The MAK Collection for Occupational Health and Safety

Citric acid and its alkali metal salts

MAK Value Documentation, addendum – Translation of the German version from 2018

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Citric acid and its alkali metal salts[1)] / 2-Hydroxypropane-1,2,3-tricarboxylic acid and its alkali metal salts

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 re-evaluated citric acid [77-92-9] and its alkali metal salts, considering all toxicological endpoints.

The critical effect of citric acid is the irritation of the respiratory tract with an acute LOAEC of 225 mg/m³ in humans and 81 mg/m³ in guinea pigs. At this concentration coughing is induced due to the lowering of the pH value. The NOAEC in guinea pigs is 31 mg/m³, the corresponding NOAEC in humans is not known. Studies with repeated inhalation are not available. Therefore, the maximum concentration at the workplace (MAK value) has been set by analogy with the MAK value for phosphoric acid of 2 mg/m³ as inhalable fraction. Since a local effect is critical, Peak Limitation Category I is designated. The excursion factor of 2 is set by analogy with phosphoric acid.

The alkali metal salts of citric acid are not irritating, which precludes setting the same MAK value for the salts as for citric acid. However, a higher MAK value cannot be established because the systemic NOAEL is unclear. Therefore, no MAK value can be set for the alkali metal salts of citric acid.

The oral NOAEL for developmental toxicity in rats, mice, rabbits and hamsters is higher than 200 mg citric acid/kg body weight, which after toxicokinetic scaling corresponds to more than 200 mg/m³ at the workplace. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and citric acid is assigned to Pregnancy Risk Group C.

Citric acid does not possess a relevant genotoxic potential in vivo. The same is assumed for its alkali metal salts. There are no valid carcinogenicity studies with citric acid. A tumour promoting effect of sodium citrate but not citric acid in the rat urinary bladder is due to excessively high sodium concentration in the urine and is therefore not relevant for humans at the workplace.

According to skin absorption models, percutaneous absorption of citric acid does not contribute significantly to systemic toxicity. The same is assumed for its alkali metal salts. Citric acid and its alkali metal salts are not sensitizing to skin or airways.

Keywords

citric acid; sodium dihydrogen citrate; disodium hydrogen citrate; trisodium citrate; potassium dihydrogen citrate; dipotassium hydrogen citrate; tripotassium citrate; 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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1) The MAK value for citric acid (2 mg/m³) protects from irritation, a higher value for alkali metal salts is not justifiable.

Citric acid and its alkali metal salts

Citric acid [77-92-9]
Sodium dihydrogen citrate [18996-35-5]
Disodium hydrogen citrate [144-33-2]
Trisodium citrate [68-04-2]
Potassium dihydrogen citrate [866-83-1]
Dipotassium hydrogen citrate [3609-96-9]
Tripotassium citrate [866-84-2]

Supplement 2018

MAK value (2017)	**citric acid: 2 mg/m³ I (inhalable fraction)** **alkali metal salts: not yet established, see Section II b of the List of MAK and BAT Values[1)]**
Peak limitation (2017)	**citric acid: Category I, excursion factor 2** **alkali metal salts: –**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2017)	**citric acid: Pregnancy Risk Group C** **alkali metal salts: –**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 25 °C	citric acid: 7.3×10^{-9} hPa (calculated; OECD 2001) alkali **metal** salts: no data
log K_{OW}[2)] at 20 °C	citric acid: –1.72 at 20 °C (OECD 2001) alkali **metal** salts: no data

1) The MAK value for citric acid (2 mg/m³) protects from irritation, a higher value for alkali metal salts is not justifiable.

2) octanol/water partition coefficient.

Solubility	citric acid: 600 g/l water (documentation "Citric acid" 2001); 576–771 g/l water (OECD 2001) sodium dihydrogen citrate: 135 g/l water (ECHA 2016 b) trisodium citrate: 425 g/l water (ECHA 2016 c) tripotassium citrate: 606 g/l water (ECHA 2016 d)
pKa value at 25 °C	3.13, 4.76 and 6.4 (ECHA 2016 a)
pH	citric acid: 1.8 at 50 g/l water (OECD 2001) sodium dihydrogen citrate: 3.8 at 1% in water (ECHA 2016 b) trisodium citrate: 8.4 at 5% in water (ECHA 2016 c) tripotassium citrate: 8.7 at 5% in water (ECHA 2016 d)

Documentation for citric acid was published in 1998 (documentation "Citric acid" 2001). However, a MAK value could not be derived at the time because of a lack of data for the toxic effects of the substance after repeated inhalation. In metal-working fluid concentrates, a maximum 2% of the substance is used, primarily in the form of salts with alkali metals and alkaline earth metals and amines (documentation "Komponenten von Kühlschmierstoffen, Hydraulikflüssigkeiten und anderen Schmierstoffen" 2014, available in German only).

This assessment is in part based on the REACH datasets for citric acid and its alkali metal salts (ECHA 2016 a, b, c, d). No datasets are available (status 2017) for disodium hydrogen citrate, potassium dihydrogen citrate and dipotassium hydrogen citrate. Toxicological investigations have not been carried out for tripotassium citrate.

1 Toxic Effects and Mode of Action

Undiluted citric acid is corrosive to rabbit eyes and causes only slight irritation of the skin.

A single exposure to a citric acid concentration of 225 mg/m^3 induced coughing in test persons. The corresponding LOAEC (lowest observed adverse effect concentration) in guinea pigs was 81 mg/m^3.

The substance has low systemic toxicity. Haematological and clinico-chemical effects were observed in a number of different animal species at doses of about 600 mg/kg body weight and day and above.

Citric acid does not cause sensitization of the skin in humans.

In studies of developmental toxicity in rats, rabbits, hamsters and mice, incomplete closure of the skull, a reversible delay in development, was observed only in rats at the highest citric acid dose tested of 295 mg/kg body weight.

In a number of in vitro studies, in some cases with toxic concentrations, citric acid was found to be clastogenic. However, it was not found to be clastogenic in vivo in the chromosomal aberration test and in the dominant lethal test in rats. There are no valid carcinogenicity studies available.

The alkali metal salts of citric acid do not cause irritation of rabbit eyes or rabbit skin. The systemic toxicity has not been investigated, but can be assumed to be low in analogy to that of citric acid. It has been demonstrated that the tumour-promoting effect of sodium citrate in the bladder of rats is caused by the unphysiologically high concentration of sodium in the urine. Sodium dihydrogen citrate and trisodium citrate do not cause sensitization of the skin.

2 Mechanism of Action

The local toxicity of citric acid in the eyes and respiratory tract has been found to be caused by the decrease in pH that results from the acidity of the substance because the less acidic and neutral sodium salts do not cause irritation in either the respiratory tract or eyes. Citric acid may play a role in metal homeostasis as a result of complexation (documentation "Citric acid" 2001).

3 Toxicokinetics and Metabolism

Citric acid is an intermediate in the citric acid or Krebs cycle in human metabolism (estimated turnover about 100–2000 g/day). It is a natural component of foodstuffs and one of the most widely used food additives. The average daily intake of citric acid or its salts from natural sources and through its use as a food additive can exceed 400 mg/kg body weight and day. The physiological plasma levels of citrate in middle-aged adults are 9–25 mg/l plasma (documentation "Citric acid" 2001).

There are no data for absorption via inhalation.

Albino rats given a gavage dose of citric acid of 1000 mg/kg body weight had absorbed about 90% of the dose after 5 hours (Kuether and Smith 1941). It can be concluded from this that 100% oral absorption takes place within 24 hours.

Dermal flux values of 76, 4 and 15 μg/cm^2 and hour, respectively, were calculated for the dermal absorption of a saturated aqueous solution of citric acid using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). Assuming 1-hour exposure of 2000 cm^2 of skin, this would be equivalent to absorbed amounts of 152, 8 and 30 mg, respectively.

No individual log K_{OW} values have been determined for the alkali metal salts, which means that calculations cannot be made based on the above models. It is assumed that the alkali metal salts are absorbed through the skin to an extent similar to that of citric acid.

The excretion of citric acid (no other details) in 82 adults was 80–1690 mg per day. The reference values for the excretion of citric acid in the 24-hour urine are between 290 and 710 mg (OECD 2001).

4 Effects in Humans

Citric acid aerosols induce coughing and are used to test the efficacy of antitussives. This has been investigated in a large number of studies. However, the majority of them did not determine the concentration of citric acid in the air; instead, they reported only the concentration in the aqueous phase from which the aerosol was generated.

Test persons inhaled a citric acid aerosol 3 times per concentration at increasing concentrations at a respiration rate of 50, 100 and 150 l/min. The test persons tolerated a concentration of 21 mg/l at 50 l/min and a cumulative amount of 5.2 mg citric acid before coughing was induced (Barros et al. 1990; documentation "Citric acid" 2001). The study did not report the citric acid concentration in the air.

In another study in test persons with exposure to the aerosol of a 25% aqueous citric acid solution, inhalation exposure to a single citric acid concentration of 0.045 mg per 200 ml air induced coughing. This is equivalent to 225 mg/m^3 (Bickerman et al. 1956; documentation "Citric acid" 2001).

Severe eye damage was described in a man who was splashed in the eye with a saturated solution of citric acid (OECD 2001).

The treatment of patients with renal calculi with daily oral doses of up to 15 g sodium citrate and potassium citrate did not cause any clear adverse effects (OECD 2001).

Men who ingested 60 ml of an aqueous solution containing 100 mg of sodium citrate per ml (86 mg/kg body weight and day at 70 kg body weight) daily for 4 days were found to have a more alkaline urine and eliminated more sodium and less magnesium and potassium (OECD 2001).

Based on the available studies in humans, it was concluded in the documentation from 1998 (documentation "Citric acid" 2001) that citric acid does not cause sensitization of the skin or airways.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Coughing was induced in guinea pigs that had been exposed by inhalation for 30 minutes to an aerosol with a citric acid concentration of 81 mg/m^3. The NOAEC (no observed adverse effect concentration) was 31 mg/m^3 (documentation "Citric acid" 2001).

Exposure for 10 minutes to the aerosol of a 0.5 M sodium citrate solution (pH 8.53) did not induce coughing in guinea pigs, as opposed to exposure to the same

concentration of citric acid (pH 1.07; mass median aerodynamic diameter in both cases 0.9 µm). Therefore, irritation is caused by the acid and not the anion (Lalloo et al. 1995; documentation "Citric acid" 2001).

5.1.2 Oral administration

There are no new data available.

5.1.3 Dermal application

There are still no data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are still no data available.

5.2.2 Oral administration

The most important studies were already discussed in the documentation from 1998 (documentation "Citric acid" 2001). They do not comply with today's test guidelines.

In a 2-year study in male rats, a diet containing 5% citric acid (calculated based on the data provided by the authors: 2000 mg/kg body weight and day) resulted in slightly reduced feed consumption and reduced growth, but no changes in the tissues of the 11 organs that were examined. A concentration of 3% citric acid (1200 mg/kg body weight) was the NOAEL (no observed adverse effect level) (Horn et al. 1957).

The haematocrit value was reduced in guinea pigs given citric acid doses of 670 mg/kg body weight and day and above for 60 days. In a 29-week one-generation study in rats with dietary administration of citric acid, the sodium levels in the liver and phosphorus levels in the muscles were reduced at doses of 600 mg/kg body weight and day. Higher doses led to changes in calcium and zinc homeostasis (documentation "Citric acid" 2001).

Overall, no clear NOAEL was determined. The LOAEL (lowest observed adverse effect level) for systemic effects was 600 mg/kg body weight and day in rats.

5.2.3 Dermal application

There are still no data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Citric acid causes no or only slight irritation of the skin of rabbits (documentation "Citric acid" 2001; ECHA 2016 a).

In a study carried out according to OECD Test Guideline 404 in 3 rabbits, sodium dihydrogen citrate did not cause irritation of the skin with an irritation score of 0 out of a maximum of 8 (ECHA 2016 b).

In a study carried out according to OECD Test Guideline 404 in 3 rabbits, trisodium citrate did not cause irritation of the skin with an irritation score of 0.11 out of a maximum of 8 (ECHA 2016 c).

An additional test with trisodium citrate carried out according to OECD Test Guideline 404 in 6 rabbits yielded a primary irritation index of 0 (ECHA 2016 c).

Skin irritation studies are not available for tripotassium citrate (ECHA 2016 d).

It is assumed that none of the alkali citrates cause irritation of the skin.

5.3.2 Eyes

In unrinsed rabbit eyes, crystalline anhydrous citric acid was severely irritating or corrosive (documentation "Citric acid" 2001).

Undiluted sodium dihydrogen citrate did not cause irritation in the rabbit eye in a study carried out according to OECD Test Guideline 405 (ECHA 2016 b).

Undiluted trisodium citrate did not cause irritation in the rabbit eye in 2 studies carried out according to OECD Test Guideline 405 (ECHA 2016 c).

Eye irritation studies are not available for tripotassium citrate (ECHA 2016 d).

It is assumed that none of the alkali citrates cause irritation of the eyes.

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a maximization test carried out according to OECD Test Guideline 406, 20 male guinea pigs were treated with 5% sodium dihydrogen citrate for intradermal induction, 75% for topical induction, and 25%, 50% and 75% for the challenge. Water was used as the vehicle for all applications. Open treatment with 10% sodium dodecyl sulfate in petrolatum was carried out 1 day before topical induction treatment. At the challenge, none of the animals reacted to any of the 3 test preparations after 24 or 48 hours (ECHA 2016 b).

In a maximization test carried out according to OECD Test Guideline 406, 20 male guinea pigs were treated with 5% trisodium citrate for intradermal induction, 75% for topical induction, and 25%, 50% and 75% for the challenge. Water was used as the vehicle for all applications. Open treatment with 10% sodium dodecyl sulfate in petrolatum was carried out 1 day before topical induction treatment. At the challenge, none of the animals reacted to any of the 3 test preparations after 24 or 48 hours (ECHA 2016 c).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

In one-generation studies with dietary administration, no effect on fertility was observed up to the highest citric acid doses tested of 1200 mg/kg body weight and day in rats and 600 mg/kg body weight and day in mice (documentation "Citric acid" 2001).

5.5.2 Developmental toxicity

Reports from 1973 describe studies of the developmental toxicity of citric acid in hamsters, mice, rats and rabbits that were sponsored the US Food and Drug Administration. Maternal toxicity was registered in the form of feed consumption, body weights and mortality. The number of implantation sites, resorptions, live and dead foetuses, and the weight, sex and mortality of the foetuses were recorded. All foetuses of rabbits were assessed for external, skeletal and visceral abnormalities. In the other species, 2/3 of the foetuses were examined for external and skeletal anomalies and 1/3 for visceral. The negative controls were treated with the vehicle (no other details). The mice of the control groups were sham treated.

Groups of 22 to 25 mated Wistar rats were given citric acid by gavage in daily doses of 0, 2.95, 13.7, 63.6 or 295 mg/kg body weight from gestation days 6 to 15. Caesarean section was performed on day 20. The incidence of incomplete closure of the skull (controls: 27/153 (18%); 295 mg/kg body weight: 56/167 (34%)) was increased in foetuses of the high dose group.

Groups of 13 to 18 artificially inseminated Dutch-belted rabbits were given citric acid by gavage in daily doses of 0, 4.25, 19.75, 91.7 or 425 mg/kg body weight from gestation days 6 to 18. Caesarean section was performed on day 29. The incidence of incomplete ossification of the sternum (sternebrae) (controls: 1/43 (2%), 425 mg/kg body weight: 5/54 (9%)) was increased in foetuses of the high dose group.

Groups of 24 to 28 mated CD1 mice were given citric acid by gavage in daily doses of 0, 2.41, 11.2, 52 or 241 mg/kg body weight from gestation days 6 to 15. Caesarean section was performed on day 17. The incidence of hyoid bones that were reduced in size (controls: 18/154 (12%), 241 mg/kg body weight: 33/186 (18%)) was increased in foetuses of the high dose group.

Groups of 25 to 29 mated Syrian hamsters were given citric acid by gavage in daily doses of 0, 2.72, 12.6, 58.7 or 272 mg/kg body weight from gestation days 6 to 10. Caesarean section was performed on day 14. No treatment-induced findings were observed in the foetuses.

Maternal toxicity and malformations were not reported in any of the studies. The data were not analysed statistically (FDA 1973). Retrospective statistical analysis using the chi-squared test at the significance level of 0.05 (one-sided) yielded statis-

tical significance only for the incomplete closure of the skull observed in Wistar rats.

Incomplete closure of the skull without any other signs of developmental toxicity indicates a generally reversible delay in development, as ossification of the skull takes place rapidly and with great variation at the end of gestation and different conclusions can be drawn within a span of just a few hours depending upon the exact preparation time period. This effect has no influence on the further postnatal development (Carney and Kimmel 2007). The Commission considers the findings reported in rats of the high dose group to be a reversible delay in development and not an adverse effect. As a result, the NOAELs for developmental toxicity in rats, rabbits, mice and hamsters are 295, 425, 241 and 272 mg/kg body weight and day, respectively.

5.6 Genotoxicity

5.6.1 In vitro

Citric acid was not mutagenic in the Salmonella mutagenicity test at concentrations up to 5 mg/plate and was not clastogenic in Chinese hamster lung fibroblasts up to concentrations of 1 mg/ml (Ishidate et al. 1984).

In the Comet assay, DNA strand breaks were induced in human lymphocytes after treatment with citric acid at the highest non-toxic concentration of 200 µg/ml. Cytotoxicity was reported at 3000 µg/ml (Yilmaz et al. 2014).

Sister chromatid exchange and chromosomal aberrations were investigated in the human peripheral lymphocytes of 2 non-smoking donors after treatment with citric acid concentrations of 0, 50, 100, 200 or 3000 µg/ml. After treatment for 24 and 48 hours, citric acid induced sister chromatid exchange at concentrations of 100 and 50 µg/ml, respectively, and above. The incidence of sister chromatid exchange was twice as high at 200 µg/ml than after treatment with the control. After a 24-hour incubation period, there was a concentration-dependent and statistically significant increase in the percentage of aberrant lymphocytes: controls 2.50% ± 0.70%, 50 µg/ml 12.50% ± 2.34%, 100 µg/ml 19.00% ± 2.77%, 200 µg/ml 20.00% ± 2.83%. After a 48-hour incubation period, the percentage of aberrant lymphocytes was about 19% at every concentration; the control value was 2%. Both structural as well as numerical aberrations were found. At the same time, the mitotic index was significantly reduced at every concentration. Toxic effects were induced by citric acid at a concentration of 3000 µg/ml; no metaphases were detected at either of the time points (Yilmaz et al. 2008). Most of the aberrations were sister chromatid unions, which are usually not reported (ECHA 2016 a). The incidence of other structural aberrations was also increased, even though a statistical analysis was not carried out. However, sister chromatid exchange and chromosomal aberrations were observed only if at the same time the mitotic index was significantly reduced; therefore, clastogenic effects occurred only at cytotoxic doses.

A micronucleus test carried out using a similar procedure to OECD Test Guideline 487 investigated the same donor lymphocytes with exposure to the same citric acid concentrations. The lymphocytes were cultured for a total of 72 hours, with exposure to citric acid in the medium beginning after 24 hours and lasting for 48

hours. The cytokinesis inhibitor cytochalasin was added 44 hours after the test began and the lymphocytes were examined for micronuclei after 72 hours. Concentrations of 50 µg/ml and above yielded a concentration-dependent and statistically significant increase in the fraction of binuclear lymphocytes with micronuclei: controls 0.3% ± 0.12%, 50 µg/ml 1.65% ± 0.28%, 100 µg/ml 2.35% ± 0.34%, 200 µg/ml 2.60% ± 0.36%. Toxic effects were induced at the high concentration of 3000 µg/ml. The pH of the medium remained unchanged by the citric acid concentrations that were used. The cytokinesis block proliferation index (CBPI) was determined as a measure of cell proliferation. The CBPI was not significantly reduced (Yilmaz et al. 2008).

5.6.2 In vivo

Citric acid was tested for the induction of chromosomal aberrations in the bone marrow cells of groups of 5 male Sprague Dawley rats per dose and test time point. The test, which was performed in 1975, analysed only 50 cells and thus does not comply with OECD Test Guideline 475. The rats were given either a single dose of 0, 1.2, 12, 120, 500 or 3500 mg/kg body weight or gavage doses of 0, 1.2, 12 or 120 mg/kg body weight and day on 5 consecutive days. In the group treated with a dose of 3500 mg/kg body weight, chromosomal aberrations were found in 29% of the cells 6 hours after the dose was administered; in comparison, 0% were found in the cells of the negative controls. No aberrant cells were detected 24 and 48 hours after the substance was administered. Compared with the negative controls, the mitotic index remained unchanged. The positive control triethylene melamine caused the expected effects. The registrants did not consider citric acid to be clastogenic (ECHA 2016 a). The registrants did not include any details about the number of specific types of chromosomal aberrations per animal in their description of the study. The original study report is not available. The test can only be assessed on the basis of the data submitted to ECHA by the registrants. As the increased percentage of cells with chromosomal aberrations after 6 hours is an unconfirmed, single finding, it is considered to be coincidental. In addition, the dose of 3500 mg/kg body weight and day exceeds the recommended maximum dose of 2000 mg/kg body weight and day. Overall, the findings of the chromosomal aberration test are considered to be negative.

A dominant lethal test was carried out with groups of 10 male Sprague Dawley rats per dose using the same dosages. The rats were given either a single dose of 0, 1.2, 12, 120, 500 or 3500 mg/kg body weight or gavage doses of 1.2, 12 or 120 mg/kg body weight and day on 5 consecutive days. The increase in preimplantation losses observed at mating 4 weeks after repeated treatment with doses of 1.2 and 12 mg/kg body weight was not detected after the dose of 120 mg/kg body weight or in the animals given a higher, single dose of the substance. The registrants considered the results to be negative overall because there was no increase in the number of dead implantations. The positive control triethylene melamine caused the expected effects (ECHA 2016 a). The original study report is not available. The test can only be assessed on the basis of the data submitted to ECHA by the registrants. The results of the test are considered to be negative based on the data submitted.

5.7 Carcinogenicity

Overall, the available studies that investigated the effects of sodium citrate and citric acid on the rat bladder found that sodium citrate, ingested in large quantities, has a tumour-promoting effect. This effect appears to result from the stimulation of DNA synthesis in the epithelial cells of the bladder caused by an increase in the urinary sodium concentration or urinary pH of the animals (documentation "Citric acid" 2001).

6 Manifesto (MAK value/classification)

The critical effect of citric acid is local irritation of the respiratory tract. A 29-week study with dietary administration in rats reported a LOAEL for systemic effects of 600 mg/kg body weight.

MAK value. **Citric acid**: Coughing was induced in test persons after single exposures to citric acid aerosols of 225 mg/m^3. However, a MAK value cannot be derived from the threshold concentrations for the induction of coughing in humans because they vary greatly between individuals and depend on the inspiratory flow rate (documentation "Citric acid" 2001). In guinea pigs, the respective LOAEC for citric acid was 81 mg/m^3, the NOAEC was 31 mg/m^3.

A NAEL (no adverse effect level) of 200 mg/kg body weight is assumed based on the LOAEL for systemic effects in rats of 600 mg/kg body weight. The following toxicokinetic data are taken into consideration for the extrapolation of the NAEL to a concentration in workplace air: the corresponding species-specific correction value for the rat (1:4), the daily exposure of the animals in comparison with 5 days per week exposure at the workplace (7:5), the confirmed oral absorption of 100%, the body weight (70 kg) and the respiratory volume (10 m^3) of the person as well as the assumed 100% absorption by inhalation. After extrapolating the data from animal experiments to humans (1:2), this results in a concentration of 245 mg/m^3. The LOAEC for the induction of coughing in guinea pigs is lower, which is why local irritation due to the acidity is decisive for determining the limit value. However, there are no relevant studies with repeated inhalation exposure available. Citric acid is corrosive to rabbit eyes. As in the case of other corrosive solid organic acids such as tartaric acid (documentation "Weinsäure" 2015, available in German only) for which studies on inhalation toxicity were lacking, for citric acid a MAK value of 2 mg/m^3 I has been established in analogy to the more extensively investigated phosphoric acid.

Alkali metal salts: Sodium dihydrogen citrate and trisodium citrate do not cause irritation in rabbit eyes. The same should also be true for disodium hydrogen citrate and the corresponding potassium citrates. Therefore, the local irritation induced by inhalation exposure to alkali metal salts should be much less than that caused by citric acid. For this reason, the MAK value for the acid cannot be taken over for the alkali metal salts. As the systemic NOAEL has yet to be conclusively determined, the alkali metal salts remain classified in Section II b of the List of MAK and BAT Values.

Peak limitation. Citric acid is classified in Peak Limitation Category I because irritation is the critical effect. As the MAK value was derived in analogy to phosphoric acid, the excursion factor of 2 established for phosphoric acid is also used for citric acid.

Prenatal toxicity. In a study of the toxic effects of citric acid on prenatal development, reversible delays in development in the form of incomplete closure of the skull were observed in rats after gavage administration at the highest dose tested of 295 mg/kg body weight and day. No maternal toxicity was reported. No developmental toxicity was observed in rabbits, hamsters and mice up to the highest dose tested of 425, 272 and 241 mg/kg body weight and day, respectively. The Commission does not consider the reversible delay in development in rats to be an adverse effect because ossification of the skull takes place rapidly and with great variation at the end of gestation and different conclusions can be drawn within a span of just a few hours depending upon the exact preparation time period (Carney and Kimmel 2007). Moreover, no malformations were observed. Therefore, the NOAELs for the toxic effects on prenatal development in rats, rabbits, mice and hamsters were 295, 425, 241 and 272 mg/kg body weight and day, respectively.

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL for developmental toxicity to a concentration in workplace air: the corresponding species-specific correction values for the rat, rabbit, mouse and hamster (1:4, 1:2.4, 1:7, 1:5), the experimental oral absorption of 100% in the rat, which is assumed also for the other species, the body weight (70 kg) and the respiratory volume (10 m^3) of the person and the assumed 100% absorption by inhalation. The concentrations calculated from this are 516, 1240, 241 and 381 mg/m^3, respectively, which are equivalent to a 258-fold, 620-fold, 121-fold and 191-fold margin to the MAK value of 2 mg/m^3. As these margins are sufficiently large, citric acid has been classified in Pregnancy Risk Group C.

Even if the effects observed in the rats of the high dose group were considered adverse, the margin between the second highest dose of 63.6 mg/kg body weight and the MAK value would still be sufficiently large for the substance to be classified in Pregnancy Risk Group C.

Carcinogenicity. The tumour-promoting effect on the rat bladder observed after exposure to sodium citrate, but not after exposure to citric acid, results from the stimulation of DNA synthesis in the epithelial cells of the bladder caused by an increase in the urinary sodium concentration or urinary pH. This effect occurs only after ingestion of sodium citrate in large quantities, which is unlikely in humans (documentation "Citric acid" 2001). As genotoxic effects are also not likely to occur in vivo, citric acid and its alkali metal salts are not classified in any of the categories for carcinogenic substances.

Germ cell mutagenicity. Citric acid was not mutagenic in bacteria. In human lymphocytes, the substance induced DNA strand breaks, chromosomal aberrations at cytotoxic concentrations and a slightly increased incidence of micronuclei at non-toxic concentrations. In contrast, a chromosomal aberration test and a dominant lethal test in rats yielded negative results. Therefore, overall, citric acid can be assumed not to have any relevant genotoxic effects. This is also true for its alkali

metal salts, as the systemic effects are dependent upon the anion. For this reason, citric acid and its alkali metal salts are not classified in any of the categories for germ cell mutagens.

Absorption through the skin. There are no data available for absorption through the skin. A model calculation yielded a maximum amount for dermal absorption of 152 mg in humans after exposure to a saturated aqueous solution under standard conditions (2000 cm^2 area of skin, exposure for 1 hour). The systemic long-term NAEL in rats from studies with dietary administration of citric acid should be in the range of 200 mg/kg body weight. Using the above procedure, a concentration of 245 mg/m^3 is extrapolated from the NAEL to the human. At a respiratory volume of 10 m^3 per day and 100% absorption by inhalation, this is equivalent to a systemically tolerable amount of 2450 mg. As the absorption of citric acid through the skin is thus under 25% of the systemically tolerable amount, and similar assumptions can be made for its alkali metal salts, citric acid and its alkali metal salts are not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. In the documentation published in 1998 (documentation "Citric acid" 2001), it was concluded from the available studies in humans that citric acid is not sensitizing to the skin or airways. There are no new studies of citric acid or its alkali metal salts in humans or animals that yielded positive findings. For this reason, citric acid and its alkali metal salts are not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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