium assay except that agar was supplemented with Oxoid nutrient broth to provide a trace of tryptophan. All platings were performed in duplicates and all tests were repeated on a different day. Concurrent positive controls were run with each test. The results were considered valid only if the positive control compound induced increase in mutant counts to at least twice background. The following positive control compounds were used in the absence of S9: 2-nitrofluorene (5 or 10 µg per plate) for S. typhimurium strains TA98 and TA1538; sodium azide (0.5 or 1 µg) for TA100 and TA1535; 9-aminoacridine (50 or 100 µg) for TA1537; and AF-2 (furylframide, 0.1 µg) or N-methyl-N'-nitro-N-nitrosoguanidine (ENNG) (10 µg) for E. coli. 2-Anthramine (1 to 10 µg) was the positive control compound requiring S9 metabolic activation used for all bacterial strains.

Result : Adipic acid gave no evidence of mutagenicity in any of the bacterial strains used. Negative and positive controls were functional.

Reliability : (2) valid with restrictions
No GLP, short documentation, purity not specified, similar to TG471

Flag : Critical study for SIDS endpoint

26.11.2003 (115) (116)

Type	:	Ames test
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	
Method	:	
Year	:	1985
GLP	:	no data
Test substance	:	other TS

Method : Pyrolysed apidic acid was used for standard S. typhimurium

plate-incorporation assays. Neither positive nor negative controls were performed.

Result : In this study only pyrolysed material was used, not apidic acid itself. No controls were performed. The pyrolysed compound gave no evidence of mutagenicity in any of the bacterial strains used.
Test substance : Apidic acid after pyrolysis at 500 - 800 degree Celsius
Reliability : (3) invalid
otherTS

19.11.2003 (117)

Type : Ames test
System of testing : Salmonella typhimurium TA 100, TA 98, TA 1535, TA 1537, TA 1538, E. coli WP2uvrA
Test concentration : 5 mg/plate
Cycotoxic concentr. : not determined
Metabolic activation : with and without
Result : negative
Method :
Year : 1985
GLP : no data
Test substance : other TS: 99% purity

Method : The S. typhimurium pre-incubation assay was performed. The S9 mix used as an in vitro metabolic activator system S9 from male Sprague-Dawley rats. Each substance was tested in the presence and in the absence of S9 mix. In addition the trytophan requiring E. coli strain WP2 was tested. This test was performed by the same procedure as the S. typhimurium assay except that tryptophan was added to the top agar.
Positive controls: AF-2, ENNG, 9-aminoacridine(9AC), 4-nitroquinoline-1-oxide (4nQO), benzo(a)pyrene (BaP), 2-aminoanthracene (2AA), and 2-nitrofluorene (12NF).

All tests were performed in duplicates.
Result : Adipic acid gave no evidence of mutagenicity in any of the bacterial strains used. Positive controls gave the expected results.
Reliability : (2) valid with restrictions
Short ducumentation, similar to TG471, cytotoxicity was not observed, however, highest dose used was 5 mg/plate.
Flag : Critical study for SIDS endpoint
26.11.2003 (118)

Type : Ames test
System of testing : Salmonella typhimurium TA-1530, G-46
Test concentration : 0, 2, 20, 200 mg/l
Cycotoxic concentr. : not determined
Metabolic activation : without
Result : negative
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : The indicator organisms were two histidine auxotroph Salmonalla typhimurium strains (G-46 and TA-1530). The bacteria were plated on appropriate media. Test compound was then added to the plate, either in the form of a microdrop applied to a small filter paper or a small crystal applied directly to the agar. Tenfold serial dilutions

of the culture were employed and plated so as not to miss the optimal cell density for mutant growth. Mutant colonies were observed and scored.

Negative and positive controls (dinethyl nitrosamine) were run concurrently.

Result : Tests were negative. Negative and positive controls were functional. No in vitro metabolic activator system (S9) was used in this study.

Reliability : (2) valid with restrictions
No GLP, no metabolic activator used, purity not specified.

21.11.2003 (92)

Type : Yeast gene mutation assay
System of testing : Saccharomyces cerevisiae D-3
Test concentration : 0, 2, 20, 200 mg/l
Cycotoxic concentr. : not determined
Metabolic activation : without
Result : negative
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Saccharomyces cerevisiae D-3 cells (diploid strain, presumptive his 8 homozygotes) were used. Yeast mitotic recombinants were seen as red colonies or as red sectors on a normally white yeast colony. Negative and positive controls (ethyl methane sulfonate) were run in parallel.

Result : Tests were negative. Negative and positive controls were functional. No in vitro metabolic activator system (S9) was used in this study. No data on cytotoxicity.

Reliability : (2) valid with restrictions
No GLP, no metabolic activator used, purity not specified. No data on cytotoxicity.

Flag : Critical study for SIDS endpoint

26.11.2003 (92)

Type : Cytogenetic assay
System of testing : human fibroblasts (WI-38)
Test concentration : 0, 2, 20, 200 mg/l
Cycotoxic concentr. : 400 mg/l
Metabolic activation : without
Result : negative
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Human embryonic lung fibroblast cultures (WI-38) were suspended in tissue culture medium and plated. The test compound was added at three dose levels using three bottles for each level, 24 hours after plating. A preliminary determination of tissue culture toxicity was performed (cytotoxic effects were observed at 400 mg/l). Cells were incubated at 37 degree Celsius and examined twice daily to determine when an adequate number of mitoses were present. Cells were harvested and fixed (3:1 absolute methanol : glacial acetic acid). The specimens were centrifuged, decanted, and suspended in acetic acid-orcein stain and dropped on a slide. The preparations were examined by microscopy. Cells in anaphase were observed for non-disjunction as indicative of cytogenetic damage. Analyzed aberrations include bridges, pseudochiasmata,

multipolar cells, and acentric fragments. The positive control was triethylene melamine (TEM) and the negative control was saline. 100 cells were investigated per dose.

Result : Negative and positive controls were functional. The negative controls contained two cells with bridges one of which contained an acentric fragment. The test compound was negative except for one cell which contained a bridge at the high dose level.
In summary, the compound produced no significant aberration.

Reliability : (2) valid with restrictions
No GLP, but good documentation, purity not specified, no metabolic activation

Flag : Critical study for SIDS endpoint

26.11.2003 (92)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : rat
Sex : male
Strain : no data
Route of admin. : gavage
Exposure period : Acute study: single dosing; subacute study: once a day for 5 consecutive days
Doses : Test 1: acute and subacute: 3.75, 37.5, 375 mg/kg bw/day; Test 2: acute 5000 mg/kg bw and subacute 2500 mg/kg bw/day
Result : negative
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Groups of 5 treated and 3 control animals were used. Animals were killed 6, 24 and 48 hours after a single administration in the acute study. In the subacute study 5 doses, 24 hours apart, were administered and animals were killed 6 hours after the last dose. Four hours after the last compound administration, and two hours prior to killing, each animal was given 4 mg/kg bw of colcemid intraperitoneally in order to arrest the bone marrow cells in C-mitosis. The marrow "plug" was removed and aspirated into Hanks' balanced salt solution. The specimen were centrifuged and resuspended in hypotonic 0.5% KCl. The specimens were placed in a 37 degree Celsius water bath in order to swell the cells. Following centrifugation the cells were resuspended in a fixative (3:1 absolute methanol : glacial acetic acid) and again centrifuged. Cells were resuspended and placed at 4 degree Celsius overnight. The following day cells were again centrifuged and freshly prepared fixative was added. The suspension was dropped onto a slide and ignited by an alcohol burner and allowed to flame. Slides were stained with 5% Giemsa solution. The preparations were examined by microscopy. The chromosomes of each cell were counted and only diploid cells were analyzed. They were scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with greater than ten aberrations, polyploidy, pulverization, and other chromosomal aberrations which were observed. Fifty metaphase spreads were scored per animal. Mitotic indices were obtained by counting at least 500 cells and the ratio of the number of cells in mitosis / the number of cells observed was expressed as the mitotic index. Negative and positive (TEM) controls were run in each experiment.
Two tests were performed at different time intervals.

Result : Test I (3.75, 37.5 and 375 mg/kg bw/day dosing):
Acute study: The negative control group cells contained no aberrations. The compound produced no aberrations except for one cell containing a break in the 6-hour sample of the intermediate dose level. The expected severe chromosomal damage was observed for the positive control group (triethylene melamine treated animals). The mitotic indices were within normal limits. Negative and positive controls were functional.
Subacute study (5 days): The negative control group and the low level test group contained no aberration. The intermediate level contained one cell with a reunion and one cell that was polyploid. The highest level contained three cells with breaks and one fragment. These were considered to be within the normal limits of the historical negative controls of the laboratory. Negative control was functional, no positive control.

Test 2:
Acute study: Adipic acid was administered at a single dose of 5000 mg/kg bw. The compound produced no aberrations except for 3 cells with polyploidy (2 in the 6-hour sample and 1 in the 24-hour). Neither the variety nor the number of these aberrations differed significantly from the negative controls (polyploidy observed in 4 cells). Negative and positive controls were functional.
Subacute study (5 days, 2500 mg/kg bw/day). Only 218 metaphases have been evaluated. The compound produced no aberrations except for 1 cell with polyploidy.
Polyploidy was also observed in the negative control group.
These are considered to be within the normal limits of the historical negative controls. Negative control was functional, no positive control.

In summary, adipic acid can be considered non-mutagenic as measured by the cytogenetic test.

Reliability : (2) valid with restrictions
No GLP but overall good documentation, purity not specified, no positive control for every experiment.

Flag : Critical study for SIDS endpoint

21.11.2003 (92)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : no data
Route of admin. : gavage
Exposure period : Acute study: single dosing; subacute study: once a day for 5 consecutive days
Doses : Test 1: acute and subacute: 3.75, 37.5, 375 mg/kg bw/day; Test 2: acute 5000 mg/kg bw and subacute 2500 mg/kg bw/day
Result : negative
Method :
Year : 1974
GLP : no
Test substance : other TS: purity not specified

Method : Adipic acid was administered by gavage to 10-12 weeks old male rats (10 per group) once (acute studies) or one dose per day for five consecutive days (subacute studies). Following treatment, the males were sequentially mated to two virgin females per week for eight weeks (7 weeks in the subacute studies). Two weeks after mating, female rats were sacrificed and the following parameters were recorded and compared with those same parameters calculated from negative (saline dosed) and

positive (0.3 mg/kg TEM (triethylene melamine)-dosed) control animals and historical control data: fertility index, average number of implantations per pregnant female, average corpora lutea per pregnant female, average preimplantation loss per pregnant female, average resorptions (dead implants) per pregnant female, proportion of females with one or more dead implantations, proportion of females with two or more dead implantations, and dead implants per total implants.

Result : Test 1 (3.75, 37.5 and 375 mg/kg bw/day):
Acute study: significant decreases were seen in the intermediate dose groups in average implantations in females mated at week 1 (10.2 compared to 12.2 or 12.4 in the negative control and the historical control, respectively) and at week 4 (10.0 compared to 12.1 or 11.9), and in corpora lutea in females mated at weeks 4 (11.7 compared to 14 or 13) and 7 (12.4 compared to 14 or 13). Significant increase in preimplantation losses were shown at week 1 for both the low and intermediate dose groups (3.75 mg/kg: 28/12=2.3; 37.5 mg/kg: 36/13=2.8; negative control: 11/14=0.8, and historical control 142/95=1.5).
Subacute study: Significant difference between the negative control and experimental groups were shown in a few instances, but no clear indications of change were seen. The positive control was functional.

Test 2 (acute single dose of 5000 mg/kg bw and subacute five doses of 2500 mg/kg bw/day): The values from animals dosed with adipic acid did not significantly vary from those obtained from the negative control. The positive control showed significant effects.

In summary, no dose-response or time-trend patterns were observed in test 1 and no effects were seen in test 2, indicating that adipic acid does not induce dominant lethal mutations.

Reliability : (2) valid with restrictions
No GLP but overall good documentation, purity not specified.

Flag : Critical study for SIDS endpoint

21.11.2003 (92)

Type : other
Species : Drosophila melanogaster
Sex : male/female
Strain :
Route of admin. : oral feed
Exposure period : during the whole larval period
Doses : 4000 ppm
Result : negative
Method :
Year : 1979
GLP : no
Test substance : other TS: purity not specified

Method : Genetically marked X and Y chromosomes were used to test simultaneously in the offspring: nondisjunction, chromosome loss and induced recombination or translocation involving the Y-chromosome. Positive controls: colchicine, organic mercury, triethyllead chloride, trimethyltin chloride.

Result : No effects were reported. Positive controls were functional.

Reliability : (2) valid with restrictions
No GLP but overall good documentation, purity not specified.

Flag : Critical study for SIDS endpoint

19.11.2003 (119)

Type	:	other: host mediated assay
Species	:	mouse
Sex	:	male
Strain	:	other: Flow Laboratories ICR random-bred
Route of admin.	:	gavage
Exposure period	:	acute study: single administration; subacute study: once a day for 5 consecutive days
Doses	:	Test 1: acute and subacute: 3.75, 37.5, 375 mg/kg bw/day; Test 2: acute 5000 mg/kg bw and subacute 2500 mg/kg bw/day
Result	:	negative
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: purity not specified

Method	:	Ten animals were employed at each dose level. The indicator organisms were two histidine auxotroph Salmonalla typhimurium strains (G-46 and TA-1530) and a diploid Saccharomyces cerevisiae strain (D-3). The induction of reverse mutation was determined with Salmonella; mitotic recombination was determined with yeast. Only animals on the subacute studies were not fed the evening prior to compound administration. All animals received the indicator organisms intraperitoneally (6 x 10EE8 cells for Salmonella and 1 x 10EE9 cells for Saccharomyces) within 30 minutes after the last dosing. Three hours later, each animal was killed and sterile saline was introduced intraperitoneally. As much fluid as possible was then aseptically removed from the peritoneal cavity. Tenfold serial dilutions were made of each peritoneal exudate. For enumeration of total bacterial counts tryptone-yeast agar plates were used. In plating for the total mutant counts minimal agar was used. Yeast-complete agar plates were used for enumeration of total yeast counts and plates were examined after additional 40 hours at 4° degree Centigrade for red sectors indicating a mutation. Solvent and positive controls were run at all times. The positive control (dimethyl nitrosamine) was run during the acute study only at a dose of 100 mg/kg for Salmonella. For yeast EMS intramuscularly injected at a dose of 350 mg/kg was used.
Result	:	Test 1 (3.75, 37.5 and 375 mg/kg bw/day acute and subacute): Adipic acid produced no significant increase in mutation frequencies at the dose levels tested with Salmonella TA-1530 or G-46 nor significant recombinant count increase in the subacute test when tested against Saccharomyces D-3. Tests using Saccharomyces at acute levels showed increased frequencies as well as dose responses. Negative and positive controls were functional. Test 2 (5000 mg/kg acute; 2500 mg/kg bw/day subacute): The result was negative for all three indicator strains. Negative and positive controls were functional.
Reliability	:	(2) valid with restrictions No GLP but overall good documentation, purity not specified.
Flag	:	Critical study for SIDS endpoint

21.11.2003 (92)

5.7 CARCINOGENICITY

Species	:	rat
Sex	:	male/female

Strain : other: Carworth Farm
Route of admin. : oral feed
Exposure period : 2 a
Frequency of treatm. :
Post exposure period : no data
Doses : male rats: 0, 0.1, 1, 3, and 5%; (ca. 75, 750, 2250, 3750 mg/kg bw/day)
female rats: 0, 1%; (ca. 750 mg/kg bw/day)
Result :
Control group : yes
Method : other: see chapter 5.4 Horn et al. 1957
Year : 1957
GLP : no
Test substance : other TS: purity not specified

Remark : This study is also described in detail in chapter 5.4 Repeated Dose Toxicity.
Result : During the rapid growth of the 2-year feeding studies, weight gains for the male rats receiving 3 or 5% adipic acid was significantly less than the controls. Growth for other groups, 0, 0.1, 1% male and 0, 1% female, was comparable to that of the respective controls. 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%. There was no evidence of gross pathology associated with the feeding of adipic acid (see chapter 5.4, Repeated Dose Toxicity).

Results males (control, 0.1, 1, 3, 5% adipic acid; 20 male animals/group):
Autopsy data for the male animals that died during the course of the two-year feeding program and for the sacrificed rats were analyzed for incidence of tumors and/or lung pathology. Only tumors presenting gross evidence of being a new growth were scored.

Male group: 0/0.1/1/3/5%

Deaths:	
total deaths	12/7/5/4/5
lung pathology	7/3/1/3/-
tumors	3/2/2/-/4
other causes	3/3/2/1/1

Sacrificed:	
lung pathology	4/7/7/3/4
tumors	1/2/2/-/-

Results females (10 control animals and 19 animals dosed with 1% adipic acid):
The results of microscopic examination appeared to be within normal limits. One experimental and two control animals died during the final six months. Upon autopsy, one control rat and one experimental rat were found to have tumors.Two of the surviving control animals and one of the experimental animals had ovarian tumors, ovarian cysts were noted in both control and experimental rats.

In summary: the incidence of tumors observed in the adipic acid treated groups was as frequent as in the control groups.
Reliability : (2) valid with restrictions
No GLP, short description of the results, low number of animals, few organs examined, unclear number of animals examined histopathologically,

only one dose for females, purity not specified

Flag : Critical study for SIDS endpoint
20.11.2003 (95)

Species : mouse
Sex :
Strain : other: BC
Route of admin. : other: intravaginally
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Result :
Control group :
Method :
Year : 1959
GLP : no data
Test substance : other TS: purity not specified

Result : A group of mice received intravaginally, three time weekly, applications of a powdered mixture containing urea, adipic acid and carboxmethyl cellulose. There was a high incidence of vaginal cancer after prolonged treatment (usually >400 days). Experiments extended over one year, in which the three ingredients were given separately, yielded no tumors. No further data given.
Reliability : (4) not assignable
04.09.2003 (120)

Species : other: in vitro
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Result :
Control group :
Method :
Year : 2002
GLP : no data
Test substance : other TS: purity not specified

Remark : Adipic acid was negative in the viral enhanced cell transformation assay in Syrian hamster embryo (SA7/SHE) cells at doses from 62 to 1000 µg/ml. No further data
Reliability : (4) not assignable
04.09.2003 (121)

5.8.1 TOXICITY TO FERTILITY

Type : other: Dominant lethal assay
Species : rat
Sex : male
Strain : no data
Route of admin. : gavage

Exposure period	:	Acute study: single dosing; subacute study: once a day for 5 consecutive days
Frequency of treatm.	:	
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	
Control group	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: purity not specified

Method : Adipic acid was administered by gavage to 10-12 weeks old male rats (10 per group) once (acute studies) or one dose per day for five consecutive days (subacute studies).
Following treatment, the males were sequentially mated to two virgin females per week for eight weeks (7 weeks in the subacute studies). Two weeks after mating, female rats were sacrificed and the fertility index, preimplantation loss and lethal effects on the embryos were determined and compared with those same parameters calculated from negative (saline dosed) and positive (0.3 mg/kg TEM (triethylene melamine)-dosed) control animals.

The following tests were performed:
Test 1: male animals were dosed with 3.75, 37.5 and 375 mg/kg bw/day for one day (acute study) and five consecutive days (subacute study)

Test 2: male rats were dosed with a single dose of 5000 mg/kg bw (acute study) and five doses of 2500 mg/kg bw/day (subacute study)

Result : Data on preimplantation loss, corpora lutea and lethal effects on the embryos were summarized in Chapter 5.6. (Genetic Toxicity "In vitro").

Fertility indices in all experiments and all doses did not differ from the control indices. Positive controls were functional.

Reliability : (4) not assignable
No GLP, limited number of parameters, purity not specified

05.01.2005 (92)

Type	:	other: chronic two-year study
Species	:	rat
Sex	:	male/female
Strain	:	other: Carworth Farm strain
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	

Doses	:	male rats: 0, 0.1, 1, 3, and 5%; (ca. 75, 750, 2250, 3750 mg/kg bw/day) female rats: 0, 1%; (ca. 750 mg/kg bw/day)
Control group	:	
Method	:	
Year	:	1957
GLP	:	no
Test substance	:	other TS: purity not specified

Method	:	See Chapter 5.4. Repeated Dose Toxicity, Horn et al, 1957.
Result	:	During the rapid growth of the 2-year feeding studies, weight gains for the male rats receiving 3 or 5% adipic acid was significantly less than the controls. Growth for other groups, 0, 0.1, 1% male and 0, 1% female, was comparable to that of the respective controls. There was no evidence of gross pathology associated with the feeding of adipic acid (see chapter 5.4, Repeated Dose Toxicity). Males (control, 0.1, 1, 3, 5% adipic acid; 20 male animals/group): When the surviving males were sacrificed there was no significant gross pathology that could be related to adipic acid. Histopathologic examination of the testes revealed no evidence of an adverse effect on the reproductive organs up to the highest dose. Soft edematous testes were noted at least as frequent in the controls as in the experimental animals. Females (10 control animals and 19 animals dosed with 1% adipic acid): When the surviving females were sacrificed there was no significant gross pathology that could be related to adipic acid. Histopathologic examination of the ovaries and uterus revealed no evidence of an adverse effect on the reproductive organs. Two of the surviving control animals and one of the experimental animals had ovarian tumors, ovarian cysts were noted in both control and experimental rats. In summary: histopathologic examination of the testes, ovaries and uterus revealed no evidence of an adverse effect on the reproductive organs.
Reliability	:	(2) valid with restrictions No GLP, short documentation, unclear number of animals examined histopathologically, only one dose for females, purity not specified.
Flag	:	Critical study for SIDS endpoint

20.11.2003 (95)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	10 d
Frequency of treatm.	:	6.-15. day of gestation, daily
Duration of test	:	
Doses	:	0, 2.9, 13, 62, 288 mg/kg bw/day
Control group	:	yes
NOAEL maternal tox.	:	288 mg/kg bw

other: NOAEL developm. tox.	:	288 mg/kg bw
Method	:	
Year	:	1972
GLP	:	no
Test substance	:	other TS: purity not specified
Method	:	Virgin adult females (25 animals per group) were mated with young adult males, and observation of a vaginal sperm plug was considered day zero of gestation. Pregnanat females (20 - 24 animals per group) were dosed by gavage from gestation days 6-15. 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 animals were subjected to cesarean section, and the number 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 normality. The body weights of the liver 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 up to 288 mg/kg bw/day of the compound to pregnant rats for 10 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissue of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No maternal toxicity observed. 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 No GLP but overall good documentation. Study did not include a high dose that caused maternal toxicity, no statistical evaluation. Data on purity of adipic acid are lacking. No justification for dose selection was given.
Flag	:	Critical study for SIDS endpoint

13.02.2006 (122)

Species	:	mouse
Sex	:	female
Strain	:	other: albino CD-1
Route of admin.	:	gavage
Exposure period	:	10 d
Frequency of treatm.	:	6.-15. day of gestation, daily
Duration of test	:	
Doses	:	0, 2.6, 12, 56, 263 mg/kg bw/day
Control group	:	yes
NOAEL maternal tox.	:	263 mg/kg bw
other: NOAEL developm. tox.	:	263 mg/kg bw
Method	:	
Year	:	1972
GLP	:	no
Test substance	:	other TS: purity not specified
Remark	:	Virgin adult females (25 animals per group, 31 in the high dose group) were mated with young adult males, and observation of a vaginal sperm plug was considered day zero of gestation. Pregnant females (20 - 24 animals per group) were dosed by gavage from gestation days 6-15. Body weights were recorded on days 0, 6, 11, 15, 17 of gestation, and all animals were observed daily for

appearance and behavior with particular attention to food consumption and weight. On day 17 all animals were subjected to cesarean section, and the number 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 normality. The body weights of the liver 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. Positive control: 150 mg Aspirin/kg bw; administration volume: 10 ml/kg bw

Result : The administration of up to 263 mg/kg bw/day of the compound to pregnant mice for 10 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissue of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No maternal toxicity observed. 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
No GLP but overall good documentation. No statistical evaluation. The highest dose did not cause maternal toxicity. Data on purity of adipic acid are lacking. No justification for dose selection was given .

Flag : Critical study for SIDS endpoint

13.02.2006 (122)

Species	:	rabbit
Sex	:	female
Strain	:	other: Dutch-belted
Route of admin.	:	gavage
Exposure period	:	13 d
Frequency of treatm.	:	6.-18. gestation day, daily
Duration of test	:	
Doses	:	0, 2.5, 12, 54, 250 mg/kg bw/day
Control group	:	yes
NOAEL maternal tox.	:	>= 250 mg/kg bw
other: NOAEL developm. tox.	:	250 mg/kg bw
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: purity not specified

Method : On day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck. Beginning on day 6 and continuing daily through day 18 the females (10-14 animal per dose) were dosed with the indicated dosages by oral intubation. Body weights were recorded on days 0, 6, 12, 18 and 29 of gestation, with particular attention to food consumption and body weight. On day 14 all animals were subjected to cesarean section, and the number of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. The urogenetal tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities and examined

for skeletal defects. 6-Aminonicotinamide (2.5 mg/kg), dosed on day 9, was used as a positive control.

Result : The administration of up to 250 mg/kg bw/day of the compound to pregnant rabbits for 13 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissue of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. No difference 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 weights. No maternal toxicity observed. The resultes were not evaluated statistically, but inspection of tables shows no effects in the treated groups vs. control.

Reliability : (2) valid with restrictions
No GLP but overall good documentation. 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. No justification for dose selection was given

Flag : Critical study for SIDS endpoint

05.01.2006 (123)

Species : hamster
Sex : female
Strain : no data
Route of admin. : gavage
Exposure period : 5 d
Frequency of treatm. : 6.-10. day of gestation, daily
Duration of test :
Doses : 0, 2, 9.5, 44, 205 mg/kg bw/day
Control group : yes
NOAEL maternal tox. : 205 mg/kg bw
NOAEL teratogen. : 205 ml/kg bw
Method :
Year : 1972
GLP : no
Test substance : other TS: purity not specified

Method : Virgin adult females (25-27 animals) were mated (1:1) with mature males, and the appearance of motile sperm in the vaginal smear was considered day zero of gestation. Pregnanat females (21 - 24 animals per group) were dosed by gavage from gestation days 6-10. Body weights were recorded on days 0, 8, 10 and 14 of gestation, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight. On day 14 all animals were subjected to cesarean section, and the number 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 normality. The body weights of the liver 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 up to 205 mg/kg bw/day of the compound to pregnant hamsters for 5 consecutive days had no effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissue of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. 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
No GLP, study did not include a dose that caused maternal toxicity, treatment period too short, no statistical evaluation, limited documentation. Data on purity of adipic acid are lacking. No justification for dose selection was given

13.02.2006 (122)

Species : rat
Sex :
Strain : no data
Route of admin. : oral feed
Exposure period : 33 weeks
Frequency of treatm. : daily
Duration of test :
Doses : 0, 400, 800 mg/day (0, 1600 and 3200 mg/kg bw/day)
Control group : no
Method :
Year : 1953
GLP : no
Test substance : other TS: purity not specified

Method : See Chapter 5.4. Repeated Dose Toxicity; Lang et al. 1953. Groups of 13-15 animals with a weight of 60-80 g received adipic acid in a standard diet (80% bruised wheat, 20% milk powder). Weight gain and general behavior were recorded.

Remark : Some of the animals in the 400 mg and in the 800 mg dosing group were gravid (number not given). These animals gave birth and raised their young normally. No further data.
No justification for dose selection was given

Reliability : (4) not assignable

10.01.2005 (109)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Remark : 20 mg/m3 was described as threshold concentration for eye irritation.

Reliability : (4) not assignable
No details described

20.11.2003 (96)

Type of experience : Human

Remark : Effects on the following organs were reported in laboratory worker in a factory handling with adipic acid: autonomic nervous system, upper respiratory tract and the workers were suffering from indigestion.
No data on exposure.

Reliability : (4) not assignable

No details described
20.11.2003 (96)

Type of experience : other: ADI value estimation

Remark : The ADI-value was noted to be 0-5 mg/kg bw/day
Reliability : (4) not assignable
Review
20.11.2003 (124)

Type of experience : Human

Remark : 7 of 12 workers exposed (for an average of 9.2 years) to various glycols and adipic acid dust particles (concentration 0.47-0.79 mg/m3 [0.08-0.13 ppm]) (8 h average value) complained of mucosal irritation (eye, nose, throat). There was no local exhaust ventilation and the workers did not wear respiratory protection. They reported that clouds of adipic acid and other materials were routinely generated during charging of reaction vessels. The investigators suggested that, since the glycol level was kept below 1 ppm, adipic acid was more likely to be the cause of these complaints.
Reliability : (2) valid with restrictions
Human case report, due to the acidic character of the substance, a local irritation potential is plausible
Flag : Critical study for SIDS endpoint
07.05.2003 (125)

Type of experience : Human

Remark : Adipic acid was seen in small amounts in the urine of newborns. Large amounts of adipic acid was reported in children eating gelatins. A three days diet free of gelatin revealed normal adipic acid levels in the urine. The presence of large amounts of this compound in the urine is usually indicative of an error of metabolism (diabetic ketoacidosis).
Reliability : (2) valid with restrictions
Human case report
09.05.2003 (126)

Type of experience : Human

Remark : A five-year old girl (suspected of having Kearn-Sayres Syndrome) was found to be excreting massive amounts of adipic acid but without substantial amounts of suberic, sebatic and ethylmalonic acids. Adipic acid excretion accompanied by these other metabolites is often a sign of several metabolic diseases. This unexpected finding was reproduced in successive urine samples and seemed to have no correlation to time of day or meals. Examination of the patient's medicamentations revealed that she was taking K and Mg in form of the adipate salt (Kaluim-Magnesium Apogepha). On changing to other forms of K and Mg medicamentation the adipic aciduria disapeared. This observation was classified as "metabolically unexciting".
Reliability : (2) valid with restrictions
No GLP but overall good documentation.
02.06.2003 (127)

5.11 ADDITIONAL REMARKS

Type : Cytotoxicity

Remark : HeLa cells were used for measuring the substance-induced cytotoxicity in vitro. Kim et al. (2001) reported that that the viability of the HeLA cells decreased to 78, 48 and 0% in the presence of 0.1, 1 and 5% adipic acid in the medium. Sheu et al. (1975) published an IC50 value of 7 mM (corresponds to ca. 0.1%).

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

09.05.2003 (35) (128)

Type : Immunotoxicity

Remark : The lymphocyte mitogenesis test was used to test for immunotoxicity in vitro. In this test lymphocytes were stimulated by a polyclonal mitogen specific for either B or T cells. Neither B nor T lymphocyte mitogenesis was inhibited by adipic acid at concentrations up to 0.3%.

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

09.05.2003 (129)

Type : other: Calcium binding capacity of the urine

Remark : In rats orally administered adipic acid (2000 mg/kg) increased the Ca2+-binding capacity of the urine while the excretion of oxalate was decreased.

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

09.05.2003 (130)

Type : other: In vitro acid-phosphatase release

Remark : Rat nasal explants were incubated in vitro in media containing 0, 10, 25 and 50 mM of adipic acid, respectively. The media were assayed for acid phosphatase activity. Statistically significant increase in acid phosphatase activity was observed at 25 mM (corresponds to 3.7 g/l). Similar results were obtained with adipic acid esters that are hydrolyzed in vitro to form adipic acid.

Reliability : (2) valid with restrictions
No GLP

Flag : Critical study for SIDS endpoint

01.12.2003 (131)

Type : other: estrogenic activities

Remark : To investigate estrogenic activities of chemicals the authors developed a yeast two-hybrid assay with the nuclear hormone receptor, which binds specifically to the steroid hormone and regulates its gene expression. Adipic acid showed no effect in this test. The reported REC10 value (the concentration showing 10% activity of 10EE-7 M 17b-estradiol) was > 10 mM.

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

09.05.2003 (132)

Type : other: in vitro cell proliferation

Remark : The antiproliferative effect of adipic acid (1-50 mM) was examined with neonatal mouse keratinocyte cultures. Fifty per cent inhibition of thymidine incorporation was seen at 50 mM. The antiproliferative effect was completely reversible after cessation of treatment.

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

03.09.2003 (133)

Type : other: liver glycogen levels

Remark : Liver glycogen levels were investigated in the presence and absence of adipic acid. Male rats (mean bw 110-130 g) were fed with 0.25 g of sodium adipate and glycogen levels were detected after 4-8 hours. The glycogen level in the presence of the compound (0.066%) was the same as in the control group (0.074%).

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

20.05.2003 (134)

Type : other: rectal membrane

Remark : The use of adipic acid was investigated to develop sustained-release suppositories. Morphological studies revealed that adipic acid in formulation did not damage the rectal membrane.

Reliability : (2) valid with restrictions
No GLP but overall good documentation.

09.05.2003 (135)

(1) Kennedy GL (2002). Toxicity of adipic acid. Drug Chem. Tox. 25 (2), 191-202.

(2) Davis DD (1985). Adipic acid. Ullmann´s Encyclopedia of Industrial Chemistry A01, 269-278, Verlag Chemie, Weinheim.

(3) BUA (1994). GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) Report 68, Adipic acid, S. Hirzel Wissenschaftliche Verlagsgesellschaft, Stuttgart.

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