The MAK Collection for Occupational Health and Safety

Adipic acid

MAK Value Documentation – Translation of the German version from 2017

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Adipic acid / hexanedioic acid

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated adipic acid [124-04-9] to derive a maximum concentration at the workplace (MAK value), considering all toxicity endpoints.
The critical effect is moderate local irritation as shown with the Draize test in the rabbit eye. Available inhalation studies are limited and not suitable to derive a MAK value. Systemic toxicity only occurs at high doses. In a limited oral 2-year study the body weight of rats was reduced at 2250 mg/kg body weight/day. The resulting systemic NOAEL is 750 mg/kg body weight/day.
After comparing adipic acid with other solid acids, a MAK value of 2 mg adipic acid/m^3 I has been set in analogy to phosphoric acid, which is considered to be the worst-case.
As the critical effect is local, adipic acid is assigned to Peak Limitation Category I. In analogy to phosphoric acid, a default excursion factor of 2 is set.
Damage to the embryo or foetus is unlikely when the MAK value is observed; thus, the substance is classified in Pregnancy Risk Group C.
Adipic acid is not genotoxic and not carcinogenic. No contact sensitizing effects have been observed. Skin contact is not expected to contribute significantly to systemic toxicity.
Completed: February 24, 2016

Keywords

adipic acid; 1,4-butanedicarboxylic acid; 1,6-hexanedioic acid; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Adipic acid

MAK value (2016)	**2 mg/m³ I (inhalable fraction)**
Peak limitation (2016)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	1,4-butanedicarboxylic acid
Chemical name	1,6-hexanedioic acid
CAS number	124-04-9
Structural formula	$HO_2C–(CH_2)_4–CO_2H$
Molecular formula	$C_6H_{10}O_4$
Molar mass	146.14 g/mol
Melting point	145–155 °C (ECHA 2015) 152 °C (OECD 2004)
Boiling point at 1013 hPa	337.5 °C (ECHA 2015; OECD 2004)
Vapour pressure	4.24×10^{-7} hPa at 25 °C (US EPA 2008)
log K_{OW}[1)]	0.08–0.09 at 25 °C (ECHA 2015; OECD 2004)
Solubility	23–25g/l water at 25 °C (ECHA 2015; OECD 2004), readily soluble in methanol and ethanol, soluble in acetone and ethyl acetate, poorly soluble in cyclohexane and benzene (ECHA 2015)
pKa value	4.43 at 25 °C (ECHA 2015), pKa1 = 4.34; pKa2 = 5.44 (OECD 2004)
pH	saturated solution: pH 2.7; 0.1% solution: pH 3.2 (ECHA 2015; OECD 2004)
Stability	not stable in alcohol, the corresponding esters are formed (ECHA 2015)

Production	from a mixture of cyclohexanol (93%) and cyclohexanone (7%) by means of oxidative ring cleavage using concentrated nitric acid; or alternatively from cyclohexane by means of catalytic oxidative ring cleavage or by hydration of phenol to obtain cyclohexanol, which is oxidized to adipic acid (OECD 2004)
Purity	> 99.6% w/w (food quality); 99.8% (polyamide synthesis, which reacts very sensitively to impurities) (OECD 2004)
Impurities	typical impurities include other acids (monobasic acids and lower dibasic acids (60 mg/kg), nitrogenous materials, trace metals such as iron (2 mg/kg) and other heavy metals (10 mg/kg), arsenic (3 mg/kg) and hydrocarbon oil (10 mg/kg); water (< 0.2% w/w) (OECD 2004)
Use	as food additive E355 (acidifier) (BMJV 2012); nylon production (up to 70% of adipic acid production), monomer for polyester and polyester polyurethanes, monomer for polyamides, synthetic intermediate in the production of 1,6-hexanediol, plasticizers, dyes, pharmaceuticals, insecticides, adhesives, preparation of leather treatment formulations, miscellaneous uses including perfume fixative and foodstuff additive (OECD 2004); lubricant oil additive (Kennedy 2002)

The documentation is based mainly on the publicly available registration data REACH (ECHA 2015).

In the EU, adipic acid is a registered food additive with the number E355 (BMJV 2012).

Since 1977, the ADI (acceptable daily intake) value for the sum of all adipates is 5 mg/kg body weight and was confirmed in 1991 (JECFA 1977; EC 1991). It is assumed that this value is easily attained (OECD 2004).

1 Toxic Effects and Mode of Action

In rats, no signs of airway irritation were reported in either a short-term inhalation study with 4-hour exposure to adipic acid concentrations of up to 7700 mg/m^3, or in a 2-week inhalation study with inadequate documentation after daily 6-hour exposure to 126 mg/m^3. In both studies, however, the nose was not examined. On the other hand, in another study with only limited availability of the results, effects in the

1) Octanol/water partition coefficient.

upper airways of the mouse at concentrations of 13 mg/m^3 and above are reported. It is plausible that adipic acid causes local irritation in the respiratory tract as this acid is slightly irritating to the rabbit skin and severely irritating to the rabbit eye.

In a 2-year oral study in rats with limited documentation and scope carried out in the 1950s, toxic effects were first found in the form of reduced body weights at 2250 mg/kg body weight and day. A specific target organ was not identified and tumour incidences were not increased. Adipic acid was not found to be genotoxic in various in vitro and in vivo tests.

In developmental toxicity studies in rats, mice and rabbits with oral doses of up to 288, 263 and 250 mg/kg body weight and day, respectively, adipic acid did not induce foetotoxic or teratogenic effects. Maternal toxicity did not occur in any of the studies.

A carcinogenicity study with many shortcomings, in which adipic acid doses of up to 3750 mg/kg body weight and day were administered with the diet to rats, provided no evidence of carcinogenic effects.

There are no reliable clinical findings available for the sensitizing effects of adipic acid or corresponding evidence from animal experiments.

2 Mechanism of Action

In nasal explants, adipic acid concentrations of 25 mM (3.7 g/l) had cytotoxic effects similar to those of adipic acid ester (OECD 2004).

In a 3-week feeding study of peroxisome proliferation dating from the 1970s, in which 4 male F344 rats received 2% adipic acid (dissolved in alcohol; about 2000 mg/kg body weight and day), no differences in behaviour, liver weights, peroxisome proliferation or the hepatic activities of catalase or carnitine acetyltransferase were observed compared with the findings in the controls. Hypolipidaemia did not occur (OECD 2004).

3 Toxicokinetics and Metabolism

Humans

Adipic acid was administered orally to 4 test persons and their urine was subsequently collected and the adipic acid concentration analysed. One person (70 kg body weight) was given 7 g adipic acid per day (100 mg/kg body weight and day) for 10 days in several portions over the day. The urine was collected over the entire duration of treatment and for two additional days and contained 61% of the administered dose. The three other test persons received 23.4, 19.0 and 23.4 g adipic acid over 6, 5 and 9 days, respectively (1.46 to 7.3 g/day; no other details). The amounts recovered with the urine were between 15% and 75% (ECHA 2015; OECD 2004). It is not clear whether the method of detection was valid. The amount exhaled in the form of CO_2 was not investigated (OECD 2004).

With the models of Guy and Potts (1993), Wilschut et al. (1995) and Fiserova-Bergerova et al. (1990) and assuming a saturated aqueous adipic acid solu-

tion, dermal fluxes of 0.006, 0.009 and 0.035 mg/cm² and hour, respectively, are obtained. For exposure of both hands and forearms (about 2000 cm²) for one hour, this corresponds to a total uptake of 1.3, 1.8 and 6.9 mg adipic acid, respectively.

Animals

After gavage administration of 50 mg radioactively labelled adipic acid (position C1 or C2) to fasting rats, up to 70% of the radioactivity was exhaled in the form of CO_2 within 24 hours. In the urine, which was collected for 24 hours, the following metabolites could be identified: urea, glutamate, lactate, beta-ketoadipic acid, citrate and adipic acid. In the tissues, little radioactivity was detected. In rats given 100 mg radioactively labelled adipic acid by gavage together with 400 mg glucose, a high concentration (no other details) of radioactively labelled glycogen was found in the liver after 2 hours. After gavage administration of 50 mg radioactively labelled adipic acid and intraperitoneal injection of 2 ml of a 0.5 M sodium malonate solution, labelled succinic acid was found in the 24-hour urine of rats. This suggests that adipic acid is degraded via β-oxidation. The demonstration of citrate in the first experiment also supports this conclusion (ECHA 2015).

After gavage administration of 2430 mg adipic acid/kg body weight and day for 28 days, 67% of the substance was eliminated in unchanged form in the urine of rats. The urine was continuously collected up to 2 days after the end of exposure (ECHA 2015).

In 4 rabbits given gavage doses of adipic acid of 2430 mg/kg body weight and day (neutralized) on 2 subsequent days, 53% to 61% (on average 57%) of the administered dose was recovered in unchanged form in the 2-day urine collected during the treatment as well as in the urine collected on 4 further days. The maximum amount was eliminated on day 2. In 2 other animals given the same dose by intravenous injection, 59% to 71% of the unchanged substance was detected in the urine on the first day. Elimination of the substance was complete 24 hours after the second administration (ECHA 2015).

The sodium salt of adipic acid was administered with the diet to a female dog in doses of 1000 mg twice a day for 5 days (150 mg/kg body weight and day, total dose 10 g) or 5000 mg twice a day for 7 days (750 mg/kg body weight and day, total dose 70 g). In the urine, 18% and 63.6% of the adipic acid were recovered in unchanged form, respectively (ECHA 2015).

4 Effects in Humans

There are no studies available for single exposures, reproductive toxicity, genotoxicity and carcinogenicity.

4.1 Repeated exposure

Inhalation

Seven of 12 workers, who had been exposed for an average of 9.2 years to various glycols, glycerine, other components and adipic acid dust particles, reported muco-

sal irritation of the eyes, nose and throat. The average 8-hour concentration was 0.47 to 0.79 mg adipic acid/m³. There were no local ventilation systems and the workers did not wear respiratory protection. They reported that clouds of adipic acid and other materials were generated during charging of the reaction vessels. As the glycol concentration was below 1 ppm, the authors suspected that adipic acid was responsible for these symptoms. The findings are difficult to evaluate, because exposure was to a mixture of different substances. A local irritation potential of adipic acid is, however, plausible (OECD 2004). In particular, it is not clear how high the peak concentrations were during charging of the reaction vessels.

The clinical examination of workers employed in the production of adipic acid provided evidence of effects on the autonomic nervous system, the gastrointestinal tract, the mucous membrane of the upper respiratory tract, and of eye irritation. A concentration of 20 mg/m³ was reported as the threshold value for eye irritation. In the authors' opinion, the findings support a threshold value for occupational exposure of 4 mg/m³ (ECHA 2015; OECD 2004). The study report was published in Russian only.

The regular medical examination of 7 workers exposed to adipic acid and glutaric acid at maximum concentration levels of 11.6 mg/m³ and 1.23 mg/m³, respectively, between 2006 and 2009 included the patient's medical history, physical examinations, lung function, ECG (electrocardiography)/ergometry, and visual and acoustic tests. No irritation of the eyes, skin or mucous membranes of the upper respiratory tract was found (ECHA 2015). Data for the average exposure and frequency of exposure peaks are lacking.

Oral administration

The ingestion of up to 7 g adipic acid per day (about 100 mg/kg body weight and day) for 10 days lead to no apparent toxicity in test persons (see Section 3) (OECD 2004).

4.2 Allergenic effects

4.2.1 Sensitizing effects on the skin

A machine repairman aged 51 years, with work-related dermatitis which had occurred over the last 3 to 4 years on contact with base materials for polyester production, produced a 2+ reaction to 1% adipic acid in alcohol in a patch test after 48 and 120 hours. The authors report that the preparation was adjusted with borate buffer to a pH of 6.0. The patient did not react to a 0.1% preparation, but he did react to paraben mix, budesonide, desoximetasone, fluocinolone, gold sodium thiosulfate, MDBGN (methyldibromo glutaronitrile/2-bromo-2-(bromomethyl)pentane dinitrile) and cobalt chloride. The result was questionably positive with 1% terephthalic acid and four other substances. The 1% preparation produced no reaction in control persons (no other details) (Guin 2001).

Without giving details, a publication dating from the 1960s likewise reported a positive patch test result with adipic acid in a laboratory worker at a factory producing polyester resins (OECD 2004).

4.2.2 Sensitizing effects on the airways

Two cases of work-related asthma were reported in workers of a pharmaceuticals factory after exposure to a spiramycin adipate powder. In both patients, a dual reaction occurred in the bronchial provocation test with spiramycin adipate or with spiramycin. The immediate reaction could be inhibited with sodium cromoglycate only in one of the two patients. In this patient, also after provocation with an aerosolized adipic acid solution with 10 mg adipic acid/ml, there was an immediate reaction with a decrease in the expiratory one-second capacity of 20%. Also this reaction could be inhibited by a previous dose of sodium cromoglycate. Data for reactions in control persons, however, are lacking (Moscato et al. 1984).

In a female worker engaged in soldering and desoldering work, symptoms of rhinitis occurred 3 years after starting work. Around 4 years later, a colophony-free solder containing adipic acid was introduced into the workplace. Two years later, she experienced increasing episodes of breathlessness and chest tightness. The PEF (peak expiratory flow) measurements carried out 4 times a day for 4 weeks indicated work-related asthma (OASYS irritation score 3.1). During the 30-minute provocation test the patient melted colophony-containing solder wire at about 170 °C and in the 12-minute provocation test solder wire containing adipic acid. Only after provocation with the second challenge she exhibited a delayed asthmatic reaction, starting after approximately three hours, with a decrease in the expiratory one-second capacity (FEV1) of about 28%. The methacholine reactivity was approximately doubled after challenge ($PC_{20(Methacholine)}$ before provocation 3.45 µg, before provocation: 1.73 µg) Despite changing her workplace and assuming a new task, the asthma symptoms persisted, with occasional episodes during the night, but with a normal non-specific bronchial reactivity ($PC_{20(Methacholine)}$ > 4.8 µg) (Moore and Burge 2010).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In a study performed in the 1980s with 10 male and 10 female Sprague Dawley rats per concentration group, an LC_{50} of more than 7700 mg adipic acid/m^3 was determined. Two independent experiments with 5400 and 7700 mg/m^3 (analysed concentrations) were carried out; the MMAD (mass median aerodynamic diameter) was 3.5 µm (GSD: geometric standard deviation = 2.6) and the purity of the test substance was 99.8%. The animals were exposed nose-only for 4 hours. Neither mortality, nor signs of toxicity or gross pathological changes were observed. The recovery period was 14 days (ECHA 2015; OECD 2004).

5.1.2 Oral administration

In a study dating from the late 1970s with groups of 5 male and 5 female Sprague Dawley rats and a 14-day recovery period, an LD_{50} of 5560 mg/kg body weight was

determined. The purity of the test substance was 99.8%. The animals died within the first 48 hours after administration of the substance (dose not specified). Acute cardiac dilation, acute congestive hyperaemia, ulceration of the glandular stomach (bleeding, corrosive gastritis), pale liver, intestinal atony and reddening of the intestinal mucosa were observed. No gross pathological changes were found in the surviving animals. In rats given doses of 3160 mg/kg body weight and above, wheezing, apathy, salivation and nasal discharge occurred. The staggering and spastic gait observed at 4640 mg/kg body weight and above were reversible within 3 days. At doses of 6810 mg/kg body weight and above, also lateral or prone position and a poor general condition were observed. In the surviving animals, all clinical symptoms were reversible within 3 days (ECHA 2015; OECD 2004).

Another study with 5 Sprague Dawley rats per dose group (2 to 3 male and 2 to 3 female animals each) yielded an LD_{50} of 5050 mg/kg body weight. Adipic acid was administered in the form of a 20% solution in wheat germ oil in doses of 3160, 3980, 5010 or 6310 mg/kg body weight, and the animals were observed during a recovery period of 14 days. For 2 to 3 days, the appetite and activity of the survivors was reduced. Gross-pathological examination yielded haemorrhagic areas in the lungs, liver discoloration and acute inflammation of the gastrointestinal tract (no other details; ECHA 2015).

LD_{50} values were reported of 3600 mg/kg body weight in Wistar rats, of more than 10 000 mg/kg body weight in a non-specified rat strain, and of 940 mg/kg body weight in a study with only male rats. In another study with a recovery period of only one week, the LD_{50} was above 5000 mg/kg body weight. The latter studies are described only in short, the rat strains used are not specified (ECHA 2015).

In mice (no other details), an LD_{50} of 1900 mg/kg body weight was determined after groups of 13 males were given adipic acid (6% solution in 0.5% methyl cellulose). Mortality occurred during the first night, continuing for up to one week after exposure. Necropsy of the deceased animals revealed distention of the stomach, irritation and haemorrhage of the intestine, and spastic contraction of the caecum (ECHA 2015; OECD 2004). In a study with mice (no other details) described only in short, the LD_{50} was 4200 mg/kg body weight (ECHA 2015).

In rabbits (no other details) given doses of 2430 mg/kg body weight, apathy and diarrhoea occurred. The dose of 4860 mg/kg body weight was lethal. At necropsy, the intestine was found to be swollen and filled with a brown liquid. Clear signs of venous obstruction were found in the tissue of the liver and kidneys (no other details; ECHA 2015).

5.1.3 Dermal application

In a study from the 1970s with 24-hour occlusive application of 40% adipic acid in corn oil to the skin of rabbits (New Zealand White), an LD_{50} of more than 7940 mg/kg body weight was obtained. In this study, one rabbit was treated with a dose of 5010 mg/kg body weight and two rabbits were treated with 7940 mg/kg body weight; the animals were subsequently observed for 14 days. These doses were not lethal. For one to two days, the appetite and activity of the animals was reduced (ECHA 2015; OECD 2004).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In 2 male and 2 female rats (Alderley Park), which were exposed to adipic acid dust in concentrations of 126 mg/m³ for 6 hours a day, for a period of 15 days, no symptoms of irritation of the airways were found. The test atmosphere was generated by injecting the solid in powder form into the airstream. Body weights and the clinical appearance of the animals were documented on a daily basis. Urine and blood were analysed at the end of the study. The rats were then sacrificed and the organs subjected to gross pathological examination. The lungs, liver, kidneys, spleen, adrenal glands and in some cases the heart, jejunum, ileum and thymus were examined histopathologically. According to the authors, the no observed adverse effect concentration (NOAEC) was 126 mg/m³. No signs of toxicity occurred; analysis of the blood and pathological examinations yielded no unusual findings (ECHA 2015; OECD 2004). As the study was inadequately documented, only a limited number of animals was used, the MMAD was not determined and a histopathological examination was carried out in a maximum nine organs only, and in addition the nose was not examined, the study is of only limited usefulness.

In a study published in Russian only, in which mice (strain, sex, number of animals not specified) were exposed to 13 or 129 mg/m³ for 4 months, or to 460 mg/m³ for 1.5 months, effects in the upper respiratory tract and on the liver, kidneys and CNS (central nervous system) were reported. The body weight gains were reduced and the oxidase activity (no other details) was changed (no other details; OECD 2004).

5.2.2 Oral administration

Groups of 8 to 10 male rats were given the sodium salt of adipic acid in protein-deficient feed in doses of 0, 420, 840, 1700 or 3400 mg/kg body weight and day for 19 weeks. Gross pathological examination was carried out after 7 weeks and at the end of the study. Body weight gains and general behaviour were recorded and the liver, kidneys and intestine were subjected to histopathological examination. Several unexplained deaths occurred in all groups (including the controls), so that only 5 to 7 animals per dose group survived to the end of the study. No clinical symptoms were observed. In rats given doses of 3400 mg/kg body weight and day, body weight gains were reduced and the body weights were decreased by the end the study. In this dose group, there were slight effects on the liver (no other details) and irritation of the intestine was observed. The no observed adverse effect level (NOAEL) was 1700 mg/kg body weight and day (OECD 2004). As a result of the insufficient data and limited scope of the study, it is of only limited usefulness for the evaluation.

In another study by the same group of authors, adipic acid (neutralized with NaOH) was administered with the standard diet to groups of 13 to 15 male and female rats for 33 weeks. The dose levels were 0, 1600 or 3200 mg/kg body weight and day. Body weight gains and general behaviour were recorded. After 8, 23 and 25 weeks interim necropsies and histopathological examination of the liver, kidneys and intestine were carried out. The high dose was lethal for 10 of the 14 rats within the first four weeks. The surviving animals had retarded body weight gains, an unkempt appearance, were apathetic and suffered from severe diarrhoea during the

first three weeks. They had recovered by week 5, and their body weights were similar to those of the animals in the low dose group after 33 weeks. There are no data for the control group. In the low dose group of 1600 mg/kg, slight effects on the liver (no other details) and inflammation of the intestine were observed. The lowest observed adverse effect level (LOAEL) in this study was 1600 mg/kg body weight and day, the lowest tested dose (OECD 2004). As a result of insufficient data and the limited scope of this study, it is likewise of only limited usefulness for the evaluation.

In a 2-year study from the 1950s, feed containing 0%, 0.1%, 1%, 3% or 5% adipic acid was administered to groups of 20 male Carworth Farm rats. The dose levels corresponded to 0, 75, 750, 2250 or 3750 mg/kg body weight and day. Groups of 10 or 19 female rats were given 0% or 1% adipic acid with their diet (0 or about 750 mg/kg body weight and day). Body weights, food intake and general appearance were recorded weekly. The brain, thyroid, lungs, heart, liver, spleen, kidneys, adrenal glands and the stomach were weighed at the end of the study. In addition, the thyroid, lungs, heart, liver, spleen, kidneys, adrenal glands, stomach, pancreas, bone marrow, large and small intestine, uterus, ovaries and testes from a representative number of animals were examined histopathologically (no other details). The number of surviving animals in the treated groups was higher than in the controls. The body weight gains in male rats were significantly reduced compared with those in the controls at doses of 2250 mg/kg body weight and day and above. In the high dose group, there was a slight but consistent reduction in food intake. Neither gross pathological nor histopathological examination revealed substance-related findings. In all groups there were animals with wheezing, blood-stained noses and sores; the incidence in the high dose group was the lowest. It is therefore assumed that an infection of the airways was involved. The NOAEL from this study was 750 mg/kg body weight and day (OECD 2004). As only 15 organs were examined, the number of animals was too small, only one dose was administered to the female rats, the MTD (maximum tolerable dose) was not reached and the animals presumably had an infection, the usefulness of this study for the evaluation is only limited.

5.2.3 Dermal application

There are no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a study from the late 1970s, in which 0.5 g adipic acid (purity 99.8%) in the form of a 50% aqueous solution was applied occlusively to the intact and to the scarified skin of 6 Vienna White rabbits for 24 hours, the skin reactions were recorded after periods of 24 hours, 3 and 8 days. The test substance was not washed off. After 24 hours, erythema (irritation value 2–3 on a scale with a maximum of 4) was observed on the intact skin, which was reversible after 72 hours. The 24 to 72-hour irritation value according to Draize was 1.1 of a maximum of 4.0. No oedema occurred (score 0 of a maximum of 4). Moderate to pronounced erythema and oede-

ma (irritation scores after 24 hours: 2 of a maximum of 4, after 72 hours: 0–2 of a maximum of 4) occurred on the scarified skin, which were reversible after one week with eschar formation (ECHA 2015; OECD 2004).

Also from the 1970s is a study with 6 male albino rabbits (no other details). Here, 0.5 g adipic acid (purity 99.99%), mixed to a paste with propylene glycol, was applied occlusively to the skin for 24 hours. Immediately after removal and again 24 hours later, the skin reactions were recorded. After 24 hours of treatment, no or slight erythema and no or very slight oedema occurred. The oedema was reversible after a further 24 hours, very slight erythema was still present. Slight to weak irritation was observed in 3 of the 6 animals (ECHA 2015; OECD 2004).

Another study from the 1970s with 24-hour occlusive application to the rabbit skin resulted in an irritation score of 0. In this study, adipic acid was not irritating to the skin (no other details; ECHA 2015).

Also from the 1970s there is a study in 6 rabbits, in which 0.5 g adipic acid was applied to the skin in the form of a solid and covered occlusively for 4 hours. The substance was then washed off and the skin reaction recorded immediately and after 24 and 48 hours. No skin damage indicative of a corrosive effect was found in any of the animals (no other details; ECHA 2015).

In 10 guinea pigs, a 25% to 50% suspension of adipic acid in propylene glycol caused no to very mild skin irritation (no other details; ECHA 2015; OECD 2004).

In a study from the late 1970s, adipic acid (purity 99.8%) was applied in the form of an 80% aqueous paste occlusively for 20 hours to the dorsal skin or to the ear of 2 rabbits. Skin reactions were recorded after 24 and 72 hours, and after 8 days. No irritation was observed on the dorsal skin (irritation scores 0 on a scale of 4 for erythema and oedema). The irritation score for the ear was 2 for erythema, and was reversible within 72 hours (no other details; ECHA 2015; OECD 2004).

In another study from the 1970s, only described in short, no skin irritation was found in the rabbit after the application of 0.5 g adipic acid in the form of an aqueous paste for 24 hours. The study was carried out with 6 New Zealand White rabbits, whose skin was evaluated after 4, 24, 48, 72, and 168 hours. At each of these times, the irritation score was 0 on a scale with a maximum of 4 (no other details; ECHA 2015).

To summarize, adipic acid is slightly irritating to the rabbit skin.

5.3.2 Eyes

In the Himalayan rabbit, eye irritation was investigated according to OECD Test Guideline 405. For this purpose, 100 mg adipic acid (purity > 99.9%) was instilled into the conjunctival sac of one eye in 3 animals. The irritation of the cornea was scored as 2.3 on a scale with a maximum of 4 after 24, 48 and 72 hours and was reversible after 16 days. For the iris the score was 1.8 of a maximum of 2, the findings were reversible within 9 days. The irritation score for the redness of the conjunctiva was 1 of a maximum of 3, the findings were reversible within 13 days. Conjunctival swelling was evaluated with an irritation score of 1 on a scale with a maximum of 4 and was reversible within 12 days. Adipic acid was classified as highly irritating to the eyes (ECHA 2015; OECD 2004).

In a study from the 1970s, in which 100 mg adipic acid was instilled into the conjunctival sac of one eye in 6 rabbits (New Zealand White), the test substance was classified as irritating (ECHA 2015).

Also from the 1970s, a study is available in which 0.1 ml (57.1 mg) adipic acid (purity 99.9%) was instilled into the conjunctival sac of one eye of 2 albino rabbits. In one animal the test substance was rinsed out after 20 seconds. Assessment of the eyes was carried out after 1 and 4 hours, and after 1, 2, 3, and 7 days. In the unrinsed eye, mild clouding of the cornea was observed, which reverted to slight clouding within three days. Slight effects in the iris were found as well as mild conjunctivitis (up to 3 days) and moderate swelling of the conjunctiva. This had reverted to mild swelling by day 3. All effects were reversible after 7 days. In the rinsed eye, mild corneal clouding was found after 1 hour. No unusual findings were obtained in the iris. However until day 2 there was mild reddening of the conjunctiva and mild swelling of the conjunctiva up to 4 hours after exposure. These effects had reverted within 1 to 2 days except for some slight swelling. All findings were reversible after 3 days (ECHA 2015).

In another study from the 1970s, a smaller amount of the substance (10 mg adipic acid (99.9%)) was instilled into one conjunctival sac of 2 albino rabbits, and rinsed out in one of the animals after 20 seconds. No clouding of the cornea was found. In the non-rinsed eye, slight effects on the iris occurred after one hour. There were no effects on the iris in the rinsed eye. In the conjunctiva of the non-rinsed eye a slight redness was found after 1 hour and up to 3 days afterwards. In the rinsed eye, this lasted for only 4 hours. Minimal swelling of the conjunctiva after 1 hour in the non-rinsed eye was still present after 7 days. In the rinsed eye, only slight swelling occurred after 1 to 4 hours. In the non-rinsed eye, the findings were reversible by day 14, in the rinsed eye after 3 days (ECHA 2015).

After the instillation of 50 mg adipic acid (purity 99.8%) into the conjunctival sac of one eye in 2 rabbits, the eyelid was held closed for one second in each case. The substance was not rinsed out. The findings were recorded 24 hours, 48 hours, and 8 days after the instillation. For corneal clouding, the irritation score (24 and 48 hours) was 1 on a scale up to 4. For the iris, the irritation score was 0 on a scale up to 2, and for redness and swelling of the conjunctiva 1 and 2, respectively, on a scale up to 4. In one animal, eschar formation on the conjunctiva was observed. None of the findings were completely reversible within 8 days (ECHA 2015; OECD 2004).

The instillation of 0.1 ml adipic acid (purity 99.8%) into the conjunctival sac of one eye of 6 rabbits led to severe irritation. After instillation of the test substance, the eyelid was held closed for one second and not rinsed. The irritation scores after 24, 48 and 72 hours were 1.3 of a maximum of 4 for the cornea, 0.83 of a maximum of 2 for the iris, 2 of a maximum of 3 for conjunctival redness, and 2 of a maximum of 4 for conjunctival swelling. None of the findings were reversible within 8 days. The substance was classified as highly irritating (ECHA 2015).

To summarize, adipic acid is highly irritating to the rabbit eye.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a study not conforming to test guidelines, guinea pigs were given 4 intradermal injections of 0.1 ml of a 1% adipic acid solution in water once a week for 3 weeks. Two weeks later, challenge treatment was carried out by means of open epicutaneous application of 50 µl of a 25% and 50 µl of a 50% adipic acid preparation in propylene glycol. None of the 10 animals had produced a reaction at the readings after 24 and 48 hours (ECHA 2015).

The results of a maximization test with a mixture containing 23.8% adipic acid, 50.9% glutaric acid and 18.6% succinic acid were likewise negative. Intradermal and topical induction were carried out using a 0.1% and a 10% preparation of the mixture, respectively, in physiological saline solution, followed by challenge treatment with a 5% preparation in the same vehicle. At the readings after 24 and 48 hours, there were discrete erythematous reactions in 1 of 10 female Hartley guinea pigs in each group (ECHA 2015).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no studies available for effects of the substance on fertility.

In the 2-year study (see Section 5.2.2), histopathological examination did not reveal any effects on the testes of male rats up to the high dose of 3750 mg/kg body weight and day. In the females, no effects on the ovaries or uterus were found up to the highest dose tested of 750 mg/kg body weight and day (OECD 2004).

5.5.2 Developmental toxicity

Groups of 20 to 24 pregnant Wistar rats were given gavage doses of adipic acid of 0, 2.9, 13, 62 or 288 mg/kg body weight and day from gestation days 6 to 15. No embryotoxicity, foetotoxicity or teratogenicity occurred up to the high dose. In similar experiments, adipic acid doses of up to 263 mg/kg body weight and day (0, 2.6, 12, 56 or 263 mg/kg body weight and day) were administered by gavage to groups of 20 to 24 pregnant CD-1 mice from gestation days 6 to 15. No adverse effects were observed. Neither were adverse effects found in groups of 10 to 14 Dutch Belted rabbits after gavage doses of adipic acid of up to 250 mg/kg body weight and day (0, 2.5, 12, 54 or 250 mg/kg body weight and day) from gestation days 6 to 18. The studies are of limited usefulness, as no maternal toxicity occurred even at the highest dose and, according to current test guidelines, doses of up to 1000 mg/kg body weight and day have to be tested (OECD 2004; ECHA 2015).

In hamsters (no other details) given gavage doses of 0, 2, 9.5, 44 or 205 mg/kg body weight and day on gestation days 6 to 10, no foetotoxic or teratogenic effects occurred. In the high dose group, the number of resorptions/implantation site increased from 3% to 7.7%. Correspondingly the average number of live foetuses decreased from 12.6 to 11.4. As no statistical evaluation is available, the findings cannot be assessed conclusively (ECHA 2015).

5.6 Genotoxicity

5.6.1 In vitro

Adipic acid was neither mutagenic nor cytotoxic in several tests with the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 as well as Escherichia coli WP2 at concentrations of up to 10 mg/plate either with or without metabolic activation (ECHA 2015; OECD 2004).

In human embryonic lung fibroblast cells (Wi-38), adipic acid did not induce chromosomal aberrations at concentrations of up to 200 mg/l without metabolic activation. Cytotoxicity occurred at 400 mg/l and above (ECHA 2015; OECD 2004).

An HPRT test carried out according to OECD Test Guideline 476 in Chinese hamster V79 cells yielded negative results for concentrations of up to 10 mM both with and without metabolic activation. No cytotoxicity occurred up to the high concentration. The expected results were obtained with the positive controls (ECHA 2015).

Overall, adipic acid was not found to be mutagenic or clastogenic in vitro.

5.6.2 In vivo

Adipic acid did not induce chromosomal aberrations in groups of 5 male rats after single gavage doses of up to 5000 mg/kg body weight or 5-day doses of up to 2500 mg/kg body weight and day (ECHA 2015; OECD 2004).

In a dominant lethal test, 10 male rats per group were given single gavage doses of adipic acid or were treated for 5 days. Each animal was mated with two virgin female animals per week for 7 weeks (5-day study) or 8 weeks (single dose study). The female animals were examined two weeks after mating. After single doses of 3.75, 37.5 or 375 mg/kg body weight, a decrease in implantations in weeks 1 and 4 (10.2 and 10.0 compared with 12.2 and 12.1, respectively) and in corpora lutea in weeks 4 and 7 (11.7 and 12.4 compared with 14) was observed in the middle dose group only. An increase in preimplantation losses was observed in week 1 (3.75 mg/kg: 28/12 = 2.3; 37.5 mg/kg body weight: 36/13 = 2.8; negative control: 11/14 = 0.8) only in animals of the low and the middle dose groups. Administration of the same dose levels for 5 days also produced effects, although no clear dose or time-dependency was found. A second test with single doses of 5000 mg/kg body weight or doses of 2500 mg/kg body weight and day for 5 days did not yield substance-related findings. The expected results were obtained with the positive controls. Overall, the dominant lethal test yielded negative results (ECHA 2015; OECD 2004).

Overall, adipic acid was therefore not mutagenic or clastogenic in vivo.

5.7 Carcinogenicity

In a 2-year study from the 1950s already described in Section 5.2.2 with groups of 20 male and up to 19 female rats, dietary administration of adipic acid did not induce carcinogenic effects at doses of up to about 3750 mg/kg body weight and day in males and up to 750 mg/kg body weight and day in females (ECHA 2015; OECD 2004). As only 15 organs were examined, the number of animals used was too small, only one dose was administered to the females, the MTD was not reached and the animals presumably suffered from an infection, the study is only of limited usefulness for the evaluation.

6 Manifesto (MAK value/classification)

The critical effect of adipic acid is considered to be local irritation.

MAK value. The inhalation studies with adipic acid are not suitable for deriving a MAK value (see Section 4.1 and Section 5.2.1).

In a limited 2-year study with oral administration in rats, toxicity was first observed in the form of reduced body weights at dose levels of 2250 mg/kg body weight and day and above. The NOAEL was 750 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 750 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction values for the rat (1:4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, the assumed 100% absorption by inhalation and the origin of the data from an experimental animal study (1:2). The concentration calculated from this is 920 mg/m^3. In view of the highly irritative effect on the eyes, this concentration is too high for a threshold limit value at the workplace.

In analogy to phosphoric acid, a MAK value can be established for adipic acid, as was also carried out in the case of tartaric acid (documentation "Weinsäure" 2015, available in German only) and succinic acid (documentation" Succinic acid" 2017). All these substances are solids at room temperature. In contrast to tartaric acid (pH 1.24; pKa values 2.98 and 4.34), however, adipic acid (pH 2.71; pKa values 4.34 and 5.44) has a lower acidity, but the pKa values are approximately in the same order of magnitude as those of succinic acid (pKa values 4.21 and 5.64; documentation "Succinic acid" 2017). The irritative effects of adipic acid on the eyes are, however, markedly less severe than those of succinic acid. As, however, no data are available with which a higher MAK value can be derived, and taking as a basis phosphoric acid, which has a MAK value of 2 mg/m^3 (0.02 $mmol/m^3$, corresponding to 2.92 mg/m^3 for adipic acid), a MAK value of 2 mg/m^3 I (inhalable fraction) has been established for adipic acid by analogy until suitable data become available. Taking into account its lower acidity, this value is to be considered as the "worst case" for adipic acid.

Peak limitation. As a result of its critical local effects, adipic acid is classified in Peak Limitation Category I with an excursion factor of 2, also in analogy to phosphoric acid.

Prenatal toxicity. Adipic acid was not found to be foetotoxic or teratogenic in developmental toxicity studies with rats, mice and rabbits after gavage administration of up to 288, 263 and 250 mg/kg body weight and day, respectively. Maternal toxicity did not occur in any of the studies. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL from the rat, mouse and rabbit to a concentration in workplace air: the corresponding species-specific correction values (1:4, 1:7, and 1:2.4), the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 504, 263 and 729 mg/m^3 air, respectively. The 252, 132 and 365-fold differences between these concentrations and the MAK value of 2 mg/m^3 are sufficiently large. There are no studies available up to the limit dose of 1000 mg/kg body weight and day. However, adipic acid is a food additive and indications of embryotoxicity have not been found up to the dose levels mentioned above. Adipic acid is therefore classified in Pregnancy Risk Group C.

Carcinogenicity. In a 2-year study carried out in the 1950s with rats, adipic acid administered with the diet in doses of up to about 3750 mg/kg body weight and day did not induce carcinogenic effects. As only 15 organs were examined, the number of animals was too small, only one dose of 750 mg/kg body weight and day was used in the females, the MTD was not reached and the animals presumably had an infection, the usefulness of the study for the evaluation is only limited. As, however, from the genotoxicity studies, no carcinogenic potential is reasonably to be suspected, there is no need to classify adipic acid in one of the categories for carcinogens.

Germ cell mutagenicity. No genotoxic effects of adipic acid were found in various in vitro and in vivo tests. A dominant lethal test with rats likewise yielded negative results. Adipic acid is therefore not classified in one of the categories for germ cell mutagens.

Absorption through the skin. There are no data available for the dermal penetration of adipic acid. In acute toxicity studies with dermal application to the skin of rabbits, no LD_{50} for dermal exposure could be determined (> 7940 mg/kg body weight). Based on model calculations, the exposure of both hands and forearms for one hour would produce a maximum penetration quantity of 6.9 mg. In a 2-year study with oral doses given to rats, a systemic NOAEL of 750 mg/kg body weight and day was determined. This is the starting point for estimating a systemic NOAEL in humans. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 750 mg/kg body weight and day to humans: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value (1:4) for the rat, the body weight (70 kg) of the person, and the origin of the data from an experimental animal study (1:2). From this, a systemically tolerable dose of 9187 mg is calculated. Thus, the amount absorbed through the skin is less than 25% of the systemically tolerable amount. Therefore, adipic acid is not designated with an "H".

Sensitization. There are no reliable clinical findings available for the sensitizing effects of adipic acid on the skin or airways. Studies not carried out in accordance with the test guideline provided no evidence of contact sensitization in guinea pigs. The substance is therefore not designated with "Sh" or "Sa"

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