The MAK Collection for Occupational Health and Safety

Succinic acid

MAK Value Documentation – Translation of the German version from 2017

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Keywords: succinic acid; MAK value; maximum workplace concentration; peak limitation; developmental toxicity

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Succinic acid / butanedioic 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 succinic acid to derive a maximum concentration at the workplace (MAK value), considering all toxicity endpoints.
The critical effect is severe local irritation as shown with the Draize test in the rabbit eye. Inhalation studies are not available, however, effects on the respiratory tract have to be assumed. Systemic toxicity in rats in the form of reduced body weight gain occurred at 1900 mg/kg body weight/day given in drinking water. After gavage administration, blood urea nitrogen was increased in female rats from 1000 mg/kg body weight/day and urinary protein was increased in males from 300 mg/kg body weight/day. The lower LOAEL in the gavage study as compared with the drinking water study suggests adverse effects on the kidney presumably due to the bolus application.
After comparing succinic acid with other solid acids, a MAK value of 2 mg succinic 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, succinic acid is assigned to Peak Limitation Category I. In analogy to phosphoric acid an 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.
Succinic 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.

Keywords

succinic acid; 1,4-butanedioic acid; 1,2-ethanedicarboxylic 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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Succinic 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-butanedioic acid
Chemical name	1,2-ethanedicarboxylic acid
CAS number	110-15-6
Structural formula	$HOOC–CH_2–CH_2–COOH$
Molecular formula	$C_4H_6O_4$
Molar mass	118.09 g/mol
Melting point	190.3 °C (ECHA 2014); 188 °C (US EPA 2008)
Boiling point at 1013 hPa	235 °C (US EPA 2008)
Vapour pressure at 25 °C	2.53×10^{-7} hPa (US EPA 2008)
log K_{OW}[1)]	–0.59 (ECHA 2014; US EPA 2008)
Solubility at 25 °C	83 g/l water (ECHA 2014; US EPA 2008)
pKa value	4.21 (SRC 2013; US EPA 2008) 4.207 and 5.635 (ECHA 2014) 4.67 (ECHA 2014)
pH	2.7 as 0.1 M aqueous solution (O'Neil 2001)
Stability	completely biodegradable, hydrolysis or photolysis are not expected (US EPA 2008)

1) octanol/water partition coefficient

Manufacture	catalytic hydrogenation of maleic acid, maleic acid anhydride or fumaric acid; various catalysts can be used (Ni, Cu, NiO, CuZnCr, Pd-Al_2O_3, Pd-$CaCO_3$) (Cukolovic and Stevens 2008); oxidation of 1,4-butanediol; hydrocarboxylation of acetylene glycol, catalyzed via $RhCl_3$-pentachlorothiophenol, acetylene, acrylic acid, 1,4-dioxane or propiolactone (Cornils and Lappe 2014); biotechnological process involving fermentation from carbohydrates, primarily from starch and various oligosaccharides (C6 and C5 sugars) (Werpy et al. 2006)
Purity	99.1% to 99.7% (EFSA 2012 a)
Impurities	no data
Uses	as food additive E363 (flavour enhancer, acidity regulator with a mild acidic taste) (BMJV 2012); as a component of plastics such as polyamides or polyester (Sahm et al. 2013); for the manufacture of alkyd resins, for dyestuffs, pharmaceuticals, pesticides and as a plasticizer and lubricant after esterification (Cornils and Lappe 2014); in coatings, paints, diluents, paint removers, as a laboratory reagent, as a monomer for the manufacture of thermoplastic plastics, the manufacture of bulk chemicals (including petroleum products), the manufacture of fine chemicals, pH regulator (ECHA 2014)

This documentation is based primarily on an evaluation by the US EPA (2008) and the registration data publicly available under REACH (ECHA 2014).

In the EU, succinic acid has been registered as a food additive under the number E 363. An ADI has not been established. Statutory maximum amounts that may not be exceeded are: 6 g/kg in desserts, 5 g/kg in soups or broths and 3 g/l in powder for making drinks in private households (BMJV 2012).

Studies with the salts of succinic acid are used to evaluate systemic effects because the anion is responsible for systemic effects.

1 Toxic Effects and Mode of Action

Succinic acid is a component of the citric acid cycle in which it is metabolized to fumaric acid and subsequently undergoes fatty acid β-oxidation. Succinic acid causes severe irritation and irreversible corneal opacity in the rabbit eye. However, skin irritation was not observed in valid studies in rabbits. In a 90-day drinking water study in rats, the succinate anion led to systemic effects in the form of reduced body weight gains at doses of about 1900 mg/kg body weight and day and above, and caused weight loss at higher doses. A screening study in rats revealed an increased protein level in the urine after gavage doses of 130 mg/kg body weight and day and above; this is a sign of nephrotoxicity, but there were no histopathological findings. Conclusive studies of the developmental toxicity of succinic acid are not available. A screening study with disodium succinate hexahydrate provided no evidence of impaired fertility in rats.

Succinic acid was not sensitizing to the skin of guinea pigs or mice.

Mutagenicity tests in Salmonella typhimurium with and without the addition of a metabolic activation system and a chromosomal aberration test in Chinese hamster lung cells (CHL) yielded negative results. No in vivo genotoxicity studies are available for succinic acid. In a 2-year carcinogenicity study in F344 rats, body weights were reduced by 10% after exposure to about 1000 mg/kg body weight and day via the drinking water. The incidence of C-cell adenomas in the thyroid gland was increased, but did not exceed the historical control levels. C-cell carcinomas were not induced.

2 Mechanism of Action

Specific studies with succinic acid are not available.

The acidity of the substance is responsible for the severely irritating effects on the eyes.

Oral administration of the dimethylester of succinic acid, which after absorption is cleaved by carboxylesterases to form a mono acid, produced a rapid rise in the insulin level and in some cases also a decrease in the plasma glucose concentration in rats. In studies using pancreatic islet cells of rats, the release of insulin was demonstrated in vitro. In rat hepatocytes, a rise in gluconeogenesis was observed after incubation with succinic acid dimethyl ester (see documentation "Dicarboxylic acid (C4–C6) dimethylester, mixture (dimethyl succinate, dimethyl adipate, dimethyl glutarate and their mixture)" 2007).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

Specific studies with succinic acid are not available.

The studies in rats described in Section 5.2.2 showed that succinic acid is absorbed orally.

With the models of Guy and Potts (1993), Wilschut et al. (1995) and Fiserova-Bergerova et al. (1990), dermal fluxes of 0.011, 0.021 and 0.065 mg/cm^2 and hour are obtained for a saturated aqueous succinic acid solution. This corresponds to the total absorption of 21.9, 41.5 and 129 mg succinic acid after the exposure of both hands and forearms for 1 hour (about 2000 cm^2).

3.2 Metabolism

Simple aliphatic dicarboxylic acids (succinic acid and fumaric acid) are metabolized via fatty acid β-oxidation or the tricarboxylic acid cycle (citric acid cycle) (EFSA 2012 a). Succinic acid is metabolized in the citric acid cycle to form fumaric acid. As one of the intermediate metabolites of the citric acid cycle, succinic acid leads to the synthesis of glucose and other sugars and to the synthesis of fatty acids (ECHA 2014).

4 Effects in Humans

There are no data available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no studies available.

5.1.2 Oral administration

Groups of 3 to 5 rats (no other details) per dose were given gavage doses of succinic acid of 400, 800, 1600 or 3200 mg/kg body weight and the animals were observed for 14 days. The LD_{50} was 2260 mg/kg body weight (US EPA 2008).

Groups of 4 male and 4 female F344 rats were given 500, 1000, 2000, 4000 or 8000 mg/kg body weight and were observed for 10 days. Except for congestion in the lungs at high doses (no data), there was no clear evidence of toxicity. The LD_{50} was greater than 8000 mg/kg body weight (US EPA 2008; ECHA 2014).

A study carried out with a salt of succinic acid (disodium succinate hexahydrate; CAS number 6106-21-4) in male and female F344 rats yielded an LD_{50} of more than

8000 mg/kg body weight (corresponding to more than 3400 mg succinic acid/kg body weight). No treatment-related effects were observed in the 10-day observation period (Maekawa et al. 1990).

5.1.3 Dermal application

There are no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no studies available for succinic acid.

5.2.2 Oral administration

A 13-week drinking water study from the 1990s was carried out in male and female F344 rats according to OECD Test Guideline 408 with a salt of succinic acid (sodium hydrogen succinate; 2922-54-5). The concentrations in the drinking water were 0%, 0.3%, 0.6%, 1.25%, 2.5%, 5% or 10% (about 270, 540, 1125, 2250, 4500 and 9000 mg/kg body weight and day; conversion factor: 0.09 (subchronic) according to EFSA 2012 b). Each group included 10 males and 10 females. In this study, the NOAEL (no observed adverse effect level) was 1125 mg/kg body weight and day for sodium hydrogen succinate; body weight gains were reduced at 2250 mg/kg body weight and day and above. During the first 4 weeks of the study, the dose of 9000 mg/kg body weight and day was lethal for all animals; severe weight losses were observed and the animals consumed less drinking water than the control animals. Substance-induced histopathological findings or effects on haematological or clinico-chemical parameters were not observed (ECHA 2014; US EPA 2008). Details of the study are not available. There is no information indicating whether urinalysis was carried out. The NOAEL was about 950 mg/kg body weight and day (converted for succinic acid).

In a combined study of toxicity after repeated administration and reproductive toxicity carried out according to OECD Test Guideline 422, Sprague Dawley rats were given gavage doses of disodium succinate hexahydrate of 0, 100, 300 or 1000 mg/kg body weight and day. The males received the test substance for 52 days, beginning 14 days before mating. The females were likewise exposed from day 14 before mating and up to day 4 of lactation. Blood urea nitrogen levels were increased in the females of the high dose group. The number of males with higher urinary protein levels was increased at 300 mg/kg body weight and above, which suggests toxic effects on the kidneys. There were no histopathological changes. The NOAEL in this study was 100 mg/kg body weight and day for the males and 300 mg/kg body weight and day for the females (OECD 2003). These disodium hexahydrate doses correspond to about 45 and 130 mg succinic acid/kg body weight and day. Bolus administration may be the reason for the much lower NOAEL compared with that obtained in the 13-week drinking water study.

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 carried out according to OECD Test Guideline 404 with 3 New Zealand White rabbits and semi-occlusive application of 0.5 g succinic acid mixed to a paste, the skin of the animals was scored 1 hour and 24, 48 and 72 hours after removal of the test substance. The irritation index was 0 on a scale with a maximum of 4. Erythema or oedema was not observed and the test substance was assessed to be non-irritating (ECHA 2014).

Succinic acid is a mild skin irritant (no other details; US EPA 2008).

5.3.2 Eyes

In a study carried out according to OECD Test Guideline 405, 0.1 ml (about 100 mg) succinic acid was instilled into the conjunctival sac of 1 eye of 1 New Zealand White rabbit and the treated eye was rinsed with water after 24 hours. Findings were recorded 1 hour and 24, 48 and 72 hours after instillation of the test substance and after 6, 8, 10, 13, 15 and 21 days. The irritation index for corneal opacity was 4 on a scale with a maximum of 4 after 24 and 72 hours and on day 21. The irritation index for the iris was 2 out of a maximum of 4 after 24 and 72 hours. The findings could not be read after 21 days because of the corneal opacity. The irritation index for reddening of the conjunctiva was 3 out of a maximum of 3 after 24 and 72 hours and on day 21. Conjunctival swelling had an irritation index of 3.7 out of a maximum of 4 after 24 and 72 hours and was reversible by day 15. According to these results, succinic acid induces severe, irreversible damage (ECHA 2014).

Succinic acid caused severe irritation to the rabbit eye as well as damage to the cornea and severe necrosis (no other details; US EPA 2008).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

A maximization test with succinic acid formulations in cottonseed oil yielded negative results in female Dunkin Hartley guinea pigs. Intradermal injection and topical induction were carried out with 0.5% and 25% formulations, respectively. After challenge treatment with a 10% formulation, 1 of 10 animals reacted after 24 hours and 72 hours, but no animal reacted after 48 hours. There was no reaction in any of the animals upon re-challenge (ECHA 2015).

In a valid local lymph node assay, succinic acid was not sensitizing in female CBA mice up to a concentration of 25%. In this study, the application of 5%, 10% and 25% succinic acid led to stimulation indices of 1.2, 1.2 and 1.3, respectively. Therefore, the tripling of lymphocyte stimulation was not achieved at any test concentration.

The lymph node weight index was about 1.1 for all test concentrations (ECHA 2015).

A maximization test carried out in female Hartley guinea pigs with a mixture of 18.6% succinic acid, 23.8% adipic acid and 50.9% glutaric acid likewise yielded negative results. Intradermal injection and topical induction were carried out with a 0.1% and 10% formulation of the mixture in physiological saline, respectively, and a 5% formulation in the same vehicle was used for challenge treatment. A mild erythematous reaction was observed in 1 of 10 animals at the reading after 24 hours and in another after 48 hours (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

In a study from the 1940s, the oestrogenic properties of succinic acid and their effects on the reproductive organs were investigated in 2-month-old ovariectomized rats (strain not specified) given daily subcutaneous injections of 5 mg succinic acid in sesame oil (about 31 mg succinic acid/kg body weight and day) for 3 weeks. Daily vaginal smears were prepared from the 5 animals, and the uterine horn, cervix and vagina were examined histopathologically at the end of the 3-week study. No changes were found compared with the findings in untreated control animals (ECHA 2014).

In a combined study of toxicity after repeated administration and reproductive toxicity carried out according to OECD Test Guideline 422, Sprague Dawley rats were given gavage doses of disodium succinate hexahydrate of 0, 100, 300 or 1000 mg/kg body weight and day (see also Section 5.2.2). The males received the test substance for 52 days, beginning 14 days before mating. The females were likewise exposed from day 14 before mating and up to day 4 of lactation. Substance-induced effects on the oestrus cycle, mating index, fertility index, gestation period or the number of corpora lutea or implantations were not observed. The exposure did not result in changes to the number of offspring or the sex ratio per litter. The NOAEL for fertility was thus 1000 mg/kg body weight and day (OECD 2003), which corresponds to about 440 mg succinic acid/kg body weight and day.

5.5.2 Developmental toxicity

In the combined study of toxicity after repeated administration and reproductive toxicity carried out with disodium succinate hexahydrate in Sprague Dawley rats according to OECD Test Guideline 422 (see Section 5.5.1), the exposure had no effect on survival up to lactation day 4 or body weights. Anophthalmus and polydactyly were observed in 1 offspring of the middle dose group. These findings were not dose-related. Moreover, they were also sporadically observed in historical control animals and are therefore regarded as incidental and not as substance-induced. The

NOAEL for fertility was thus 1000 mg/kg body weight and day (OECD 2003), which corresponds to about 440 mg succinic acid/kg body weight and day.

There are no studies available for teratogenicity.

5.6 Genotoxicity

5.6.1 In vitro

A publication from 1984 described a mutagenicity test in Salmonella typhimurium TA98, TA100, TA1535 and TA1537 with and without the addition of a metabolic activation system by rat liver S9 mix at succinic acid concentrations of 5000 µg/plate. The assay was carried out with pre-incubation for 20 minutes. Succinic acid was not found to be mutagenic in this study (ECHA 2014; US EPA 2008).

In a study from 1975, succinic acid was tested in Salmonella typhimurium TA1535, TA1537 and TA1538 at concentrations of 0%, 0.00035%, 0.0007% or 0.0014% and in Saccharomyces cerevisiae D4 at concentrations of 0%, 0.00025%, 0.0005% or 0.001%. The tests were carried out with and without the addition of a metabolic activation system (S9 mix from mice, rats or macaques) and the concentrations of the test substance were established in advance by determining the solubility and toxicity threshold. Positive controls were used concurrently. In the study, none of the selected concentrations was cytotoxic. A twofold increase in the number of revertants compared with that in the controls was observed in the Salmonella typhimurium strain TA1535 with the addition of rat liver S9 mix. The overall result of the test was regarded as negative (ECHA 2014).

A mutagenicity test carried out in Salmonella typhimurium TA98, TA100, TA1535, TA1537 and Escherichia coli WP2 uvrA with disodium succinate hexahydrate, the salt of succinic acid, likewise yielded negative results. In this study, which was carried out according to OECD Test Guideline 471, concentrations up to 5000 µg/plate were tested with and without the addition of a metabolic activation system (OECD 2003).

A study from the 1980s for chromosomal aberrations in CHL cells (Chinese hamster fibroblasts) yielded negative results at succinic acid concentrations of up to 0.001 mg/ml. The cells were incubated for 24 and 48 hours without metabolic activation and 100 metaphases were analysed. There are no data available for cytotoxicity (ECHA 2014; US EPA 2008).

A chromosomal aberration test carried out according to OECD Test Guideline 473 using disodium succinate hexahydrate concentrations of up to 5000 µg/ml with and without the addition of a metabolic activation system likewise yielded negative results. The substance induced neither structural aberrations nor polyploidy in Chinese hamster CHL/IU cells (OECD 2003).

5.6.2 In vivo

There are no data available.

5.7 Carcinogenicity

A report from 1990 described a 2-year carcinogenicity study in which 50 male and 50 female F344 rats per dose group were given sodium hydrogen succinate concentrations of 0%, 1% or 2% with the drinking water. After 104 weeks, the animals were given drinking water without the test substance for another 9 weeks and were investigated after 113 weeks. At concentrations of 1% and 2% in the drinking water, the amounts absorbed were 196 and 437 mg/rat and day for the males and 146 and 309 mg/rat and day for the females. Doses of about 500 and 1000 mg/kg body weight and day, respectively, were estimated from the concentrations in the drinking water (conversion factor: 0.05 according to EFSA 2012 b). The body weights of the animals and feed and water consumption were recorded during the study period and the organs of all animals were examined histopathologically. Haematological or clinico-chemical data are not available. Body weight gains were reduced in relation to treatment and the dose by up to 10%. There was no statistically significant difference in the survival of exposed animals of both sexes compared with that of the control animals. Specific toxicity caused by sodium hydrogen succinate was not found. The incidence of C-cell adenomas (see Table 1) of the thyroid gland was increased in the females of the high dose group compared with that in the control animals; it was not significant in the chi-squared test, but a positive trend was determined with a Peto's test adjusted for age. C-cell carcinomas were not induced (Maekawa et al. 1990). C-cell adenomas are spontaneous tumours that occur frequently in male F344 rats (an average incidence of 13% in the period from 1990 to 1997) (Haseman et al. 1998). No significant differences were found between exposed and non-exposed females for pre-neoplastic changes of the thyroid gland (C-cell hyperplasia in 10, 6 and 10 animals at 0%, 1% and 2% in the drinking water). Moreover, the incidence of C-cell tumours was lower in the control group than in the historical control animals of the laboratory (7% to 19%).It was therefore concluded that the increase in the tumour incidence in the high dose group and the positive trend probably resulted from experimental variability and were not substance-induced (Maekawa et al. 1990).

Table 1 Incidence of C-cell adenomas in the thyroid gland of F344 rats after 2-year administration of sodium hydrogen succinate (Maekawa et al. 1990)

	Males			Females		
concentration (%) in the drinking water	0	1	2	0	1	2
number of animals	50	48	50	49	48	49
animals with C-cell adenomas of the thyroid gland	12	11	6	2	4	7

6 Manifesto (MAK value/classification)

Local irritation to the eye is the critical effect.

MAK value. There are no studies available for the effects of succinic acid after inhalation exposure. Systemically, succinic acid given with the drinking water as the monosodium salt led to reduced body weight gains at about 1900 mg/kg body weight and day and above; the NOAEL was 950 mg/kg body weight and day. In a combined study of toxicity after repeated administration and reproductive toxicity carried out according to OECD Test Guideline 422, in which rats were given gavage doses of disodium succinate hexahydrate, increased blood urea nitrogen levels in the females (NOAEL: 130 mg succinic acid/kg body weight and day) and an increase in urinary protein levels in the males (NOAEL: 45 mg succinic acid/kg body weight and day) indicated nephrotoxicity. Bolus administration may be the reason for the much lower NOAEL compared with that obtained in the 13-week drinking water study. The following toxicokinetic data are used to extrapolate the NOAEL of 950 mg succinic acid/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the exposure for 5 days per week at the workplace (7:5), the corresponding species-specific correction value for the rat determined on the basis of the toxicokinetic data (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this was higher than 2000 mg succinic acid/m^3. In view of the corrosive effect on the eye and compared with the limit values for other strong acids, this concentration is too high for a limit value at the workplace.

A MAK value can be established for succinic acid in analogy to phosphoric acid, as carried out for tartaric acid (documentation "Weinsäure" 2015, available in German only) and adipic acid (documentation "Adipic acid" 2017, translation is in progress). Data available for similar acids are used to evaluate the local effects on the respiratory tract. The pKa level and structure of succinic acid are similar to those of tartaric acid, which, like succinic acid, is a solid. A MAK value of 2 mg/m^3 I (inhalable fraction) has been established for tartaric acid in analogy to phosphoric acid (documentation "Weinsäure" 2015, available in German only). Phosphoric acid has a MAK value of 2 mg/m^3 I, which was derived from a NOAEC (no observed adverse effect concentration) of 37.5 mg phosphoric acid/m^3 from a 13-week inhalation study in rats (documentation "Phosphorsäure" 2006, available in German only).

Succinic acid is a somewhat weaker acid than tartaric acid with pKa levels of 4.207 and 5.635 for succinic acid compared with 2.98 and 4.34 for tartaric acid (documentation "Weinsäure" 2015, available in German only). The pKa level of phosphoric acid is 2.2 (most acidic proton) (documentation "Phosphorsäure" 2006, available in German only).

Therefore, until suitable data become available, a MAK value of 2 mg/m^3 I has also been established for succinic acid in analogy to phosphoric acid (MAK value: 2 mg phosphoric acid/m^3 = 0.02 mmol/m^3 = 2.36 mg succinic acid/m^3). This, however, should be considered the worst case for succinic acid because of its lower acidity.

A systemic effect of succinic acid is expected only at concentrations that far exceed the MAK value (see above).

Peak limitation. The substance has been classified in Peak Limitation Category I because local irritation is the critical effect. In analogy to phosphoric acid, an excursion factor of 2 has been established for peak limitation.

Prenatal toxicity. A screening study carried out with disodium succinate hexahydrate in Sprague Dawley rats according to OECD Test Guideline 422 (see Section 5.5.1) revealed anophthalmus and polydactyly in 1 offspring of the middle dose group. As this finding was also observed sporadically in historical control animals, it was regarded as incidental and not as substance-induced. The NOAEL for foetotoxicity was thus 1000 mg/kg body weight and day (OECD 2003), which corresponds to about 440 mg succinic acid/kg body weight and day. No studies are available for teratogenicity; this would normally lead to classification in Pregnancy Risk Group D. However, succinic acid is an endogenous substance. The following toxicokinetic data are used to extrapolate the NOAEL for foetotoxicity of 440 mg/kg body weight and day in rats to a concentration in workplace air: the corresponding species-specific correction value for the rat determined on the basis of the toxicokinetic data (1:4), the assumed oral absorption (100%), the body weight (70 kg) and the respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this was 770 mg succinic acid/m^3; this is 385 times higher than the MAK value of 2 mg/m^3 I.

Exposure in the range of the MAK value would result in an absorbed dose of 20 mg succinic acid per day. As large amounts of succinic acid are formed in the citric acid cycle of the body (estimated amount of about 100 to 2000 g/day; Rechenberger and Benndorf 1957), an increase in endogenous exposure is expected to occur only at exposure levels far exceeding the MAK value of 2 mg/m^3. As long as the endogenous exposure is not disturbed, teratogenic effects are not expected. Also, the NOAEL for nephrotoxicity (45 mg succinic acid/kg body weight and day) and the NOAEL for foetotoxicity (see above) are far higher than the MAK value. Succinic acid has therefore been classified in Pregnancy Risk Group C.

Carcinogenicity. The available in vitro studies of genotoxicity provided no evidence of a genotoxic potential. There are no in vivo studies available for genotoxicity. In a 2-year carcinogenicity study in F344 rats, body weights were reduced by 10% and the incidence of C-cell adenomas was increased after exposure to about 1000 mg/kg body weight and day via the drinking water. The positive trend test for this finding probably results from the low control incidence of C-cell adenomas, which are a spontaneous, age-related finding in this rat strain. As the increase in the incidence of C-cell adenomas was within the range of that in historical controls in female F344 rats and as succinic acid did not cause C-cell carcinomas, succinic acid has not been classified in any of the categories for carcinogens.

Germ cell mutagenicity. Mutagenicity tests in Salmonella typhimurium, with and without the addition of a metabolic activation system, and a chromosomal aberration test in CHL cells yielded negative results. No in vivo genotoxicity studies are available for succinic acid. Therefore, the substance is not classified in any of the germ cell mutagen categories.

Absorption through the skin. There are no data available for the dermal penetration of succinic acid. Model calculations showed that the exposure of both hands and forearms for 1 hour would result in the penetration of maximum amounts of 129 mg. A systemic NOAEL for humans can be estimated on the basis of the systemic NOAEL of 950 mg/kg body weight and day from a 90-day drinking water

study in rats (see above). The following toxicokinetic data are used to extrapolate this NOAEL to humans: the daily exposure of the animals in comparison with the exposure for 5 days per week at the workplace (7:5), the corresponding species-specific correction value for the rat determined on the basis of the toxicokinetic data (1:4), a possible intensification of the effects after long-term exposure (1:2), extrapolation from animal studies to humans (1:2), and the body weight of the person (70 kg). This results in a systemically tolerable dose of 5819 mg. Absorption through the skin is thus lower than 25% of the systemically tolerable amount. Therefore, succinic acid has not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no clinical findings available for the sensitizing effects of succinic acid on the skin or any experimental animal studies of the sensitizing effects on the respiratory tract. Studies carried out according to valid guidelines provided no evidence of contact sensitization in guinea pigs or mice. Therefore, succinic acid has not been designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

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