The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Glutaric acid

MAK Value Documentation – Translation of the German version from 2019

A. Hartwig[1,*] MAK Commission[2,*]

1 Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany

2 Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* E-Mail: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Keywords

glutaric acid, irritation, maximum workplace concentration, MAK value, toxicity, hazardous substance, peak limitation

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated glutaric acid [110-94-1] considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.

The critical effect is a moderate local irritation as shown with the Draize test in the rabbit eye. Inhalation studies are not available. Systemic toxicity occurs only at high doses. 500 and 1800 mg/kg body weight and day, respectively. The lowest systemic NOAEL is 250 mg/kg body weight and day for dogs, which corresponds to a concentration of 146 mg/m^3 at the workplace.

To prevent irritation, a maximum concentration at the workplace (MAK value) of 2 mg/m^3 is derived for the respirable fraction by analogy with phosphoric acid and adipic acid and the substance is classified in Peak Limitation Category I with an excursion factor of 2.

Glutaric acid is not genotoxic and carcinogenicity studies are not available. After toxicokinetic scaling, the NOAELs from oral developmental toxicity studies in rats and rabbits correspond to concentrations of 2275 mg/m^3 and 1458 mg/m^3, respectively. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and glutaric acid is classified in Pregnancy Risk Group C. Skin contact is not expected to contribute significantly to systemic toxicity. Limited data show no sensitization.

Citation Note:
Hartwig A, MAK Commission. Glutaric acid. MAK Value Documentation – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2020 Oct;5(3):Doc053. DOI: 10.34865/mb11094e5_3or

Manuscript completed:
25 Jul 2017

Publication date:
09 Oct 2020

MAK value (2018)	**2 mg/m³ I (inhalable fraction)**
Peak limitation (2018)	**Category I, excursion factor 2**
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2018)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
Synonyms	pentanedioic acid 1,5-pentanedioic acid 1,3-propanedicarboxylic acid
Chemical name	1,5-pentanedioic acid
CAS number	110-94-1
Structural formula	HOOC–CH_2–CH_2–CH_2–COOH
Molecular formula	$C_5H_8O_4$
Molar mass	132.12 g/mol
Melting point	97.5–99 °C (BUA 1996; DuPont 2002)
Boiling point	302–304 °C (BUA 1996; DuPont 2002)
Vapour pressure at 25 °C	3.88×10^{-6} hPa (calculated; DuPont 2002)
log K_{OW}	−0.29 (calculated; BUA 1996; DuPont 2002)
Solubility at 20 °C	640 000 mg/l water (BUA 1996; IFA 2016)
pKa1 value	4.34 (Merten and Bachman 1976)
pH at 25 °C	about 2.5 (Merten and Bachman 1976)

Glutaric acid is used in the tanning of leather with high exhaustion chrome tanning agents for improving chrome exhaustion, as well as in the synthesis of organic compounds and in biochemical research.

Due to the paucity of data, also studies involving a technical dicarbonic acid mixture (purity ≥ 97%, 42–47% glutaric acid, 25–30% succinic acid, 25–30% adipic acid), adipic acid, and succinic acid are included in the assessment.

1 Toxic Effects and Mode of Action

Glutaric acid is formed as an endogenous metabolite during amino acid metabolism.

LOAELs (lowest observed adverse effect levels) were obtained in 90-day studies on the basis of delayed body weight gains of 500 mg glutaric acid/kg body weight and day in dogs and 1800 mg glutaric acid/kg body weight and day in rats.

In rabbits, glutaric acid is slightly irritating to the skin and irritating to the eye.

No reliable findings of sensitization in humans or corresponding observations from animal studies are available.

In developmental toxicity studies in rats and rabbits, salivation, rales and nasal discharge were observed in pregnant rats at and above glutaric acid doses of 400 mg/kg body weight and day. Up to the highest dose tested of 1300 mg/kg body weight and day in rats and 500 mg/kg body weight and day in rabbits, no developmental toxicity was found.

Glutaric acid was not found to be mutagenic in bacteria and mammalian cells and did not induce micronuclei in the bone marrow of mice.

In the cell transformation test, glutaric acid caused an increased incidence of transformed Balb/3T3 cells at 6.7 mg/ml and above.

Long-term carcinogenicity studies are not available.

2 Mechanism of Action

No data are available.

Due to its acidity, local respiratory irritation is to be expected.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Glutaric acid is formed as an endogenous metabolite during amino acid metabolism (BUA 1996).

Humans excrete about 2.4 mg glutaric acid with the urine daily (BUA 1996).

As no toxicokinetic studies are available, studies with the structurally similar adipic acid are used.

After gavage administration of 50 mg radioactively labelled **adipic acid**, rats exhaled up to 70% of the radioactivity as CO_2 within 24 hours. No details were given as to the level of radioactivity in the 24-hour urine. Little radioactivity was measured in the tissues (no other data) (Hartwig and MAK Commission 2018 a).

In another study, 2430 mg **adipic acid**/kg body weight and day was administered to rats by gavage for 28 days. In the urine collected during the entire treatment period up to two days after the end of exposure, 67% of the dose was recovered as unchanged substance (Hartwig and MAK Commission 2018 a).

With the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) and assuming a saturated aqueous glutaric acid solution, dermal fluxes of 600, 113 and 186 µg/cm^2 and hour, respectively, are obtained. For exposure of 2000 cm^2 of skin for one hour, this corresponds to a total uptake of 1200, 226 and 372 mg. The high fluxes are due to the very ready solubility of glutaric acid in water.

3.2 Metabolism

After intraperitoneal injection of 3-^{14}C-labelled sodium glutarate, rats expired 50% of the dose as CO_2 within three hours. Degradation via the acetate was thought to be more likely than that via the α-ketoglutarate. As in the case of fatty acids, degradation probably therefore takes place via β-oxidation (Hobbs and Koeppe 1958). Also in the

case of **adipic acid**, degradation via β-oxidation is considered to be most likely (Hartwig and MAK Commission 2018 a).

Summary: After oral administration of **adipic acid**, the substance is probably almost completely absorbed by rats. The same can be assumed for glutaric acid. The degradation of glutaric acid most probably takes place by β-oxidation via the acetate.

4 Effects in Humans

No data are available for allergenic effects, reproductive toxicity, genotoxicity and carcinogenicity.

In 7 persons exposed for 4 years to maximum concentration levels of 1.23 mg glutaric acid/m^3 and 11.6 mg adipic acid/m^3 (no other data), there were no unusual findings in the patients' medical history, in physical examinations, and in lung function or heart, eye and ear examinations. No irritation of the eyes, skin or mucous membranes of the upper respiratory tract was found (ECHA 2017).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

All rats survived a 4-hour exposure to 30 mg/m^3 of a technical dicarbonic acid mixture (BASF AG 1983).

5.1.2 Oral administration

In a range-finding study, 10 rats were given gavage doses of glutaric acid between 727 and 1274 mg/kg body weight. Three animals died due to aspiration of the test substance. Slight intestinal inflammation was found in one animal (DuPont 1944).

An LD_{50} of 2750 mg glutaric acid/kg body weight was determined in male and female Sprague Dawley rats. Signs of intoxication included tremor, salivation, diarrhoea and weakness. Inflammation of the gastric mucosa and hyperaemia of the liver were observed (DuPont 2002).

In mice, the LD_{50} was 7500 mg glutaric acid/kg body weight (Boyland 1940).

With the technical dicarbonic acid mixture an LD_{50} of 2210 mg/kg was obtained in rats (BASF AG 1983).

5.1.3 Dermal application

A 50% glutaric acid solution (no other data) up to a dose of 10 000 mg/kg body weight was applied dermally to one male and one female New Zealand White rabbit. Both animals survived and no signs of intoxication were found (DuPont 2002).

The LD_{50} for the technical dicarbonic acid mixture was above 200 mg/kg body weight in rats (BASF AG 1983).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

No data are available.

5.2.2 Oral administration

In a 90-day study described only in the form of a summary, 15 male and 15 female Sprague Dawley rats were given a diet containing 0%, 0.5%, 1.0% or 2.0% glutaric acid (0, 5000, 10 000 or 20 000 mg/kg feed, about 0, 450, 900, 1800 mg/kg body weight and day, conversion factor 0.09; according to EFSA (2012)). In females of the high dose group, body weight gains were significantly reduced (no other data). Food consumption, the examined blood and urine parameters, the absolute or relative organ weights and histopathological examinations did not reveal treatment-related effects. Due to the delayed body weight gains, the LOAEL was 1800 mg glutaric acid/kg body weight and day and the NOAEL (no observed adverse effect level) 900 mg/kg body weight and day (DuPont 2002). The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 900 mg glutaric acid/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 at the workplace (7:5), the corresponding species-specific correction value (1:4) for the rat, 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. From this a NAEC (no adverse effect concentration) of 2205 mg glutaric acid/m^3 is calculated.

In a 90-day study also available only in summary, 4 male and 4 female beagles were fed a diet containing 0%, 1%, 3% or 5% glutaric acid from days 1 to 10 and 0%, 0.5%, 1% or 2% glutaric acid from days 11 to 90. After 10 days, body weights were decreased (no other data) at 3% glutaric acid and above (about 750 mg/kg body weight) in the females and at 5% (about 1250 mg/kg body weight) in the males. Body weight gains were delayed in all animals of the high dose group during the entire study. All other examinations, including the histology of the testes and ovaries, did not reveal unusual findings. Thus, the LOAEL was 2% (about 500 mg/kg body weight and day) and the NOAEL 1% glutaric acid in the diet (about 250 mg/kg body weight and day) (DuPont 2002). The toxicokinetic extrapolation of this NOAEL from 250 mg glutaric acid/kg body weight and day to a concentration in workplace air, using the above listed factors with the exception of the species-specific correction value of 1:1.4 for the dog, results in a NAEC of 1750 mg glutaric acid/m^3.

Summary: Due to the delayed body weight gains, NOAELs and LOAELs of 900 and 1800 mg/kg body weight and day in rats, and of 250 and 500 mg/kg body weight and day in dogs are obtained, respectively. The NAECs in the workplace air calculated from this are 2205 mg/m^3 and 1750 mg/m^3 from the data of rats and dogs, respectively.

5.2.3 Dermal application

No data are available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Occlusive application of 0.5 g glutaric acid (purity 97%) for 1 or 4 hours caused slight erythema of the skin in 2 male and 2 female New Zealand White rabbits; this was still visible 48 hours after the application (DuPont 2002).

5.3.2 Eyes

100 mg glutaric acid powder (no other data) was instilled into the conjunctival sac of 3 male and 3 female rabbits. A score of 35.2 (on a scale of a maximum 110) was determined after 24 hours. Slight irritation of the cornea, conjunctiva and iris was still present after 7 days (DuPont 2002). Glutaric acid is therefore irritating to the rabbit eye.

Summary: In rabbits, glutaric acid is slightly irritating to the skin and irritating to the eye.

5.4 Allergenic effects

In a maximization test, a mixture containing 50.9% glutaric acid, 23.8% adipic acid and 18.6% succinic acid yielded negative results. Intradermal and topical induction were carried out using a 0.1% and a 10% preparation of the mixture in physiological saline, respectively, and the challenge with a 5% preparation in the same vehicle. In the examination after 24 and 48 hours, a discrete erythematous reaction was found in 1 of the 10 female Hartley guinea pigs in each case (ECHA 2017; Hartwig and MAK Commission 2018 a).

Summary: The technical dicarbonic acid mixture did not have sensitizing effects in Hartley guinea pigs.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

Studies of the effects of the substance on fertility are not available.

Although body weight gains were markedly reduced (no other data) in a 90-day study with male and female Sprague Dawley rats (available only in the form of a summary; see also Section 5.2.2) at the highest concentration tested of 2.0% glutaric acid in the diet (about 1800 mg glutaric acid/kg body weight and day), there were no changes in the absolute or relative weights of the testes and ovaries. Microscopic examination of the testes, seminal vesicles, ovaries and uterus also did not reveal treatment-related effects (DuPont 2002).

Likewise, in the 90-day study with male and female beagles also available only in the form of a summary (see Section 5.5.2), delayed body weight gains were found throughout the entire study in all animals of the high concentration group given 2.0% glutaric acid in the diet (about 500 mg glutaric acid/kg body weight and day). All other examinations, including the absolute or relative weights of the testes and ovaries and microscopic examination of the testes, seminal vesicles, ovaries and uterus did not reveal unusual findings (DuPont 2002).

Summary: Glutaric acid causes delayed body weight development with NOAELs and LOAELs of 900 and 1800 mg/kg body weight and day in rats, and of 250 and 500 mg/kg body weight and day in dogs, respectively. Up to the highest doses tested of 1800 mg glutaric acid/kg body weight and day in rats and 500 mg/kg body weight and day in dogs, no effects on male or female reproductive organs were found.

5.5.2 Developmental toxicity

Doses of 0, 125, 400 or 1300 mg glutaric acid (purity about 98%)/kg body weight and day were administered by gavage to groups of 25 male and 25 female CD rats (no other data) from days 6 to 15 of gestation. Caesarean section and gross pathological examination were performed on day 20 of gestation. Salivation, rales and nasal discharge were observed in the dams at 400 mg glutaric acid/kg body weight and day and above. Transient delays in body weight gains were found at 1300 mg/kg body weight and day. At this dose level, one animal died and another had to be killed on day 13 of gestation due to its moribund condition. In other animals, respiratory distress, reduced body temperature, soft faeces and discoloration of the snout, nose and anogenital region were observed. Glutaric acid did not affect the number of corpora lutea, implantations, live and dead foetuses or foetal weights. There were no visceral or skeletal changes. All in all, glutaric acid did not affect pregnancy and was not teratogenic. There was an increase in resorptions that was not dose-dependent with incidences of 0.4, 0.9, 0.5 and 1.0 at 0, 125, 400 and 1300 mg glutaric acid/kg body weight and day, respectively. In this study, the NOAEL for maternal toxicity was 125 mg/kg body weight and day and the LOAEL 400 mg/kg body weight and day. The NOAEL for developmental toxicity was 1300 mg/kg body weight and day, the highest dose tested (DuPont 2002).

In a pilot study, groups of 5 male and 5 female Sprague Dawley rats were given gavage doses of 0, 100, 300 or 1000 mg glutaric acid/kg body weight and day on days 6 to 15 of gestation. The purity of the substance was not specified. Body weight gains were slightly delayed during treatment. There were no unusual findings as regards the

number of resorptions, corpora lutea, implantations and surviving foetuses or after examination of the foetuses on day 21 of gestation. The NOAELs for maternal and developmental toxicity from this pilot study were 1000 mg/kg body weight and day in each case (DuPont 2002).

In another study, groups of 18 male and 18 female New Zealand White rabbits were given gavage doses of 0, 50, 160 or 500 mg glutaric acid (purity > 98%)/kg body weight and day from days 6 to 18 of gestation. Gross pathological examinations on day 29 of gestation revealed no effects on pregnancy, the number of corpora lutea, implantations, resorptions, the number of live and dead foetuses and foetal weights. There were also no external, visceral or skeletal changes. The NOAEL for maternal, embryotoxic and teratogenic effects was therefore 500 mg/kg body weight and day, the highest dose tested (DuPont 2002).

Summary: The studies of developmental toxicity in rats yielded a NOAEL for maternal toxicity (salivation, rales and nasal discharge) of 125 mg glutaric acid/kg body weight and day and a LOAEL of 400 mg/kg body weight and day. The NOAEL for developmental toxicity was the highest dose tested of 1300 mg glutaric acid/kg body weight and day. In rabbits, the NOAELs for developmental and maternal toxicity were the highest dose tested of 500 mg glutaric acid/kg body weight and day in each case.

5.6 Genotoxicity

5.6.1 In vitro

A test for the induction of an SOS response using Salmonella typhimurium (Umu test), yielded negative results up to a glutaric acid concentration of 2000 µg/ml (Sakagami et al. 1988).

Glutaric acid was not found to be mutagenic in a Salmonella mutagenicity test using the strains TA98, TA100, TA1537 and TA1538. Up to 5000 µg glutaric acid/plate were tested in the presence and absence of a metabolic activation system. Inhibition of bacterial growth occurred, in some cases at 2000 µg/plate and above, in other cases at 5000 µg/plate and above (DuPont 2002).

In another bacterial mutagenicity test with the Salmonella strains TA98, TA100 and TA1537 at 1000 µg/plate and above and with TA1535 at 5000 µg/plate, the number of spontaneous revertants was reduced without metabolic activation. Glutaric acid was not mutagenic also in this test, both in the presence and absence of a metabolic activation system (Bayer AG 1989). Neither was glutaric acid mutagenic up to 8295 µg/ml in a $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells (DuPont 2002).

In human embryonic lung fibroblast cells (Wi-38), **adipic acid** did not increase the frequency of chromosomal aberrations up to a concentration of 200 µg/ml (ECHA 2017). In CHL (Chinese hamster lung) cells, **succinic acid** did not increase chromosomal aberrations up to a concentration of 1000 µg/ml (ECHA 2014).

5.6.2 In vivo

In 4 male and 4 female CD1 mice, intraperitoneal administration of 800 mg glutaric acid/kg body weight did not result in a significant increase in the incidence of micronuclei in polychromatic erythrocytes of the bone marrow. The cells were obtained 30 or 40 hours after the injection (DuPont 2002).

Adipic acid is not mutagenic or clastogenic in vivo (Hartwig and MAK Commission 2018 a).

Summary: Glutaric acid is not mutagenic in bacteria and mammalian cells in vitro and does not induce micronuclei in the bone marrow of mice. Other dicarbonic acids, such as adipic or succinic acid, are not clastogenic in mammalian cells. Also in vivo, adipic acid is not mutagenic or clastogenic.

5.7 Carcinogenicity

In a cell transformation test with Balb/3T3 cells, glutaric acid produced an increased incidence of transformed Balb/3T3 cells at concentrations of 6.7 mg/ml and above (without metabolic activation) or 16.8 mg/ml (with metabolic activation) (DuPont 2002). Although this test indicates that glutaric acid causes a change in cell growth, namely a loss of cell-to-cell contact inhibition, the carcinogenic effects of the substance cannot be evaluated.

Long-term studies of carcinogenicity are not available.

6 Manifesto (MAK value/classification)

The critical effect of glutaric acid is irritation of the skin and eyes of rabbits.

MAK value. In 90-day studies with dietary administration of glutaric acid, delayed body weight gains were observed in dogs (NOAEL and LOAEL about 250 and about 500 mg/kg body weight and day, respectively) and in rats (NOAEL and LOAEL about 900 and about 1800 mg/kg body weight and day, respectively). A NAEC in workplace air of 1750 mg glutaric acid/m³ can be derived by toxicokinetic extrapolation (see Section 5.2.2) from the NOAEL in dogs, and of 2200 mg/m³ from that in rats. From these NAECs, concentrations of 146 mg/m³ (dogs) and 550 mg/m³ (rats) can be calculated taking into consideration a possible increase in the effects over time (dog 1:6, rat 1:2) and the extrapolation of data from animal experiments to humans (1:2). As studies of irritant effects of glutaric acid on the airways are not available, and in order to evaluate whether irritation is possible at this concentration, adipic acid is used as a reference. Like glutaric acid (Merten and Bachman 1976), adipic acid has a pKa1 value of 4.34 (Hartwig and MAK Commission 2018 a). At 2.5 and 2.7, the pH values of both acids are very similar (Merten and Bachman 1976). In the Draize test, the eye irritation caused by glutaric acid was somewhat weaker than that caused by adipic acid. As glutaric acid, however, has the same physico-chemical properties as adipic acid, a similar irritant effect can be assumed. For adipic acid, a MAK value was derived as previously for tartaric acid (Hartwig 2015, available in German only) and succinic acid (Hartwig and MAK Commission 2018 b) in analogy to the better investigated phosphoric acid. Based on eye irritation, a MAK value of 2 mg/m³ I (inhalable fraction) was established for phosphoric acid. In analogy, a MAK value of 2 mg/m³ I has been established for glutaric acid. With a 73-fold difference between this value and the NAEC, the MAK value provides protection also against the systemic effects of glutaric acid.

Peak limitation. As the MAK value for glutaric acid is derived on the basis of irritant effects, it has been assigned to Peak Limitation Category I. Studies of irritant effects in humans are not available. In analogy to phosphoric acid, an excursion factor of 2 has been established.

Prenatal toxicity. In the studies of developmental toxicity in rats, the NOAEL for maternal toxicity (salivation, rales and nasal discharge) was 125 mg glutaric acid/kg body weight and day and the LOAEL 400 mg/kg body weight and day. The NOAEL for developmental toxicity was the highest dose tested of 1300 mg glutaric acid/kg body weight and day. In rabbits, the NOAELs for developmental and maternal toxicity were both the highest dose tested of 500 mg glutaric acid/kg body weight and day.

The following toxicokinetic data are taken into consideration for the extrapolation of these two NOAELs to a concentration in workplace air: the corresponding species-specific correction values (1:4) for the rat and (1:2.4) rabbit, the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m³) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 2275 mg/m³ and 1458 mg/m³, respectively. In view of the at least 729-fold difference between the NOAEL for developmental toxicity extrapolated to a concentration in workplace air and the MAK value of 2 mg/m³, glutaric acid is assigned to Pregnancy Risk Group C.

Carcinogenicity and germ cell mutagenicity. Glutaric acid was not mutagenic in bacteria and in mammalian cells in vitro and did not induce micronuclei in the bone marrow of mice. In a cell transformation test with Balb/3T3

cells, glutaric acid induced an increased incidence of transformed cells at concentrations of 6.7 mg/ml and above. Long-term studies with glutaric acid are not available. The partial loss of cell-to-cell contact inhibition caused by glutaric acid is not sufficient for an evaluation of its carcinogenicity. Based on the negative results in the studies of genotoxicity and as, due to its structure, no genotoxic or carcinogenic effects are to be expected, glutaric acid has not been classified in one of the categories for carcinogens or germ cell mutagens.

Absorption through the skin. Studies of the absorption of glutaric acid through the skin are not available. The dermal LD_{50} value is higher than 10 000 mg/kg body weight. Using the Fiserova-Bergerova model (Section 3.1), the maximum amount dermally absorbed in humans is estimated to be 1200 mg after exposure to a saturated aqueous solution (640 g/l) under standard conditions (2000 cm^2 of skin, one-hour exposure). Absorbed amounts of 226 and 372 mg glutaric acid, respectively, are obtained using the two other models.

The oral NOAEL for systemic effects after subchronic exposure in dogs is 250 mg glutaric acid/kg body weight and day. As demonstrated above, a concentration of 146 mg/m^3 is extrapolated from this for humans. At a respiratory volume of 10 m^3 per day and 100% absorption by inhalation, this corresponds to a systemically tolerable amount of 1460 mg glutaric acid.

Therefore, the amount absorbed through the skin according to the model by Fiserova-Bergerova is almost the same as the systemically tolerable amount but not, however, according to the two other models. The homologous dicarbonic acids succinic acid and adipic acid have not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts); however, they are markedly less soluble in water, and no experimental data for dermal absorption are available. In the case of azelaic acid (1,7-heptane dicarbonic acid), which has also not been designated with an "H", percutaneous fluxes of 1.2 to 1.3 µg/cm^2 and hour were determined in dogs and rats (Hartwig 2013, available in German only). Using the model of Fiserova-Bergerova, the calculated flux is 45 µg azelaic acid/cm^2 and hour, with the two other models about 4 µg/cm^2 and hour. The Fiserova-Bergerova model greatly overestimates the flux in this case, and thus presumably also that for glutaric acid. According to one of the two other models the amount dermally absorbed is less than 25% of the systemically tolerable amount. For this reason, glutaric acid is not designated with an "H".

Sensitization. No clinical findings for sensitizing effects of glutaric acid on the skin or airways are available. A study with guinea pigs using a mixture containing glutaric acid produced no evidence of contact sensitization. Glutaric acid has therefore not been designated with either "Sh" or with "Sa" (for substances which cause sensitization of the skin and airways).

References

BASF AG (1983) BASF Datenblatt, Dicarbonsäuregemisch, Nov 1983. BASF AG, Ludwigshafen

Bayer AG (1989) Salmonella typhimurium reverse mutation assay with pentanedioic acid, BALK No 88/034. CCR Project 156701, Bayer Project T 3032819, Cytotest Cell Research GmbH & Co KG (CCR), Rossdorf, unpublished

Boyland E (1940) Experiments on the chemotherapy of cancer: Further experiments with aldehydes and their derivatives. J Biochem 34: 1196–1201. DOI: 10.1042/bj0341196

BUA (GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance) (1996) Glutaric acid, BUA-Report 136. Hirzel, Stuttgart

DuPont (E.I. du Pont de Nemours and Company) (1944) Preliminary tests on new materials. Project No MR-125, Haskell Laboratory, 14 Jun 1944, unpublished

DuPont (E.I. du Pont de Nemours and Company) (2002) Robust summary for glutaric acid. Robust Summaries & Test Plans: Dicarboxylic Acids Category HPV Revised Test Plan, Appendix A, 12 Aug 2002. DuPont, Wilmington, DE, unpublished

ECHA (European Chemicals Agency) (2014) Information on registered substances. Dataset on succinic acid (CAS Number 110-15-6), joint submission, first publication 17 Jan 2012, last modification 12 Jun 2014. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15265/1, accessed 29 Oct 2014

ECHA (European Chemicals Agency) (2017) Information on registered substances. Dataset on adipic acid (CAS Number 124-04-9), joint submission, first publication 18 Mar 2011, last modification 03 Jun 2017. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15464/1, accessed 17 Jul 2017

EFSA (European Food Safety Authority) (2012) Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA J 10: 2579. DOI: 10.2903/j.efsa.2012.2579

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17: 617–635. DOI: 10.1002/ajim.4700170507

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. Am J Ind Med 23: 711–719. DOI: 10.1002/ajim.4700230505

Hartwig A (ed) (2013) Azelainsäure. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, 54. Lieferung. Wiley-VCH, Weinheim. Also available from DOI: 10.1002/3527600418.mb12399kskd0054

Hartwig A (ed) (2015) Weinsäure. In: Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten, 58. Lieferung. Wiley-VCH, Weinheim. Also available from DOI: 10.1002/3527600418.mb8769ismd0058

Hartwig A, MAK Commission (2018 a) Adipic acid. MAK Value Documentation, 2017. MAK Collect Occup Health Saf 3: 1010–1026. DOI: 10.1002/3527600418.mb12404kske6218

Hartwig A, MAK Commission (2018 b) Succinic acid. MAK Value Documentation, 2017. MAK Collect Occup Health Saf 3: 592–605. DOI: 10.1002/3527600418.mb11015e6218

Hobbs DC, Koeppe RE (1958) The metabolism of glutaric acid-3-C14 by the intact rat. J Biol Chem 230: 655–660. https://www.jbc.org/content/230/2/655.full.pdf, accessed 23 Nov 2016

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (2016) Glutarsäure. GESTIS-Stoffdatenbank. http://gestis.itrust.de/nxt/gateway.dll/gestis_de/033910.xml?f=templates$fn=document-frameset.htm$3.0, accessed 22 Nov 2016

Merten HL, Bachman GL (1976) Glutaric acid: a potential food acidulant. J Food Sci 41: 463–464. DOI: 10.1111/j.1365-2621.1976.tb00646.x

Sakagami Y, Yamazaki H, Ogasawara N, Yokoyama H, Ose Y, Sato T (1988) The evaluation of genotoxic activities of disinfectants and their metabolites by umu test. Mutat Res 209: 155–160. DOI: 10.1016/0165-7992(88)90034-6

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30: 1275–1296. DOI: 10.1016/0045-6535(95)00023-2