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Peracetic acid

MAK Value Documentation, addendum – Translation of the German version from 2021

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Keywords

peracetic acid; irritation; RD_{50}; genotoxicity; carcinogenicity; developmental toxicity; threshold value; maximum concentration at the workplace; MAK value; peak limitation

Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and re-evaluated the data for peracetic acid [79-21-0] to derive an occupational exposure limit value (maximum concentration at the workplace, MAK value) considering all toxicological end points. Relevant studies were identified from reviews, a literature search and also unpublished study reports were used. Peracetic acid is commercially available only in aqueous solutions, in which it exists in equilibrium with hydrogen peroxide and acetic acid. Therefore, all three substances contribute to toxicity. No specific systemic effects were observed, which is plausible because peracetic acid immediately oxidizes the tissues at the point of contact and is thereby converted to acetic acid. Peracetic acid is a promotor of skin tumours in mice. Valid long-term carcinogenicity studies with peracetic acid, particularly studies using an inhalation route, are not available. The mechanisms by which peracetic acid may induce carcinogenic effects are, as has already been demonstrated for hydrogen peroxide, local cytotoxicity leading to tissue damage and genotoxicity; both are due to the strong oxidation potency. These mechanisms do not come into play unless the endogenous detoxification capacities are overloaded. Due to this mechanism of action, hydrogen peroxide was classified in Carcinogen Category 4. As the same mechanism is likewise plausible for peracetic acid, it has also been classified in Carcinogen Category 4. Peracetic acid is the strongest irritant of the substances in the equilibrium mixture. If sensory irritation is excluded, it is also ensured that the detoxifying enzymes are not overloaded and thus neither tissue-damaging nor genotoxic effects occur. Based on the RD_{50} for pure peracetic acid in mice of 4.6 ml/m^3, the maximum concentration at the workplace (MAK value) for peracetic acid is set at 0.1 ml/m^3. The available human data are not sufficient to derive a MAK value, but do not contradict it either. As the critical effect of peracetic acid is local, Peak Limitation Category I has been designated. By analogy with hydrogen peroxide and as the data for the human experience with peracetic acid are of only limited validity, an excursion factor of 1 has been set. The few positive results for genotoxicity in vitro obtained with peracetic acid occurred at cytotoxic concentrations or in the absence of detoxification systems. All valid in vivo genotoxicity tests were negative, but the significance of the negative test results is questionable since peracetic acid induces a rapid local reaction. Therefore, it can also be concluded that classification in a category for germ cell mutagens is not required. The NOAEL for developmental toxicity in rats is 30.4 mg/kg body

Citation Note:
Hartwig A, MAK Commission. Peracetic acid. MAK Value Documentation, addendum – Translation of the German version from 2021. MAK Collect Occup Health Saf. 2024 Jun;9(2):Doc035. https://doi.org/10.34865/mb7921e9_2ad

Manuscript completed:
30 Mar 2020

Publication date:
28 Jun 2024

weight and day, which corresponds to a concentration of 53 mg/m³ at the workplace. Therefore, damage to the embryo or foetus is unlikely when the MAK value is not exceeded and peracetic acid is assigned to Pregnancy Risk Group C. Skin contact is expected to contribute only slightly to systemic toxicity. With respect to skin sensitization, there are no positive findings in humans and no reliable positive findings in animals. The respiratory symptoms that occur in exposed workers are caused by irritation.

MAK value (2020)	**0.1 ml/m³ (ppm) ≙ 0.32 mg/m³**
Peak limitation (2020)	**Category I, excursion factor 1**
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2020)	**Category 4**
Prenatal toxicity (2020)	**Pregnancy Risk Group C**
Germ cell mutagenicity	–
BAT value	–
CAS number	79-21-0
1 ml/m³ (ppm) ≙ 3.16 mg/m³	**1 mg/m³ ≙ 0.317 ml/m³ (ppm)**

Chemically, pure peracetic acid is highly reactive. It decomposes in a self-accelerating manner, accompanied by the release of heat. The oxygen–oxygen bond of the hydroperoxide is very unstable with a tendency for homolytic cleavage with the formation of two reactive radicals (ROOH ⟶ RO• + •OH). The reactive hydroxyl radical binds non-selectively to macromolecules. Due to its chemical instability and the resulting explosiveness, pure peracetic acid is scarcely available on the market (Bützer 2012).

Generally, exposure to peracetic acid solutions also results in exposure to hydrogen peroxide and acetic acid due to the production process or as a result of the hydrolysis that takes place in aqueous solution. Therefore, reference is made also to the documentations for acetic acid and hydrogen peroxide (Greim 2010 a, b) and the supplement for hydrogen peroxide (Hartwig and MAK Commission 2019).

Thus, also the methods of analysis are devised to determine the total peroxide concentration (peracetic acid and hydrogen peroxide) or the total acid concentration (peracetic acid and acetic acid) as well as peracetic acid alone (Hecht and Héry 2002).

Previous documentation (Greim 1996) is available, in which also aqueous peracetic acid is evaluated. The present addendum has been drawn up as hydrogen peroxide was classified in Carcinogen Category 4 (Greim 2010 b). It is based mainly on publicly available assessments (ECHA 2011, 2016 a, b, 2019 b) in the context of authorization under the Biocides Regulation. There is also a large number of reviews on the toxicological profile of peracetic acid (AGS 1997; ECB 2000; ECETOC 2001; NRC 2010), which are also referred to. Cited unpublished toxicological studies from companies have been made available to the Commission.

Production and use

Peracetic acid is an organic acid with strong oxidizing and thus pronounced biocidal and virucidal properties. The predominant uses of peracetic acid are in chemical synthesis, for disinfection and as a bleaching agent. Concentrations of 1% to 15% are used in germicides, disinfectants and sterilizers in the food and medical industries; higher concentrations are applied in the oxidation of organic compounds (ECETOC 2001).

Peracetic acid is produced in aqueous solution from acetic acid and hydrogen peroxide and is present in equilibrium with its starting substances (see Figure 1):

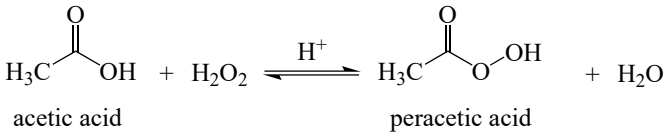

Fig. 1 Solution of peracetic acid in equilibrium with hydrogen peroxide and acetic acid

With 30% hydrogen peroxide as the starting substance, mixtures are formed with up to 15% (w/w) peracetic acid, up to 25% hydrogen peroxide, up to 35% acetic acid and up to 25% water. The position of the equilibrium depends on the temperature and pH. In pure form, peracetic acid is scarcely available on the market, but is sold in the form of these mixtures. To obtain a final product with as much peracetic acid as possible, either an excess of acetic acid (acetic acid type, epoxidation type) or hydrogen peroxide (WPO type, for example Wofasteril®, Persteril®) is used (Bützer 2012).

Peracetic acid is produced also from acetic acid and hydrogen peroxide using sulfuric acid as a catalyst. This explains the presence of sulfuric acid in most concentrated commercial products. A typical composition is (w/w): 40% peracetic acid, 40% acetic acid, 5% hydrogen peroxide, 1% sulfuric acid, 13% water together with 500 mg/l of a "stabilizer". Diluted in water, especially at concentrations of 10% to 20%, the peracetic acid decomposes. Therefore, at lower peracetic acid concentrations, decomposition is initially slower. Peracetic acid decomposes more rapidly at higher temperatures. For example, the decomposition time of a 0.2% peracetic acid solution is 1 week at 40 °C as opposed to 4 weeks at 4 °C. Likewise, a higher pH of 7 leads to 50% decomposition after 1 day, compared with almost no decomposition after 1 week at the normal pH of 2.7 for a 0.2% peracetic acid solution (NRC 2010).

1 Toxic Effects and Mode of Action

Peracetic acid is produced only in aqueous solution and exists there together with hydrogen peroxide and acetic acid. All three substances therefore contribute to the toxicity. Peracetic acid and hydrogen peroxide are both highly reactive and are rapidly degraded on initial contact with organic material. Also the acetic acid is rapidly metabolized and enters intermediary metabolism. Of the three substances, peracetic acid, due to its high oxidative reactivity, has the strongest corrosive effect and causes the strongest sensory irritation. Local burns, irritation and sensory irritation occur in a concentration-dependent manner with little or no dependence on the exposure time.

No specific systemic effects were observed, which is plausible because peracetic acid reacts completely at the site of contact.

Similar to hydrogen peroxide, the oxidative properties of peracetic acid occur when detoxification is overloaded. Genotoxicity is observed in vitro only in the absence of detoxification or at cytotoxic concentrations. The in vivo tests on systemic genotoxicity are negative due to the fact that the target sites were not reached, but are therefore also of no validity as regards local genotoxicity.

In animal studies, peracetic acid has a marked tumour-promoting effect, which may be viewed as a secondary reaction to the local irritant or oxidative effects of peracetic acid, and thus has a threshold. The hydrogen peroxide contained in the mixture, and also produced by hydrolysis in the organism, is carcinogenic.

2 Mechanism of Action

The oxidizing properties (Section 3) of peracetic acid lead to the denaturation of proteins and thus to the destruction of cell wall permeability. The high local reactivity of peracetic acid results in its rapid degradation, so that the toxic effects are consequently limited to the site of initial contact. Thus, mainly effects such as local burns and irritation are observed in animal experiments. These effects are concentration-dependent with little or no dependence on the exposure time (ECHA 2016 b).

In view of this mechanism of action, the fact that no specific systemic effects are observed is plausible. Short-term systemic exposure is possible when absorption takes place through damaged skin, but widespread systemic distribution after inhalation, oral or dermal uptake is unlikely due to the high reactivity of the substance. In vitro studies demonstrated the extremely rapid degradation of peracetic acid in the blood of rats, which takes place within seconds (see Section 3.1).

In addition to the chemical reactivity leading to the burns and irritant effects mentioned above, peracetic acid induces sensory irritation which is likewise clearly concentration-dependent, with the initial symptoms appearing shortly after the onset of exposure (ECHA 2016 b; Gagnaire et al. 2002).

2.1 Comparison of the potency of peracetic acid with that of hydrogen peroxide and acetic acid

In aqueous solution, the hydrolysis of peracetic acid takes place to form both acetic acid and hydrogen peroxide (see Section 3), so that their toxic properties come increasingly into effect (see also Greim 2010 a, b).

However, peracetic acid has a much stronger effect than hydrogen peroxide and acetic acid together. The particular cytotoxic properties can therefore not be attributed solely to the acidic or oxidizing character of acetic acid or hydrogen peroxide. For example, the hydrogen peroxide concentrations needed to act against mycobacteria are 25 times as high as those of peracetic acid (Bütze r 2012).

Two critical effects can occur in the upper respiratory tract: sensory irritation and epithelial cytotoxicity. The former results from stimulation of the ends of the trigeminal nerve, which is manifest as a burning sensation, while cytotoxicity reflects cellular destruction accompanied by irritation and inflammation (Maier et al. 2010).

2.1.1 Cytotoxicity

The cytotoxic effect of peracetic acid is stronger than that of the two hydrolysis products hydrogen peroxide and acetic acid together, although the latter is the stronger acid (see Table 1) and hydrogen peroxide likewise has oxidative properties (Bütze r 2012).

Tab. 1 Comparison of pk_a values at 20–25 °C (ECHA 2019 a, b, 2020 a, b)

Substance	pk_a value
acetic acid	4.76
hydrogen peroxide	11.62
peracetic acid	8.24
sulfuric acid	1.92

Evidence of the stronger cytotoxic effect of peracetic acid was found also in comparative studies with peracetic acid and hydrogen peroxide in unpublished mutagenicity tests in Salmonella typhimurium (ECB 2000).

One possible explanation is that peracetic acid is more lipophilic and reactive than hydrogen peroxide. Peracetic acid can bind more easily to the cell wall and thus has a stronger oxidative effect (Bütze r 2012), although the oxidation potential (1.76 V) is slightly lower than that of hydrogen peroxide (1.80 V) (Du et al. 2018). Studies of the reaction

kinetics and oxidation of various amino acids by peracetic acid showed it to have the fastest reactivity with cysteine, methionine and histidine. The oxidation of amino acids was faster at pH 5 and 7 than at pH 9. The presence of low concentrations of hydrogen peroxide contributed little to the reaction. At the same concentration (131 µM), hydrogen peroxide oxidized 15% cysteine, 5.5% methionine and 3.4% histidine in 30 minutes, whereas peracetic acid oxidized 100% cysteine, 65% methionine and 28% histidine. Primarily, thiol, thioether and imidazole groups were oxidized by peracetic acid (Du et al. 2018). The consequences are denaturation of proteins and disruption of cell wall permeability (ECHA 2016 b).

In the case of hydrogen peroxide, cytotoxic (and genotoxic) effects occur only when the detoxification capacity of the organism by catalase and glutathione (GSH) peroxidase is overloaded and reactive oxygen species are released (Greim 2010 b). Detoxification by catalase and peroxidase is possible also for peracetic acid. However, catalase cleaves hydrogen peroxide faster than peracetic acid (Bützer 2012, see also Section 3.2). No information could be found on the degradation rate with peroxidase.

In addition, non-enzymatic degradation pathways such as hydrolysis or dismutation have been demonstrated for peracetic acid (see Section 3.2), producing the less cytotoxic substances acetic acid, hydrogen peroxide and oxygen. Furthermore, reactions with reducing substances such as cysteine and GSH contribute to detoxification.

Like with hydrogen peroxide, the oxidative properties of peracetic acid thus occur when detoxification is overloaded; in the case of peracetic acid, detoxification takes place not only via catalase and peroxidase, but also non-enzymatically.

2.1.2 Sensory irritation

Also the RD_{50} in mice for peracetic acid (5.4 ml/m^3) is lower than that of hydrogen peroxide and acetic acid by a factor of about 20 and about 40, respectively. Therefore, peracetic acid contributes almost alone to the sensory irritation in a mixture of peracetic acid : acetic acid : hydrogen peroxide of 36% : 53% : 11%. At the highest concentration of the mixture examined in the RD_{50} test (peracetic acid, acetic acid, hydrogen peroxide: 11.6, 17.2 and 3.5 ml/m^3), in addition to peracetic acid only acetic acid acted. This is because of the percentages in the mixture and the higher effect thresholds for acetic acid and hydrogen peroxide of 16.1 and 7.0 ml/m^3, respectively. At 17.2 ml/m^3, the concentration of acetic acid was just above its effect threshold (see Section 5.1.1.2; Gagnaire et al. 2002). From this it can be concluded that for low concentration mixtures in equilibrium, where peracetic acid does not cause sensory irritation, no sensory irritation is caused by acetic acid or hydrogen peroxide either.

2.2 Mechanism of the genotoxic effects

The few positive results in genotoxicity tests in vitro with peracetic acid occurred at cytotoxic concentrations or in the absence of detoxification systems (S9 mix) (Section 5.6.1). The latter suggests that in this case catalase and/or peroxidase are of greater importance for detoxification and therefore the positive findings may be due solely to the hydrogen peroxide produced. As described, this is based on the fact that hydrogen peroxide, acetic acid and oxygen are formed in aqueous solution by non-enzymatic degradation pathways such as hydrolysis or dismutation. Hydrogen peroxide, on the other hand, is more long-lived than peracetic acid and can therefore presumably penetrate more readily into the cell nucleus and lead to a genotoxic effect there. If the cell system is appropriately equipped with detoxification enzymes, no genotoxic effects are therefore observed below the cytotoxicity threshold (see Section 5.6.1).

The findings on the genotoxicity of peracetic acid are in agreement with the results for **hydrogen peroxide** (see Greim 2010 b): "Hydrogen peroxide was found to be genotoxic *in vitro* in a series of test systems; bacterial strains without catalase were particularly sensitive, compared with mammalian cells with high catalase activity, which were resistant. *In vivo*, however, DNA repair synthesis (UDS) was not observed in liver cells of rats, neither were chromosomal aberrations in bone marrow cells of rats. Nor were micronuclei observed in polychromatic erythrocytes of catalase-deficient mice or in the bone marrow cells of Swiss mice. *In vivo*, therefore, sufficient catalase or other detoxifying enzymes seem to be present for protection against the systemic genotoxic effects of hydrogen peroxide."

Acetic acid induced genotoxicity in vitro only if the acid in the test medium had not been buffered. Here, too, the results from the available in vivo studies were negative. Acetic acid enters intermediary metabolism and is degraded (ECHA 2019 a; Greim 2010 a).

In the case of hydrogen peroxide, it is assumed that cytotoxicity occurs at lower concentrations than genotoxicity (Greim 2010 b). The same conclusion can be drawn for peracetic acid on the basis of the available data.

In view of all these results, it can be assumed that peracetic acid, like hydrogen peroxide, has no systemic genotoxic potential after ingestion of the substance, but, as with hydrogen peroxide (Greim 2010 b), genotoxicity cannot be excluded due to oxidative damage on local contact.

2.3 Local carcinogenic effects

In an animal experiment, peracetic acid was found to have a marked tumour-promoting effect on the skin of mice. This can be regarded as a secondary reaction to the local irritant or oxidative effects of peracetic acid and, in this case, has a threshold concentration. It is possible that the substance also has a weak initiating effect (Bock et al. 1975). This cannot be conclusively verified due to the lack of further studies. Substances with non-specific tumour-promoting mechanisms, which are mainly observed in high dose ranges, do not lead to tumour development in humans. When such substances are administered without an initiator, tumours develop only in the sensitive mouse. Such results from initiation–promotion studies in mouse skin are not considered by the Commission to be relevant for the classification of the substance (Schwarz et al. 2015).

As for hydrogen peroxide (Greim 2010 b), it can be assumed for peracetic acid that cytotoxicity occurs at lower concentrations than genotoxicity. Cytotoxicity occurs only when the detoxification capacities are overloaded by enzymatic and non-enzymatic processes (see Section 3.2); thus, there is a threshold for cytotoxic effects, namely the irritant effects of peracetic acid. Possible local carcinogenic effects (see also Section 5.7) result from a combination of genotoxicity due to oxidative damage with proliferation stimuli caused by the irritant effects.

Valid long-term studies of the carcinogenicity of peracetic acid are not available.

In long-term rodent studies with **hydrogen peroxide**, tumours were observed only when the capacity of detoxifying enzymes was overloaded. Hydrogen peroxide is therefore classified in Carcinogen Category 4. In mice, hydrogen peroxide concentrations of 0.1% and above in drinking water increased the incidences of duodenal carcinomas in a concentration-dependent manner, with the highest incidence in strains with the lowest catalase activity. In rats, which have a much higher duodenal catalase activity than mice, duodenal tumours did not occur in a 2-year study at hydrogen peroxide concentrations up to 0.6%. Forestomach papillomas occurred only at hydrogen peroxide concentrations of 1% and above in drinking water in a short-term study in rats. In addition, tumour-promoting effects were demonstrated in rats (forestomach papillomas at 1%, intestinal tumours at 1.5%), hamsters (cheek pouch carcinomas at 30%) and mice (skin papillomas at 6%) (Greim 2010 b).

In summary, the mechanisms of possible carcinogenicity of peracetic acid, as already documented for hydrogen peroxide (see Greim 2010 b), are the tissue-damaging local irritant effects with subsequent genotoxicity. In addition, if the endogenous detoxification capacities are not overloaded, genotoxicity plays no or only a minor role.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Peracetic acid reacts immediately on contact with biological material. The oxygen atoms of the peroxide group have the oxidation number –1 and, due to their electron configuration, have a high readiness to accept electrons and thus react as oxidizing agents (Bützer 2012).

3.1.1 In vivo

3.1.1.1 Inhalation

Kinetic studies with inhalation exposure to peracetic acid (in mixtures with hydrogen peroxide and acetic acid) are not available. Due to its ready solubility in water, effective exposure in the upper respiratory tract can be expected (ECHA 2016 a). However, since peracetic acid reacts immediately upon tissue contact due to its oxidative effect, its systemic availability is negligible. This has already been demonstrated in studies with rat blood (see Section 3.1.2.2) (ECHA 2019 b).

3.1.1.2 Oral

In the stomach, at a pH of about 2, predominantly non-dissociated peracetic acid is present, which allows effective uptake into the cells. After absorption, the neutral pH range inside the cell (pH of 7.4) causes hydrolysis and the further formation of hydrogen peroxide and acetic acid. In addition to other non-enzymatic rapid degradation pathways (see Section 3.2), also catalases are present in saliva and gastric juice, which can degrade peracetic acid. This means that the systemic distribution of peracetic acid is severely limited (ECETOC 2001).

3.1.1.3 Dermal

When the skin of rats is exposed to corrosive concentrations of ^{14}C-labelled peracetic acid (5.02%), the uptake of ^{14}C is considerable because the natural barrier function of the skin is destroyed by the corrosive effects. Specifically, in the 1994 study conducted in accordance with OECD Test Guideline 417, 100 µl peracetic acid (in the form of Proxitane®0510: 5% peracetic acid, 18% hydrogen peroxide, 15% acetic acid, stabilizing carrier and water; both peracetic acid and acetic acid were ^{14}C-labelled) was applied to the skin of 4 male Sprague Dawley rats over an area of 4.5 cm^2. The dose was equivalent to 457 µl Proxitane®0510/kg body weight or 25 mg peracetic acid/kg body weight (at a concentration of 5.02% peracetic acid in Proxitane®0510 and assuming a density of 1.1 g/cm^3). Another group received 100 µl of ^{14}C-labelled acetic acid (517 µl/kg body weight; concentration not specified). Water-soluble vapours of peracetic acid and acetic acid, exhaled CO_2, urine and faeces were collected and analysed. After 72 hours, the animals were killed and the radioactivity in the organs was determined. The liver, kidneys, heart, lungs, testes, brain, stomach, small intestine, large intestine (each with contents), samples from muscle and adipose tissue, and the carcass were examined. In the peracetic acid group, 10.5% of the applied radioactivity was excreted in the urine and 2.6% in the faeces, 35.7% was exhaled as $^{14}CO_2$ and 12.1% remained in the tissues and carcass (highest concentrations in the carcass, liver, gastrointestinal tract and skin). In the acetic acid group, the corresponding values were 16.7%, 3.4%, 27% and 6.9%. Thus, in summary, excretion via the faeces was about the same in both groups, the proportion of tissue-bound radioactivity was higher in the peracetic acid group and the proportion in urine was higher in the acetic acid group. The exposed skin was significantly damaged by peracetic acid after 3 hours of exposure. No skin damage occurred in the acetic acid group. The amount of radioactivity in the skin was similar in both groups. Similarly, a large fraction was converted to CO_2 in both groups. In the acetic acid group, 20% to 30% of the administered dose was volatile and detected as unchanged acetic acid within the first 24 hours. Virtually no evaporation from the treated skin was observed in the peracetic acid group. The total recovery in the air (all volatile substances including CO_2), urine, faeces, tissue and carcass was approximately 61% of the administered radioactivity in the peracetic acid group and 73% in the acetic acid group. Metabolites were not analysed. About 30% to 60% of the $^{14}CO_2$ in the peracetic acid group was detected only after an initial lag phase of 1 hour. This presumably resulted from reduced blood flow and poorer distribution due to microembolism caused by local oxygenation and skin damage. Upon contact with the peracetic acid, the skin barrier injury leads to acetic acid by degradation (Section 3.2), which is then systemically available, metabolized and eliminated. This is also shown by in vitro studies in rat blood and studies with catalase from human erythrocytes, in which immediate degradation of peracetic acid takes place. Thus, there is no systemic availability of peracetic acid. The observation of the relatively high distribution of radioactivity in tissues after dermal exposure to the peracetic acid solution can be explained by the introduction of acetic acid into the C2 pool, which is needed to maintain intermediary metabolism. The authors concluded from the similar recovery of radioactivity following acetic acid and peracetic acid treatment

that the substance absorbed is essentially acetic acid and not peracetic acid, because peracetic acid forms acetic acid on the surface of the skin due to its reactivity (ECHA 2019 b; OECD 2008). The total recovery in this experiment is very poor and is not explained.

As peracetic acid is used in the disinfection of pigsties, a peracetic acid solution (presumably aqueous, no other details) or diluted Wofasteril® (product not further specified) was applied to the skin of a total of 19 pigs for 120 days to investigate the effects on the skin and absorption of the substance. In both cases, the peracetic acid concentration in the solution was 1.5%. Every 2 days 250 ml was applied to the skin of the animals (initial weight 33 kg) and the amount remaining in muscle, liver and adipose tissue was examined at the end of the study. After the animals were slaughtered, no histopathological changes were found in the samples. Also, no effects were observed with regard to the pH and colour of the meat after the dermal treatment. The results of the analyses of muscle, liver and adipose tissue for peracetic acid and its metabolites were negative. The animals exhibited severe skin and respiratory irritation (Busch and Werner 1974; Krüger and Jancke 1976).

3.1.2 In vitro

3.1.2.1 Dermal

In an in vitro skin penetration test, 15.7 cm^2 freshly prepared pig skin was incubated for 24 hours at 37 °C with 110 ml of a 0.8% aqueous peracetic acid solution (non-corrosive concentration, diluted from a solution of 40% peracetic acid, 5% hydrogen peroxide and 40% acetic acid). The receptor fluid was analysed every 2 hours for active oxygen (detection limit 2 µg). In an experiment with skin damaged in deeper layers, active oxygen could be detected in the receptor fluid (calculated as 2.6 mg peracetic acid, which corresponds to the absorption of 0.3%). Peracetic acid could not be detected in the receptor fluid when intact skin was used (Krüger and Jancke 1976).

3.1.2.2 Blood

There are two studies with male Wistar rats from 2003 and 2005 investigating the degradation of peracetic acid in blood diluted 1000-fold with physiological saline (ECHA 2019 b).

In the first test, the peracetic acid concentrations were 1 and 5 mg/l. A test batch without blood served as a control. The solutions were incubated at 37 °C and samples were taken immediately after mixing and after 5, 15, 30, 60, 120 and 240 minutes. The peracetic acid concentration was determined by analysing the resulting methyl *p*-tolyl sulfoxide by HPLC after adding methyl *p*-tolyl sulfide to the samples. A decrease in the nominal peracetic acid concentrations of 1 and 5 mg/l by 62% and 39%, respectively, was determined as early as 20 seconds after blood and peracetic acid solution were added together. After 5 minutes, less than 0.1 mg/l peracetic acid was present in the blood solution. Thus, the half-life in 1000-fold diluted blood is less than 5 minutes. In the control without blood, the degradation of peracetic acid was slower with a half-life of over 4 hours (ECHA 2019 b).

In the second test, Peraclean 15® was used, consisting of 15.22% (w/w) peracetic acid and 14.27% (w/w) hydrogen peroxide. The test concentrations were 0, 5.4, 10.8 and 21.6 mg peracetic acid/l and 0, 5.1, 10.1 and 20.3 mg hydrogen peroxide/l. The peracetic acid concentration was analysed by means of the Reflectoquant® assay. Samples were taken immediately before and after mixing with blood after 5, 15, 30, 60, 120 and 240 minutes and after 24 hours. For solutions with peracetic acid concentrations of 10 mg/l or less, degradation was rapid. The half-life in 1000-fold diluted blood was less than 5 minutes. The concentration of 21.6 mg/l resulted in an initial sharp decrease (by 94%), whereas the concentration decreased more slowly at later time points (ECHA 2019 b).

The test concentrations of 1 to 20 mg peracetic acid/l blood are to be regarded as high compared with the concentrations to be expected in human blood during normal handling and use of peracetic acid solutions. In addition, much greater degradation is expected in undiluted blood than in 1000-fold diluted blood. Thus, in undiluted blood, the half-life should be a few seconds or less. For this reason, systemic availability of peracetic acid is unlikely. Degradation of

peracetic acid in blood leads to the formation of acetic acid and oxygen (see also Section 3.2). Acetic acid is a physiological substance that is essential to intermediary metabolism and can be excreted with the urine (OECD 2008).

3.2 Metabolism

In vitro studies with numerous enzymes revealed that there is no significant degradation of peracetic acid by lipases, proteases and butyrylcholinesterases (Kirk et al. 1994).

During the degradation of peracetic acid, reactive oxygen species (ROS) can be formed. However, these are formed locally and not systemically and the cells can initially protect themselves against the stress caused by ROS with various mechanisms (Giorgio et al. 2007). These are, for example, the non-enzymatic degradation of peracetic acid by hydrolysis, dismutation, reaction with reducing substances (cysteine, GSH, vitamin A, C, E) or the enzymatic degradation by catalase or peroxidase (ECETOC 2001; Giorgio et al. 2007).

3.2.1 Hydrolysis

In aqueous solution (in the absence of metal ions), peracetic acid hydrolyses in a pH-dependent manner to form acetic acid and hydrogen peroxide (Greim 1996).

While peracetic acid as an undissociated acid is relatively stable at pH values around 2 (gastric environment), it is rapidly hydrolysed at pH values of 7 or higher, as found in the small intestine or after local absorption into cells (cellular pH 7.4) (ECETOC 2001).

3.2.2 Dismutation

Especially in the presence of catalytically active metal ions, peracetic acid is degraded via a dismutation reaction to form oxygen and acetic acid (ECETOC 2001).

3.2.3 Reaction with reducing substances (cysteine, GSH)

The reaction with reducing substances such as cysteine or GSH leads to the rapid degradation of peracetic acid to acetic acid and is probably also important for metabolic detoxification (ECETOC 2001).

3.2.4 Enzymatic degradation

3.2.4.1 Peroxidase

The conversion of peracetic acid to acetic acid can be catalyzed by GSH peroxidases and leads to the oxidation of the hydrogen donor GSH (Greim 1996).

3.2.4.2 Catalase

Several studies have shown that peracetic acid is a substrate of catalase. The reaction equation is $2\,CH_3C(O)OOH \longrightarrow 2\,CH_3C(O)OH + O_2$. The mechanism is shown in detail in Figure 2 (ECETOC 2001).

The first step is a 1st order reaction of catalase with peracetic acid leading to the conversion of the enzyme substrate complex to the oxidized state (see Figure 2) and the release of acetic acid. The oxidized catalase is spectrophotometrically identifiable as a stable intermediate. The second step also follows 1st order reaction kinetics with respect to the theoretical intermediate. Regardless of the peracetic acid concentration, the free catalase regenerates in a reduction reaction (kinetic constant $k_4 = 2 \times 10^{-4}$/s). In this step, which is the rate-limiting step, oxygen and a second molecule of acetic acid are released. At steady state, the conversion of peracetic acid is independent of its concentration and the zero order rate constant is 4×10^{-7}/s (ECETOC 2001).

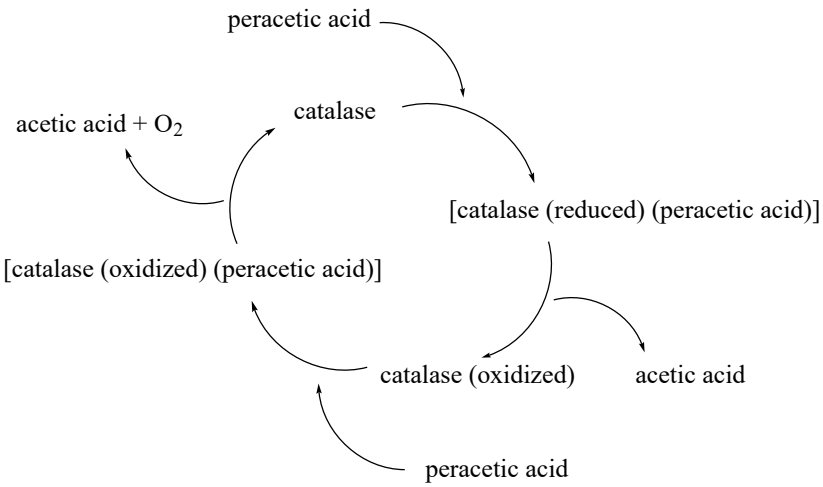

Fig. 2 Degradation of peracetic acid by catalase (according to ECETOC 2001)

The degradation of peracetic acid (0.05%) in calf serum occurred within 4 hours and increased significantly after the addition of whole blood; this is due to the presence of erythrocytes, which contain soluble catalase (ECETOC 2001).

The catalase-induced degradation of peracetic acid (see Figure 2) to form acetic acid was demonstrated in another experiment in vitro with catalase from human erythrocytes. The oxidation of catalase was pH-dependent. At pH values of 5.8 to 6.5, the rate of formation was in the same range, but slowed down when peracetic acid was deprotonated (pk_a peracetic acid = 8.2). Below a pH of 5.8, the oxidized catalase was not stable and decomposed before a steady-state was achieved (Palcic and Dunford 1980).

The significance of the catalase reaction becomes apparent when considering the distribution of catalase in the mammalian organism. Catalases are present in a wide range of concentrations in almost all mammalian cells and are particularly efficient in metabolizing large amounts of hydrogen peroxide. Catalases are located in sub-cellular compartments, mainly in peroxisomes. Soluble catalases are found in erythrocytes (ECETOC 2001).

Catalases are abundant also in skin and mucous membranes (ECETOC 2001; ECHA 2019 b). The highest concentrations are found in the cells of the duodenum, liver, spleen, kidneys, blood, mucous membranes and other highly vascularized tissues. The lowest concentrations are found in the brain, thyroid, testes and connective tissue cells. Degradation of peracetic acid by the catalase present in saliva and gastric juice has also been demonstrated (ECETOC 2001).

3.2.4.3 Comparison with hydrogen peroxide

Unlike hydrogen peroxide, peracetic acid is only slowly decomposed by catalase (Bützer 2012). Rate-limiting is the second step in the catalase cycle (reduction), while the first step occurs independently of the peracetic acid concentration. This differs from the reaction of catalase with hydrogen peroxide, the rate of which depends on the substrate concentration (ECETOC 2001).

Hydrogen peroxide is thus rapidly degraded by catalase. The restoration of equilibrium in a peracetic acid solution is probably slow. The influence of the degradation of hydrogen peroxide from the equilibrium solution on the degradation of peracetic acid cannot be estimated from the available data (ECETOC 2001).

3.3 Summary: toxicokinetics and metabolism

Peracetic acid is strongly oxidizing and reacts immediately on contact with biological material. Studies of absorption, metabolism and elimination after inhalation of peracetic acid are not available. Due to its high solubility in water, effective absorption of the substance in the upper respiratory tract would be expected, but this competes with its local reactivity. Ready penetration into cells is possible also in the stomach at a pH of about 2. After dermal exposure, peracetic acid penetrates the tissues, especially if the skin is damaged. In the case of penetration, however, the absorption of peracetic acid into the blood circulation is limited due to microembolism caused by the released oxygen in capillaries and surrounding tissues. In vitro studies with rat blood demonstrated immediate degradation of peracetic acid with a half-life of a few seconds, which severely limits its systemic availability and distribution. Peracetic acid is degraded by catalases in the blood, gastric juice, saliva and a wide variety of organs. The degradation of peracetic acid by catalase is slower than that of hydrogen peroxide. The catalase reaction is independent of the peracetic acid concentration and appears to saturate rapidly. From studies with different pH values, it can be concluded that the catalase reaction takes place preferentially with the undissociated acid. In addition, non-enzymatic degradation of peracetic acid by hydrolysis and dismutation, and reduction by cysteine and GSH occur. Peracetic acid is converted to hydrogen peroxide, acetic acid and oxygen. A large fraction enters intermediary metabolism. Elimination occurs predominantly in the form of CO_2 and with the urine.

4 Effects in Humans

4.1 Single exposures

Occupational accidents resulted in skin burns and reversible respiratory obstructive findings (AGS 1997).

In a sensory irritation study, an aerosol was generated in a henhouse from 1:20 diluted “Peratrol” (1904 mg peracetic acid/l), which was available in the form of a 4% peracetic acid equilibrium solution (no further information on composition is available), after which “test subjects” (number not specified) were exposed to various concentrations. To determine the spread and distribution of the peracetic acid concentrations, analyses were carried out at various distances from the fogging unit. The fogging unit was placed approximately one meter above the ground. Determinations were made at the apex of the roof, on the floor and at the sides of the shed (Fraser and Thorbinson 1986). In ECETOC (2001), it is reported that the air samples were drawn through an alkaline phenolphthalein solution. Peracids and hydrogen peroxide caused discoloration of the solution due to the formation of phenolphthalein, which was detected by spectrophotometry. Thus, the total peroxide concentration was determined. This was then reported as hydrogen peroxide because it was suspected that the product used had a high hydrogen peroxide concentration, which, however, is not confirmed (ECETOC 2001).

The upper half of Table 2 lists concentrations, the time of analysis and physiological responses to the peracetic acid starting 2 minutes after the fogging unit was turned on. The authors do not mention the number of exposed persons. At 5 ml/m^3 lacrimation and nasal irritation occurred, and at ≥ 2.5 ml/m^3 extreme nasal irritation. A concentration of 2 ml/m^3 caused severe discomfort and irritation of the mucous membranes and was considered unbearable in one case and tolerable for 2 minutes in the other. After 23 minutes, the fogging unit was turned off and refilled. During this time, the concentration of peracetic acid dropped to < 0.5 ml/m^3 and 0.5 to 1.0 ml/m^3 at 0.3 and 2 meters above ground level, respectively. Slight discomfort of the mucous membranes of the nose and eyes was reported during this phase. For the next 1.25 hours, the concentrations were 2.0 to 3.0 ml/m^3 and were associated with unbearable or extreme discomfort.

Tab. 2 Symptoms at various peroxide concentrations (Fraser and Thorbinson 1986)

Time in minutes	ml peroxide[a)]/m³	Symptoms
from 2 minutes after switching on the fogging system		
0	5.0	lacrimation, extreme discomfort, irritation of nasal membranes
7	5.0	lacrimation, extreme discomfort, irritation of nasal membranes
23	0.5–1.0 < 0.5	slight discomfort of the mucous membranes of the nose and eyes, decreasing with decreasing concentration
35	2.0	irritation intolerable
90	2.5	extreme discomfort of nasal membranes
100	2.5	extreme discomfort
	3.0	extreme discomfort
105	3.0	extreme discomfort
110	2.0	irritation tolerable for 2 minutes
after switching off the fogging system		
5–10	2.0	extreme discomfort of mucous membranes
15–20	1.0–1.5	discomfort of mucous membranes
25	1.0	discomfort tolerable
30	0.5–1.0	mild discomfort
35	0.5	no discomfort
45	≤ 0.5	no discomfort

[a)] the aerosol probably included a large proportion of hydrogen peroxide

The lower section of Table 2 lists the concentrations and the physiological responses observed after the fogging unit was turned off. The concentrations decreased from 2.0 ml/m³ to ≤ 0.5 ml/m³ within 45 minutes. During this time, the irritant effects decreased from extreme discomfort of mucous membranes to mild discomfort at 0.5 to 1.0 ml/m³ to no discomfort at 0.5 ml/m³. No irritation of the lungs occurred at any time during this test (Fraser and Thorbinson 1986). Due to the unclear person-related peracetic acid concentrations, the lack of information on the number of test persons and the methods with which the different effects on the eyes and nose were recorded, this study cannot be used to derive the MAK value.

In a study not available in the original, exposure to peracetic acid vapour in caprolactone monomer production was determined over a 3-hour period. In one area, the concentrations were 0.5 to 0.6 ml/m³ (1.56–1.87 mg/m³). This was considered to be not immediately irritating but unpleasant over an extended period of time (no other details) (NRC 2010). In the ECETOC report, other concentrations were reported with the same finding: concentrations of 0.28 to 0.38 ml/m³ (0.9–1.2 mg/m³) were not immediately irritating, but were considered unpleasant over an extended period (ECETOC 2001; see Table 3). In the second concentration range, the peracetic acid concentrations were 0.13 to 0.17 ml/m³ (0.4–0.5 mg/m³) and tolerable and not unpleasant. The author and his co-worker were exposed for most of the time to average peracetic acid concentrations of 0.17 ml/m³ (0.53 mg/m³) (10-minute sampling period) and during the 3-hour study did not experience lacrimation. Based on these data, the author recommended 0.15 ml/m³ (0.47 mg/m³) as an 8-hour occupational exposure limit value for peracetic acid (ECETOC 2001; NRC 2010). The authors of ECETOC (2001) described that the same method of determination was used as in the study described above. However, since vapour instead of aerosol was present, they assume that due to the higher vapour pressure of peracetic acid compared with that of hydrogen peroxide, in this case the determined peroxide concentration consisted predominantly of peracetic acid (ECETOC 2001).

As described in Section 2.1, it may be assumed that in the low concentration range exclusively the peracetic acid in the mixture is responsible for the sensory irritation. The thresholds for sensory irritation caused by hydrogen peroxide and acetic acid are higher (Gagnaire et al. 2002; see also Section 5.1.1).

Tab. 3 Symptoms at various peracetic acid concentrations (ECETOC 2001)

Peracetic acid in ml/m³ (mg/m³)	Symptoms
0.28–0.38 (0.9–1.2)	not immediately irritating, but considered unpleasant over an extended period of time
0.13–0.17 (0.4–0.5)	tolerable and not unpleasant

In summary, exposure to peracetic acid vapour (determined over a 3-hour period) at concentrations of 0.28 to 0.38 ml/m³ (0.9–1.2 mg/m³) is not acutely irritating but is considered unpleasant with prolonged exposure. Peracetic acid concentrations of 0.13 to 0.17 ml/m³ (0.4–0.5 mg/m³) were tolerable and not unpleasant.

The two volunteers were exposed for most of the time to average peracetic acid concentrations of 0.17 ml/m³ (0.53 mg/m³) (10-minute sampling period); no lacrimation occurred during the 3-hour exposure period (ECETOC 2001; NRC 2010).

4.2 Repeated exposure

After several years of occupational exposure to peracetic acid formulations, no effects detectable by regular monitoring examinations (routine) or by lung function tests have been observed in workers (AGS 1997).

Peracetic acid concentrations in air of 4.6 mg/m³ (aerosol made up of a 1% peracetic acid solution with 30% ethanol, about 1.5 ml/m³) used for room disinfection were tolerated by clinic patients and staff without symptoms of discomfort (Dworschak and Linde 1976). The same peracetic acid concentration of 4.6 mg/m³ was used twice daily for 20 weeks in nurseries in the presence of the children (n = 48–49). A statistically significant reduction in morbidity (5.5%) from acute respiratory illness was observed in the exposed group compared with the value in the unexposed control group (11.2%). The exposure to a peracetic acid concentration of 4.6 mg/m³ (about 1.5 ml/m³) was tolerated by the children without reaction (Pickroth and Fiedler 1978).

The large-scale use of the disinfectant Wofasteril® (0.5% solution corresponding to 0.2% peracetic acid) in unventilated rooms resulted in irritation of the eyes and airways in the persons working there, which was not characterized in more detail. Under these conditions, the peracetic acid concentration in the air was 3 to 8 mg/m³ (about 1–2.5 ml/m³) (Greim 1996).

In agreement with this report are a number of inadequately documented accounts from the health service and from farming which describe the irritation of the airways as being tolerable during exposure to peracetic acid concentrations of 2 mg/m³ (about 0.6 ml/m³) and intense at concentrations of 3 to 5 mg/m³ (about 1–1.6 ml/m³) (Greim 1996).

The exposure of 150 employees to peracetic acid at 45 workplaces of a university hospital was studied in the period between 1989 and 1990. The peracetic acid used for disinfection and sterilization was applied as an aqueous solution in concentrations of 0.12% and 2%. The aqueous solutions contained small amounts of sulfuric acid in addition to acetic acid and hydrogen peroxide, as they were prepared from a commercial concentrate containing about 40% peracetic acid, 46% acetic acid, 3.5% hydrogen peroxide, 0.5% sulfuric acid and 10% water (all by weight). Determinations at each workplace were carried out 2 to 6 times. Over an 8-hour working period, concentrations varied from below the detection limit (0.005 mg peracetic acid/m³) to 1.84 mg peracetic acid/m³ (about 0.58 ml/m³). Of the values determined, 60% were below 0.1 mg/m³ and only 5% exceeded 1.0 mg/m³ (about 0.3 ml/m³). A number of workers complained of irritation of the eyes, nasal and pharyngeal mucous membranes, and redness and itching of the skin, especially on the hands and face. During room disinfection, usually considerable coughing was induced. At which concentrations the symptoms occurred was not stated (Schaffernicht and Müller 1998).

Hospital staff exposed to aqueous peracetic acid solutions employed in surface disinfection were interviewed using a questionnaire to determine potential health problems. Symptoms that improved outside the workplace were assessed as workplace-related. Exposures to peracetic acid, hydrogen peroxide and acetic acid were calculated in sum according to an American Conference of Governmental Industrial Hygienists (ACGIH) formula for additive mixtures. The exposed persons were divided into exposure groups. The concentrations of the individual substances determined in the air samples are not reported. Therefore, these results cannot be used to derive an occupational exposure limit value for peracetic acid. Only for the maternity ward with 28 employees are the analysed values reported. Data were

collected over the entire work shift in the breathing zone and were 0.025 ml/m³ for peracetic acid, 0.166 ml/m³ for hydrogen peroxide and 0.142 ml/m³ for acetic acid. Data for peak exposures are not available. The frequency of watery eyes was increased in a statistically significant manner in workers in the maternity ward compared with that in clinic areas with low exposure (no other details). The prevalence of shortness of breath, coughing, wheezing, watery eyes and the diagnosis of asthma was increased in a statistically significant manner among the 28 workers compared with that in the US population: watery eyes (standardized morbidity ratio (SMR): 1.70; 95% confidence interval (CI): 1.06–2.72), previous asthma (SMR: 2.50; 95% CI: 1.07–5.85), current asthma (SMR: 3.47; 95% CI: 1.48–8.13). This study has numerous shortcomings, which are listed also by the authors. Among them are co-exposure to other cleaning agents, especially quaternary ammonium compounds, which were primarily used in surface disinfection (Casey et al. 2017). These results therefore cannot be included in the evaluation of peracetic acid.

In another publication regarding the study described above, concentrations of 0.001 to 0.048 ml/m³ for peracetic acid, 0.005 to 0.511 ml/m³ for hydrogen peroxide and 0.006 to 0.530 ml/m³ for acetic acid were reported for 49 air samples from the entire clinic. Cleaning personnel who used a product containing peracetic acid, hydrogen peroxide and acetic acid reported eye (44%) and upper (58%) and lower airway (34%) symptoms that occurred during the workshift. Acute nasal and eye irritation were associated in a statistically significant manner with increased exposure to peracetic acid and hydrogen peroxide as well as the total mixture of peracetic acid, hydrogen peroxide and acetic acid. Shortness of breath when hurrying on level ground or walking up a slight incline was likewise associated in a statistically significant manner with increased exposure to peracetic acid and hydrogen peroxide and to the mixture of peracetic acid, hydrogen peroxide and acetic acid (Hawley et al. 2017). Again, data for peak exposures are not available. In addition, co-exposures to quaternary ammonium compounds cannot be excluded (see Casey et al. 2017), so that these data cannot be used to derive a MAK value for peracetic acid.

In a clinic, 0.5% peracetic acid was sprayed several times a day for disinfection purposes. Of the nurses employed, 72.3% reported coughing, skin irritation, lacrimation and eye discomfort during the 8-hour workshift. Exposure was estimated to be 2.1 mg/m³ (0.67 ml/m³) (You et al. 2006).

In summary, in humans, the respiratory tract and the eyes are the target organs for acute and repeated exposures to vapour or aerosol. Systemic exposure is negligible (see also Sections 2 and 3).

The available data in humans provide ample evidence for the concentration range at which sensory irritation begins, but there are uncertainties arising from the exposure determinations as regards the analytical methods used, the exposure duration, peak exposures and reported clinical symptoms. The pungent odour of peracetic acid may have an influence on the symptoms reported, as odour and irritant effects are often confused in this case (Dalton 2003). The human data therefore do not suffice to derive a MAK value, but can be used as a supplement to the animal tests.

In an unpublished study in which peracetic acid in air was determined directly using FTIR spectroscopy, the odour threshold was 0.047 ml/m³ (0.15 mg/m³) or slightly lower (ECETOC 2001).

4.3 Local effects on skin and mucous membranes

Hand disinfection solutions with 0.5% peracetic acid caused irritation of the skin, whereas at 0.2% this effect did not occur (OECD 2008).

4.4 Allergenic effects

4.4.1 Sensitizing effects on the skin

There are no findings available.

4.4.2 Sensitizing effects on the airways

A 48-year-old anaesthesia assistant (non-smoker) in an endoscopy unit of a gastroenterology department developed workplace-related respiratory symptoms (rhinorrhoea, conjunctivitis, a dry cough without wheezing, breathlessness and tightness of the chest) about 5 months after the onset of exposure to a peracetic acid–hydrogen peroxide mixture. Symptoms started on Monday evening after 8 hours of exposure and persisted for the remainder of the week. After 8 days off work, the symptoms regressed completely. At work, the endoscopy equipment was treated for 15 minutes in detergent and disinfectant baths containing quaternary ammonium compounds before further cleaning. Daily for 5 days of the week, both manual and automated cleaning procedures were performed in a closed room. Baths of the peracetic acid–hydrogen peroxide mixture were used for manual disinfection, and only peracetic acid was used for automatic disinfection. The sterilization room had a ventilation system with a chemical filter. The exposure levels for peracetic acid are not available; the highest acetic acid concentration determined 20 minutes after the activity with the peracetic acid–hydrogen peroxide mixture was 1.6 ml/m^3. Protective clothing and gloves were worn during activities, and a filterless mask and goggles were used when the dishwasher was filled with disinfectant every other day. After about 2.5 years of asymptomatic work, a 47-year-old auxiliary nurse (smoker, 30 years, 20 cigarettes daily) in an otorhinolaryngology department experienced respiratory symptoms (rhinorrhoea, conjunctivitis and tightness of the chest) 1 to 4 hours after the end of exposure which persisted for several hours. She also reported contact dermatitis, epistaxis and dysphonia occurring at the end of a working week. These symptoms improved on weekends and disappeared completely during holidays. The employee was assigned to sterilize endoscopic equipment 5 days per week, full-time, using a peracetic acid–hydrogen peroxide mixture. She used protective gloves, a mask and goggles during sterilization; the ventilation system was not very effective. Again, no exposure data are available, except that an acetic acid concentration of 9.7 ml/m^3 was detected in the entrance area of the sterilization area 2 hours after the replacement of the peracetic acid–hydrogen peroxide mixture. The chest radiographs of both patients were normal, as were the results of prick tests with the exception of a reaction to cat dander in the anaesthesia assistant. The values for PC20 (methacholine) were 1.5 and 0.8 mg/ml, respectively. Baseline values for vital capacity (100.9% and 96%, respectively) and FEV1 (first-second forced expiratory volume) (105.3% and 96.7%, respectively) were normal. Values of 90.3% and 81%, respectively, were reported for the Tiffeneau quotient. Serial PEF (peak expiratory flow) measurements taken over a 2-month period yielded about 15% to 20% lower values in the anaesthesia assistant during workdays compared with those at the end of a 3-week work-free period. In the auxiliary nurse, a 2-hour bronchial provocation test with increasing concentrations of the peracetic acid–hydrogen peroxide mixture was performed, resulting in an immediate steady decrease in FEV1, as well as dysphonia occurring 50 minutes after provocation. After about 4 hours, the FEV1 was decreased by about 20%, and 200 µg of albuterol was administered. The percentage of eosinophils in sputum before and after provocation was 2% and 4%, respectively (Cristofari-Marquand et al. 2007). The respiratory symptoms experienced by exposed workers are to be regarded as a result of irritation.

Two cohort studies reported irritant effects on the eyes and upper respiratory tract of workers exposed to peracetic acid (and hydrogen peroxide and acetic acid), but not allergic reactions (Casey et al. 2017; Hawley et al. 2017).

4.5 Reproductive and developmental toxicity

There are no studies available.

4.6 Genotoxicity

There are no studies available.

4.7 Carcinogenicity

There are no studies available.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

5.1.1.1 LC_{50} studies

For rats, valid 4-hour LC_{50} values for **aerosols** of peracetic acid solutions were reported of 204, > 117 and > 241 mg/m³ and for **vapour** from > 200 to > 2000 mg/m³ (ECETOC 2001).

The 1-hour LC_{50} in mice was 524 mg/m³ in a study from the 1960s using a peracetic acid solution in water of about 40% (Greim 1996). In another mouse study, a 1-hour LC_{50} of between 1334 and 5404 mg/m³ and a 30-minute LC_{50} of 4171 mg/m³ were reported (ECETOC 2001). No information is available as to whether these studies were conducted with vapour or aerosol.

5.1.1.2 RD_{50} studies

Rats were exposed nose-only for 25 minutes to an aerosol of a commercial peracetic acid mixture (15% peracetic acid, 28% acetic acid and 14% hydrogen peroxide). Respiration rates were determined plethysmographically; these averaged 67.1% to 31.9% of the pre-exposure values after exposure to peracetic acid concentrations of 8.4 to 36.3 mg/m³. The decrease in the respiration rate showed no clear concentration dependence. The mean RD_{50} was 22.7 mg/m³. Gross pathological and microscopic examinations of the nose, trachea and lungs yielded no unusual findings (ECETOC 2001; NRC 2010).

The RD_{50} in male OF1 mice (see Table 4) for specially prepared pure peracetic acid was 5.4 ml/m³, 20-fold lower than that for hydrogen peroxide and 40-fold lower than that for acetic acid. For the mixture in water and for the 36% peracetic acid content contained in it, the RD_{50} was 10.6 ml/m³ and 3.8 ml/m³ respectively, close to the expected values of 14.3 and 5.1 ml/m³ ($[C(\text{substance 1})/RD_{50}(\text{substance 1})] + [C(\text{substance 2})/RD_{50}(\text{substance 2})] = 1/RD_{50}(\text{mixture})$). This is plausible since the other two substances at the concentration present do not have a stronger influence due to the lower irritant effects. The threshold concentrations for the irritation are 16.1 and 7.0 ml/m³ for acetic acid and hydrogen peroxide, respectively (Gagnaire et al. 2002). In summary, the RD_{50} values determined for peracetic acid for mice were in the range from 3.8 to 5.4 ml/m³. In the ECHA Assessment Report, an RD_{10} of about 0.6 ml/m³ was calculated from the mean value of 4.6 ml/m³ (ECHA 2016 b).

Tab. 4 Comparison of the RD_{50} values (Gagnaire et al. 2002)

Substance	RD_{50} (ml/m³)
acetic acid	227
hydrogen peroxide	113
pure peracetic acid	5.4
peracetic acid / acetic acid / hydrogen peroxide: 36% / 53% / 11%	10.6 (3.8 for the peracetic acid content)

5.1.2 Oral administration

The oral LD_{50} values of peracetic acid in the rat reported in the documentation from 1993 were in the range from > 210 to 1540 mg/kg body weight. It was suggested that the variability of the data may be due primarily to poor characterization of the peracetic acid concentrations used (Greim 1996).

Subsequent new data are the oral LD_{50} values presented in Table 5 from studies conducted according to current test guidelines (ECHA 2019 b), which suggest a relationship with the concentration of peracetic acid used.

Tab. 5 LD_{50} values after oral administration of peracetic acid to male and female rats (ECHA 2019 b)

Concentration of peracetic acid	LD_{50} (mg/kg body weight)
0.15% or 0.89%	> 2000
2.6%–17%	185–3622
35%	50–500

5.1.3 Dermal application

The LD_{50} value for peracetic acid after dermal application in rabbits reported in the documentation from 1993 was 1410 mg/kg body weight (Greim 1996). Subsequent new data are the dermal LD_{50} values presented in Table 6 from studies conducted according to current test guidelines (ECHA 2019 b).

Tab. 6 LD_{50} values after dermal application of peracetic acid (ECHA 2019 b)

Species	Concentration of peracetic acid	LD_{50} (mg/kg body weight)
rat ♂, ♀	< 1%	> 2000
rabbit ♂, ♀	≥ 1%	1147

5.2 Subacute, subchronic and chronic toxicity

No new studies relevant to the evaluation have become available since the documentation from 1993 (Greim 1996).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

There are numerous, well-documented studies of skin irritation. Aqueous solutions of 0.013% to 0.34% peracetic acid are not irritating to slightly irritating on the rabbit skin. Contact for 3 minutes resulted in moderate to severe irritation at a concentration of 5%, and 10% and above led to corrosion. Contact for 45 minutes or longer with aqueous solutions of 3.4% or more resulted in corrosion (OECD 2008).

5.3.2 Eyes

In a well-documented study, a solution with 0.034% peracetic acid caused no effects other than slight conjunctivitis within the first 24 hours. Even a single application of 0.15% (OECD 2008) or 0.2% peracetic acid to the rabbit eye resulted in only slight irritation, which was described as completely reversible within 24 hours in the case of the 0.2% solution (Greim 1996). Severe irritation and irreversible corneal damage were observed at peracetic acid concentrations of 0.34% and above in 2 of 6 rabbits (OECD 2008). Five drops of a 1% peracetic acid solution, on the other hand, caused severe inflammation with clouding of the cornea, leading to blindness in some animals (Greim 1996).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In two sensitization tests carried out in accordance with the Draize method with intradermal application of a 1:1000 diluted solution (in physiological saline) of preparations with 14% peracetic acid (as well as 23% hydrogen peroxide and 16% acetic acid) or 2% peracetic acid (with 7% hydrogen peroxide and 19% acetic acid), no evidence of sensitization was found (ECETOC 2001).

In a Buehler test in female and male Hartley guinea pigs, very faint erythema was observed in both the control animals (4 of 9) and the treated group (4 of 10) after challenge treatment with a 7% dilution of the preparation following 3 induction treatments with a 10% aqueous dilution of a preparation containing 5% peracetic acid (and 20% hydrogen peroxide and 10% acetic acid). No evidence of sensitization was found (ECETOC 2001; ECHA 2019 b).

A second Buehler test was performed using a 10% preparation of a formulation containing 12% peracetic acid (and 20% hydrogen peroxide and 20% acetic acid). In the challenge treatment with a 5% preparation of the formulation in water, very faint erythema occurred in the treated animals (3 of 10) and the control animals (4 of 10). No evidence of sensitization was found (ECETOC 2001; ECHA 2019 b). The information provided by ECETOC and ECHA is partly contradictory.

Another Buehler test with the application of 0.15% peracetic acid (1 : 33 dilution of a preparation containing 5%–6% peracetic acid, 22%–23% hydrogen peroxide and 10%–11% acetic acid) for the induction and the challenge treatment did not produce any reactions in the 20 treated and 10 control animals (ECETOC 2001; ECHA 2019 b).

A solution of 5% peracetic acid (1 : 4 dilution of a formulation containing 20% peracetic acid, 10% hydrogen peroxide, and acetic acid; no other details) in water was used in a maximization test in 20 female guinea pigs for intradermal and topical induction treatment. The induction treatment was carried out by intradermal injection (0.1 ml/animal) and topical application (0.5 ml/animal), the challenge with 0,5 ml/animal. The study is, however, poorly documented: there were reactions described as weak in 3 of 10 and 5 of 10 animals, but it is not apparent if they occurred in the treated or control group (ECETOC 2001). Because of the reactions in the control animals, the study cannot be used to evaluate the sensitization potential of peracetic acid.

This is true also for another maximization test listed in the dataset of the ECHA. In this case, a 5% peracetic acid solution was used for both intradermal and topical induction, and for the challenge treatment, with reactions found in 8 of 20 animals after 24, 48 and 72 hours. Data for reactions in the controls are not provided (ECHA 2019 b).

A third maximization test (intradermal induction with 5%, topical induction with 10% peracetic acid) did not produce reactions after challenge with a 2% peracetic acid solution in the 10 treated Dunkin Hartley guinea pigs and the 5 control animals (ECHA 2019 b).

5.4.2 Sensitizing effects on the airways

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no new studies relevant for the evaluation.

5.5.2 Developmental toxicity

In an earlier study already described in the documentation from 1993 (Greim 1996), groups of 19 and 10 pregnant mice (ICR-Schönwalde) were exposed to peracetic acid concentrations of 20 or 100 mg/m^3 twice daily, for 10 minutes in a desiccator from gestation days 1 to 19. Statistically significant decreases in foetal weights and length were observed at the high concentration. Skeletal abnormalities were not found. Maternal toxicity data were not provided (Kramer et al. 1990). Visceral changes were not investigated. Therefore, the study is not suitable for the evaluation of developmental toxicity.

In a teratogenicity study carried out according to OECD Test Guideline 414, groups of 20 to 21 pregnant Wistar rats were given a solution of 32% to 38% (w/w) peracetic acid and 10% to 14% (w/w) hydrogen peroxide at various concentrations in the drinking water. They were exposed from gestation days 5 to 20 to peracetic acid concentrations of 0, 100, 300 or 700 mg/l (12.5, 30.4 or 48.1 mg peracetic acid/kg body weight and day, respectively). No treatment-related clinical signs or mortality were observed in the dams. There were also no unusual findings with regard to reproductive

parameters, uterine weight or the gross pathological examination of the dams. Drinking water intake was reduced at the low dose, with a concomitant increase in food consumption. At 30.4 mg/kg body weight and day, drinking water consumption continued to be reduced without an increase in food consumption, and at 48.1 mg/kg body weight and day, water and food consumption were greatly reduced. Accordingly, the body weights of the animals in this dose group at the end of the study and their body weight gains were reduced in a statistically significant manner. Reduced body weight gains at the two low doses were transient and reversible at the end of the study. Therefore, the NOAEL (no observed adverse effect level) for maternal toxicity is 12.5 mg/kg body weight and day. Mortality was not increased in the foetuses, and there were no treatment-related effects on the number of live foetuses per dam and the sex ratio. No external abnormalities were observed. Delayed or hypertrophic ossification and decreased body weights were observed in the foetuses in the high dose group and were regarded as a result of the severe maternal toxicity. The NOAEL for developmental toxicity is 30.4 mg/kg body weight per day (ECHA 2011; OECD 2008).

In this study, discoloration of the liver and of the surrounding tissues was seen in the foetuses of the middle and high dose groups. Dose-dependent histopathological changes were found at these doses. Re-examination of the samples (ECHA 2011; OECD 2008) by the study pathologist and another independent pathologist revealed that the discolouration resulted from improper chemical fixation of the organs. A solution of 96% ethanol : formaldehyde : glacial acetic acid in a ratio of 12 : 6 : 1 was used for fixation, which is not routinely used today. This probably contributed to the discoloration of the foetal livers and other organs. The histopathological liver damage found was likewise due to the incorrect fixation.

In summary, the NOAEL for developmental toxicity is 300 mg/l drinking water (30.4 mg/kg body weight and day) based on decreased body weights and impaired ossification with severe maternal toxicity at 48.1 mg/kg body weight and day (NOAEL for maternal toxicity: 12.5 mg/kg body weight and day).

5.6 Genotoxicity

5.6.1 In vitro

The results of in vitro genotoxicity studies with peracetic acid are shown in Table 7.

Peracetic acid was not mutagenic in the tests with various Salmonella typhimurium strains (ECB 2000; ECHA 2019 b; Greim 1996; Zeiger et al. 1988) or Saccharomyces cerevisiae (Buschini et al. 2004) at non-cytotoxic concentrations with and without S9 mix. Even the peroxide-sensitive strain Salmonella typhimurium TA102 did not exhibit a statistically significant increase in mutants (ECHA 2019 b).

A comet assay with human leukocytes yielded positive results (Buschini et al. 2004), but the test was carried out only without metabolic activation. The test substance was not characterized. The extent of induced DNA damage is low and there are methodological shortcomings regarding the definition of the evaluation criteria for a positive test, and there were also no historical controls. Therefore, the test cannot be included in the evaluation of peracetic acid (ECHA 2019 b).

The results from DNA repair studies in WI-38 cells are inconsistent; this was attributed by the authors to the varying concentrations of hydrogen peroxide in the peracetic acid batches (Coppinger et al. 1983).

A chromosomal aberration test in Chinese hamster lung fibroblasts yielded negative results. The result of a second chromosomal aberration test in human lymphocytes was positive without metabolic activation, but with metabolic activation it was positive only in the cytotoxic range (BIBRA Toxicology International 1994; ECHA 2011, 2019 b).

An HPRT test in V79 cells likewise did not reveal any mutagenic effects of peracetic acid in mammalian cells (ECHA 2011, 2019 b).

Tab. 7 Genotoxicity of peracetic acid in vitro

End point	Test system	Concentration [µg/plate][a)]	Effective concentration[a)]	Cytotoxicity[a)]	Results		Remarks	References
					–m.a.	+m.a.		
gene mutation	Salmonella typhimurium TA98, TA100	50	–	–	n.i.	–		Greim 1996
gene mutation	Salmonella typhimurium TA97, TA98, TA100, TA1535	0, 0.3, 1.0, 3.3, 10, 20, 33, 100, 200	–	tested up to cytotoxicity	–	–	40% peracetic acid, preincubation	Zeiger et al. 1988
gene mutation	Salmonella typhimurium TA1535, TA1536, TA1537, TA1538, TA1978, wild type LT–2	up to 2 mg/ml	20 µg/ml	20 µg/ml	(+) in TA1978	n.i.	spot test; peracetic acid was less mutagenic than H_2O_2, but had higher cytotoxicity; test substance: 35%–37% peracetic acid, 8%–9% H_2O_2, 36%–38% AcOH	ECB 2000
gene mutation	Salmonella typhimurium TA98, TA100, TA102, TA1535, TA1537, TA1538	1st test: 0, 7, 36, 183, 915, 4576; 2nd test: 0, 57, 114, 228, 457, 915	–	highest concentration	–	–	test substance "P3 oxonia active" with 4.6% peracetic acid, 25%–30% H_2O_2, 5%–10% AcOH	ECHA 2019 b
gene mutation (mitotic gene conversion, point mutation, mitochondrial DNA modification)	Saccharomyces cerevisiae D7	0, 0.2, 0.5, 1, 2, 5, 10, 15 µg/ml	5 µg/ml	–m.a.: 2 µg/ml; +m.a.: 15 µg/ml	(+)	–		Buschini et al. 2004
DNA damage in comet assay	human leukocytes	0, 0.1, 0.2, 0.5, 1, 2, 5 µg/ml	0.5 µg/ml	> 5 µg/ml	+	n.i.	shortcomings in method and documentation (see text)	Buschini et al. 2004
DNA repair synthesis (UDS)	WI-38 cells	0.2–32 µg/ml	4 µg/ml (in 1 of 3 experiments)	32 µg/ml	(+) only 1 of 3 experiments with positive results	n.i.	test substance: 31% peracetic acid, 4.7% H_2O_2 or 40% peracetic acid, 5.5% H_2O_2	Coppinger et al. 1983; Greim 1996
DNA repair synthesis (equilibrium centrifugation)	WI-38 cells	4–32 µg/ml	–	32 µg/ml	–	n.i.		Coppinger et al. 1983

Tab. 7 *(continued)*

End point	Test system	Concentration [µg/plate][a)]	Effective concentration[a)]	Cytotoxicity[a)]	Results		Remarks	References
					–m.a.	+m.a.		
chromosomal aberrations	V79 cells test according to 67/548/EEC, Part B.10; corresponding to OECD Test Guideline 473	–m.a.: 0, 0.09, 0.13, 0.2 µl/ml; +m.a.: 0, 0.13, 0.2, 0.3 µl/ml	–	–m.a.: at 0.2 µl/ml, slight at 0.13 µl/ml; +m.a.: 0.3 µl/ml	–	–	test substance: Wofasteril®SC100 (10.7% peracetic acid); 1st test: incubation time 4 hours (+/–m.a.), investigated after 18 hours; 2nd test: incubation time 18 or 26 hours (–m.a.) and 4 hours (+m.a.); investigated after 18–26 hours	ECHA 2011, 2019 b
	human lymphocytes similar to OECD Test Guideline 473	1st test: –m.a.: 0, 0.25, 0.5, 1, 2, 4 mg/ml; +m.a.: 0, 0.31, 0.63, 1.25, 2.5, 5 mg/ml; 2nd test: –m.a.: 0, 0.25, 0.5, 0.75, 1, 1.5 mg/ml; +m.a.: 0, 0.31, 0.63, 1.25, 2.5, 5 mg/ml	–m.a.: 0.25–1.5 mg/l, but not at 0.75 mg/l +m.a.: 5 mg/ml	–m.a.: 2 mg/l and above +m.a.: 5 mg/ml	1st and 2nd test +	1st and 2nd test (+)	test substance: Proxitane®0510 (5.17% peracetic acid, H_2O_2 15%, AcOH 15%); 1st test: incubation time 20 hours (–m.a.) and 3 hours (+m.a.); investigated after 20 hours; 2nd test: incubation time 44 hours (–m.a.) and 3 hours (+m.a.); investigated after 44 hours	BIBRA Toxicology International 1994; ECHA 2011, 2019 b
gene mutation HPRT	V79 cells test according to 67/548/EEC, Part B.17; corresponding to OECD Test Guideline 476	–m.a.: 0, 0.16, 0.22, 0.31, 0.43, 0.5, 0.6 µl/ml; +m.a.: 0.5, 0.6, 0.7, 0.84, 0.98 µl/ml	–	–m.a.: at 0.22 µl/ml and above +m.a.: at 0.98 µl/ml and above	–	–	test substance: Wofasteril®SC100 (10.7% peracetic acid); incubation time 4 hours, investigated after 9 days	ECHA 2011, 2019 b

[a)] unless otherwise stated
AcOH: acetic acid; H_2O_2: hydrogen peroxide; m.a.: metabolic activation by S9 mix; n.i.: not investigated; (+) positive at toxic concentrations

5.6.2 In vivo

The results of in vivo studies of genotoxicity are shown in Table 8.

Peracetic acid caused chromosomal aberrations in bone marrow cells and sperm head abnormalities in mice after both epicutaneous and intraperitoneal treatment (Greim 1996). The studies were carried out with Wofasteril®, a mixture of 40% peracetic acid, 27% acetic acid, 14% hydrogen peroxide, about 20% water and 0.25% stabilizers such as pyridine-2,6-dicarboxylic acid, 8-hydroxyquinoline, phosphoric acid and sodium pyrophosphate. Due to the co-exposure to the stabilizers and the doubtful availability of the peracetic acid at the target site, the test results are questionable and cannot be included in the evaluation. Furthermore, changes in sperm morphology are not reliable indicators of

mutations and the relevance of the effects with respect to germ cell mutagenicity is doubtful (ICPEMC 1983; Salamone 1988; Wild 1984).

Four micronucleus tests in erythrocytes of the bone marrow of mice and two oral tests for DNA repair synthesis in the mouse liver are available. All tests yielded negative results, since peracetic acid is already degraded in the stomach to hydrogen peroxide and acetic acid and does not reach the bone marrow (ECHA 2011).

Hydrogen peroxide is very reactive and reacts at the site of contact when the detoxification capacity of catalase is overloaded (Greim 2010 b). Acetic acid is introduced into the intermediary metabolism and degraded (Greim 2010 a). Both substances were likewise negative in the mouse bone marrow micronucleus test (ECHA 2019 a; Greim 2010 b).

Tab. 8 Genotoxicity of peracetic acid in vivo

End point	Species, strain, number/group	Dose of peracetic acid administration route	Peracetic acid concentration	Results	References
DNA repair synthesis (UDS), liver OECD Test Guideline 486	rat, Fischer, 3 ♂	0, 1000, 2000 mg/kg body weight (MTD); oral (gavage), marked toxicity at 1000 mg/kg body weight and above, investigated after 2–4 and 12–16 hours	peracetic acid 5% in 5 or 10 ml distilled water	–	ECHA 2011, 2019 b
DNA repair synthesis (UDS), liver similar to OECD Test Guideline 486	rat, F344, 1–3 ♂	0, 330, 1000 mg/kg body weight (MTD); oral (gavage), investigated after 2 and 16 hours	peracetic acid in the form of Proxitane®0510 (5.17% peracetic acid, 22% H_2O_2, 10% AcOH) in 10 ml distilled water	–	BIBRA Toxicology International 1994; ECHA 2011, 2019 b
chromosomal aberrations	mouse, ICR, 5 ♂, 5 ♀	0, 5000 mg/kg body weight; epicutaneous	0.1 ml Wofasteril® (40% peracetic acid) undiluted	+	Greim 1996
chromosomal aberrations	mouse, ICR, 5 ♂, 5 ♀	0, 5 or 50 mg/kg body weight; intraperitoneal	50 mg/kg body weight: 0.2 ml Wofasteril® 0.5% in distilled water (about 0.2% peracetic acid) 5 mg/kg body weight: 0.1 ml Wofasteril® 0.1% in distilled water (about 0.04% peracetic acid)	+ at 5 mg/kg body weight and above	
micronuclei in bone marrow erythrocytes, OECD Test Guideline 474	mouse, CD-1, 5 ♂, 5 ♀	0, 8, 35, 150 mg/kg body weight (MTD); oral (gavage), investigated after 24, 48 and 72 hours	peracetic acid (as Proxitane®0510 (5.17% peracetic acid, 22% H_2O_2, 10% AcOH) in 10 ml 0.9% saline solution	– PCE/NCE ratio reduced in female animals	BIBRA Toxicology International 1994; ECB 2000; ECHA 2011, 2019 b
micronuclei in bone marrow erythrocytes, OECD Test Guideline 474	mouse, Crl:NMRIBR, 5 ♂, 5 ♀	0, 1000 mg/kg body weight (MTD); oral (gavage), investigated after 12, 24 and 48 hours, dose was selected after toxicity test at 1000, 1300 and 2000 mg/kg body weight	peracetic acid 10% in 10 ml demineralized water	– PCE/NCE ratio reduced in female animals	ECHA 2011

Tab. 8 *(continued)*

End point	Species, strain, number/group	Dose of peracetic acid administration route	Peracetic acid concentration	Results	References
micronuclei in bone marrow erythrocytes, deviations from OECD Test Guideline 474: testing time point too early (6 hours after 2nd dose); Test Guideline recommends after 18–24 hours	mouse, CF1/W68, 7 ♂, 5 ♀	0, 2× 200, 2× 400, 2× 800 mg/kg body weight; oral (gavage) in each case on 2 subsequent days, investigated 6 hours after final dose	peracetic acid as "P3 oxonia active" with 4.6% peracetic acid, 25–30% H_2O_2, 5–10% AcOH; dose administered in each case as a total volume of 10 ml	– toxic at 800 mg/kg body weight (PCE/NCE ratio reduced, presumably secondary effect due to toxicity)	ECHA 2011, 2019 b
micronuclei in bone marrow erythrocytes, OECD Test Guideline 474	mouse, Swiss Ico: OFI (IOPS Caw) 5 ♂, 5 ♀	0, 2× 250, 2× 500, 2× 1000 mg/kg body weight (MTD); oral (gavage) twice within 24 hours, investigated 24 hours after final treatment, MTD was determined in toxicity test at 1000, 1500 and 2000 mg/kg body weight and day	peracetic acid 5% in 5–20 ml distilled water	– PCE/NCE ratio unchanged	ECHA 2011

AcOH: acetic acid; H_2O_2: hydrogen peroxide; MTD: maximum tolerated dose; PCE/NCE: polychromatic/normochromatic erythrocytes

5.6.3 Summary: genotoxicity

The few positive results obtained with peracetic acid in vitro occurred at cytotoxic concentrations or in the absence of detoxification systems (without S9 mix). If the cell system is appropriately equipped with detoxification enzymes no genotoxic effects resulting from peracetic acid are observed below the cytotoxicity threshold. In the cytotoxic range, where proteins and enzymes lose their function due to oxidative damage caused by peracetic acid, clastogenic effects may occur.

All valid in vivo genotoxicity tests with peracetic acid yielded negative results. The significance of the negative test results is questionable due to the uncertainty of the availability of the test substance at the target site, as peracetic acid reacts rapidly locally with organic material.

In view of this, it can be concluded that tests in germ cells are not relevant (ECHA 2016 a).

On the basis of all the results, it can be said that peracetic acid, like hydrogen peroxide, has no systemic genotoxic potential after oral absorption of the substance. However, for peracetic acid, like for hydrogen peroxide and also due to the release of hydrogen peroxide, a genotoxic effect cannot be excluded as a result of oxidative damage on local contact.

5.7 Carcinogenicity

5.7.1 Short-term studies

An initiation–promotion test on the skin of mice (Bock et al. 1975) already presented in the documentation from 1993 (Greim 1996) is available, which is described once more in detail and re-evaluated here. In the experiments, 40% peracetic acid in a commercial product containing 40% acetic acid, 5% hydrogen peroxide, 13% water, 1% sulfuric acid, and 500 mg stabilizer/l (no other details) was used as the starting substance. Shortcomings of this initiation–promotion study include the fact that no irritation threshold was determined and that the observed irritation was not reported in detail.

5.7.1.1 Studies of promoting effects

Seven groups of 30 female ICR-Swiss mice were initially given a single dose of 0.125 µg of 7,12-dimethylbenzanthracene (DMBA) in acetone on the skin. After 3 weeks, 0.2 ml of a 0.3%, 1% or 3% peracetic acid solution in water was applied to the shaved skin of 30 animals in each case on 5 days per week, for 66 weeks. A preliminary study had shown that a 4% aqueous peracetic acid solution was lethal. Three additional groups of 30 female ICR-Swiss mice were given 0.2 ml of a 2% aqueous peracetic acid solution or a 1% or 2% peracetic acid solution in acetone applied to the shaved skin once daily for 5 days per week without prior DMBA administration. In two groups of animals pretreated with DMBA, a 2% aqueous or a 1% peracetic acid solution in acetone was applied after the peroxides in both solutions had been decomposed by a noble metal catalyst. These experiments served as a control to test only the substances present in the solution in addition to peroxides. In this experiment, also a 3% hydrogen peroxide solution was tested after pretreatment with DMBA. A finding was classified as a skin tumour if it was at least 1 mm in diameter over a period of at least 3 weeks. Tumours were classified as carcinomas if they invasively penetrated subcutaneous tissue. The results are shown in Table 9.

Tab. 9 Skin tumour incidences in ICR-Swiss mice after skin painting with commercial peracetic acid (Bock et al. 1975)

Initiation with DMBA	Peracetic acid concentration (%)	Solvent	Number of mice[a] with non-invasive tumours in week:				Number of mice with invasive tumours
			10	26	52	66	
+	3	water	22	23	24	24	5
+	1	water	1	8	8	8	1
+	0.3	water	0	0	1	2	0
+	0	–[b]	0	0	0	0	0
	2	water	0	3	3	n. i.	0
	1	acetone	0	0	0	n. i.	0
	0	water[c]	0	0	0	0	0
+	2 (degraded[d])	water[b]	0	0	1	2[e]	0
+	1 (degraded[d])	acetone[b]	0	0	2	2[e]	0
+	3% H_2O_2	water[b]	0	0	0	0	0

DMBA: 7,12-dimethylbenzanthracene; H_2O_2: hydrogen peroxide; n. i.: not investigated
[a] 30 mice/group
[b] historical control: DMBA and solvents water/acetone: 5.4% skin tumours after 58 weeks
[c] historical control without DMBA: only 1 skin tumour in thousands of controls after the application of acetone for 1.5 years
[d] degraded peracetic acid solution after passing over a noble metal catalyst
[e] evaluated after 58 weeks instead of after 66

Peracetic acid was clearly shown to be tumour-promoting in a concentration-dependent manner after pretreatment with DMBA. With 0.3% peracetic acid, 1 and 2 unclassified and non-invasive skin tumours appeared at weeks 52 and 66, respectively. When 1% or 3% peracetic acid was applied in water, 8 and 23 animals, respectively, produced skin tumours after only 26 weeks, of which 1 animal and 5 animals, respectively, developed carcinomas. The application of 4% peracetic acid was highly toxic and lethal (no other details) (Bock et al. 1975). The tumour classification does not meet current standards (ECETOC 2001).

While no tumours were observed in the concurrent control, an average of 5.4% tumours occurred in the historical controls after 58 weeks, so that the incidences of 1/30 (3.33%) at week 52 and 2/30 (6.67%) at week 66 by 0.3% peracetic acid were approximately in the range of the historical controls. This is plausible since no skin irritation is to be assumed at this concentration (see Sections 4.3 and 5.3) and provides an indication of the threshold for tumour-promotion. The authors themselves mentioned skin irritation from the peracetic acid treatment, but did not specify at which concentrations this occurred.

5.7.1.2 Studies of initiating effects

The negative result following administration of 1% peracetic acid in acetone without pretreatment with DMBA and a treatment period of 52 weeks is attributed by the authors to the fact that peracetic acid reacts with acetone. A 2% peracetic acid solution in acetone was highly toxic and lethal to the animals, so that no evaluation could take place (Bock et al. 1975).

However, using a 2% aqueous peracetic acid solution without DMBA pretreatment, non-invasive skin tumours, also not further classified, were observed after 26 weeks in 3 of 30 animals (10%). No increase in tumours was observed until week 52, when the study finished. With this result, the authors evaluated the substance as a "weak complete carcinogen". It speaks against a random finding that in thousands of control animals over recent years only one single skin tumour was found after 1.5 years of skin painting with acetone. Hydrogen peroxide and the other substances contained in the commercial peracetic acid product can likewise be ruled out as causes, since none of these (2% "decomposed" peracetic acid solution or 3% hydrogen peroxide, see Table 9) had such an effect even after pretreatment with DMBA.

Since only one concentration in aqueous solution was used in the study of the peracetic acid mixture without pretreatment with DMBA, no concentration–effect relationship can be established to verify the finding. A concurrent negative control was absent in this experiment. After the first 26 weeks, tumours were observed in 10% of the animals (3/30), but the number did not increase during the following 26 weeks. To summarize, the tumour findings in the study described here are difficult to evaluate due to the absence of further test concentrations. In addition, a substance mixture with an unknown stabilizer was tested and neither an irritation threshold was determined nor was the observed irritation described in any detail.

5.7.2 Long-term studies

There are still no long-term studies with peracetic acid sufficient to evaluate the carcinogenicity of the substance.

A symposium report mentions a study in mice in which 0.2% to 2% peracetic acid solutions were applied to the skin at regular intervals (no other details) over a period of 1 year. No evidence of carcinogenicity was found in the histopathological examination. However, 1 animal was found to have a clearly benign skin tumour (Kästner 1981).

In a 12-month study in rabbits already reported in the 1993 documentation (Greim 1996), a 0.2% peracetic acid solution (Wofasteril®) (3×/week, 153 applications in total) was irritating to the skin and mucous membranes but not carcinogenic (Müller et al. 1988).

5.7.3 Summary and discussion: carcinogenicity

No valid long-term studies of the carcinogenicity of peracetic acid are available. No tumours were observed in inadequately reported and therefore not conclusively evaluable dermal 1-year studies in mice and rabbits (Bock et al. 1975; Müller et al. 1988).

An initiation–promotion experiment showed peracetic acid to have a clear tumour-promoting effect which begins at 1% aqueous peracetic acid. The findings at 0.3% were within the range of the historical controls. The substance may also have a weak initiating effect on mouse skin (Bock et al. 1975). This cannot be conclusively verified due to the lack of further studies. It can be assumed that the tumour-promoting effect is caused by oxidative damage to the skin and the formation of reactive oxygen species as well as other reactive intermediates.

In addition to the possible effects of peracetic acid itself, the carcinogenicity of hydrogen peroxide, also present in the mixture, has to be taken into account. With hydrogen peroxide, tumours were observed in animal experiments only when the capacities of detoxifying enzymes were exceeded. In mice, concentrations above 0.1% in drinking water increased the incidence of duodenal carcinomas in a dose-dependent manner, with the highest incidence in strains with the lowest catalase activity. In rats, which have much higher duodenal catalase activity than mice, duodenal tumours did not occur in a 2-year study at hydrogen peroxide concentrations up to 0.6%. Forestomach papillomas occurred only at 1% hydrogen peroxide in drinking water in a short-term study with rats. Tumour-promoting effects were found in

rats (forestomach papillomas at 1% hydrogen peroxide, intestinal tumours at 1.5% hydrogen peroxide), hamsters (cheek pouch carcinomas at 30% hydrogen peroxide), and mice (skin papillomas at 6%) (Greim 2010 b).

6 Manifesto (MAK value/classification)

The critical effect of peracetic acid is irritation. As known from hydrogen peroxide (see Greim 2010 b), local genotoxicity and carcinogenicity is to be expected if the detoxification capacity is exceeded. Data in humans are not available.

Carcinogenicity. Genotoxic effects of peracetic acid cannot be excluded in the case of local contact due to oxidative damage (see Section 5.6.3). The cytotoxicity of peracetic acid occurs only when the detoxification capacities are exceeded (see Section 3.2), so that a threshold value for cytotoxicity is plausible. As for hydrogen peroxide (Greim 2010 b), it can likewise be assumed for peracetic acid that cytotoxicity and thus also irritation occur before genotoxicity.

An initiation–promotion experiment in mouse skin indicated a clear tumour-promoting effect in response to the local irritation caused by peracetic acid. It is possible that a weak initiating effect was also present (Bock et al. 1975), which cannot be conclusively verified due to the lack of further studies. Substances with nonspecific tumour-promoting mechanisms, which are mainly observed in high dose ranges, do not lead to tumours in humans. When such substances are administered without an initiator, they induce tumours only in the susceptible mouse. Such results from initiation–promotion studies in mouse skin are not considered by the Commission to be relevant for the classification of the substance (Schwarz et al. 2015).

Valid long-term studies of the carcinogenicity of peracetic acid are not available.

In long-term studies with **hydrogen peroxide** in rodents, tumours were observed when the capacities of detoxifying enzymes were exceeded (Greim 2010 b).

In summary, the mechanisms for possible carcinogenic effects of peracetic acid, as already documented for hydrogen peroxide (see Greim 2010 b), are, on the one hand, the tissue-damaging local cytotoxicity/irritation and, on the other hand, the genotoxicity, both of which occur when detoxification is overloaded. If the endogenous detoxification capacities are not exceeded, genotoxic effects likewise play no or only a minor role.

Due to this mechanism of carcinogenicity, hydrogen peroxide has been classified in Carcinogen Category 4.

Peracetic acid, which is present in the equilibrium mixture with hydrogen peroxide and acetic acid, is therefore likewise classified in Carcinogen Category 4.

The threshold concentration for local cytotoxicity/irritation is lower for peracetic acid than for hydrogen peroxide (Section 2.1). As it is not known at which tissue concentration the detoxification of peracetic acid in the respiratory tract is overloaded, the sensory irritation of the eyes and nose caused by peracetic acid is used to derive the MAK value. Since this end point, like carcinogenicity, is ultimately based on the release of reactive oxygen species, the exclusion of the sensory irritation simultaneously ensures that the detoxifying enzymes are not yet overloaded and thus neither tissue-damaging nor genotoxic effects occur (see also Greim 2010 b).

As peracetic acid is more strongly irritant than hydrogen peroxide, the MAK value for peracetic acid also protects against the carcinogenic effects of the hydrogen peroxide formed (MAK value: 0.5 ml/m^3 (0.71 mg/m^3).

MAK value. In aqueous solution, peracetic acid consists of peracetic acid, hydrogen peroxide and acetic acid.

Peracetic acid is the most critical component in this solution with regard to the derivation of the MAK value. Due to the percentages in the mixture and the significantly lower threshold for sensory irritation of peracetic acid compared with that of acetic acid and hydrogen peroxide (see Section 2.1.2; Gagnaire et al. 2002), at low concentrations of the equilibrium mixtures the sensory irritation is triggered exclusively by peracetic acid. The RD_{50} values determined for the mouse are in the range from 3.8 to 5.4 ml/m^3 (Gagnaire et al. 2002). ECHA (2016 b) calculated an RD_{10} of about

0.6 ml/m³ from the mean value of 4.6 ml/m³, which is consistent with the irritation threshold from the human data (see Section 4.1 and below).

Applying the relationship threshold limit value = RD_{50} (mouse; 4.6 ml/m³) × 0.03 (Schaper 1993) results in a concentration of 0.14 ml/m³. According to the preferred value approach, this would result in a MAK value of 0.1 ml/m³ (0.317 mg/m³). This is also below the MAK value of hydrogen peroxide, which is plausible due to the stronger irritant effects of peracetic acid. The human data, which in themselves are not suitable for deriving a MAK value due to numerous shortcomings, likewise do not contradict this value. In an aerosol study with an unspecified number of subjects, a concentration of 0.5 ml/m³ (1.58 mg/m³) did not cause irritation (Fraser and Thorbinson 1986). In a study not available in the original, the exposure of subjects to peracetic acid vapour at concentrations of 0.13 to 0.17 ml/m³ (0.4–0.5 mg/m³) was tolerable and not unpleasant. Two individuals exposed for 3 hours to an average of 0.17 ml/m³ (0.5 mg/m³) did not report any irritation and did not experience lacrimation (ECETOC 2001; NRC 2010). Therefore, based on the RD_{50} for mice of 4.6 ml/m³, a MAK value of 0.1 ml/m³ (0.317 mg/m³) has been established.

Peak limitation. Due to its irritant effects, peracetic acid has been assigned to Peak Limitation Category I. Like for hydrogen peroxide, and as the studies with peracetic acid in humans have only limited validity, an excursion factor of 1 has been set.

Prenatal toxicity. In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414 in Wistar rats given a solution of peracetic acid and hydrogen peroxide with the drinking water from gestation days 5 to 20, the highest dose of 48.1 mg peracetic acid/kg body weight and day resulted in decreased body weights and delayed ossification in the foetuses with concurrent maternal toxicity in the form of reduced body weights and delayed body weight gains (OECD 2008). The NOAEL for developmental toxicity was 30.4 mg peracetic acid/kg body weight per day. The following toxicokinetic data are taken into consideration for the extrapolation of this NOAEL to a concentration in workplace air: the species-specific correction value for the rat (1:4), 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 concentration calculated from this is 53 mg/m³ air, which represents a 168-fold margin to the MAK value of 0.1 ml/m³ (0.316 mg/m³). Teratogenic effects were not observed. Due to the sufficient margin between the (calculated) concentration in air and the MAK value, peracetic acid has been assigned to Pregnancy Risk Group C. Hydrogen peroxide is likewise assigned to Pregnancy Risk Group C at a MAK value of 0.5 ml/m³ (0.71 mg/m³).

Germ cell mutagenicity. The few positive results obtained with peracetic acid in genotoxicity studies in vitro occurred at cytotoxic concentrations or in the absence of detoxification systems (without S9 mix). If the cellular system is appropriately equipped with detoxification enzymes, no genotoxic effects of peracetic acid are observed below the cytotoxicity threshold. In the cytotoxic range, where proteins and enzymes lose their function due to oxidative damage caused by peracetic acid, clastogenic effects may occur. All valid in vivo genotoxicity tests with peracetic acid yielded negative results. The significance of the negative test results is questionable due to the uncertainty as to whether the test substance reached the target site, since peracetic acid reacts rapidly locally with organic material. Based on this, it can also be concluded that tests in germ cells are not relevant. Therefore, there is no justification for classification in one of the categories for germ cell mutagens.

Absorption through the skin. In an in vitro study, a small amount of peracetic acid (in the form of active oxygen) was found in the receptor solution only if deeper layers of the skin sample used were damaged (Krüger and Jancke 1976). A study in which radiolabelled 5% peracetic acid (and 15% acetic acid) was applied to the skin of rats did not reveal any higher levels of absorption than after the application of acetic acid alone (concentration not specified) as the positive control. However, it is unclear whether it can be concluded from this result that peracetic acid is not absorbed systemically, since in the solution with peracetic acid three quarters of the activity consisted of acetic acid. On the other hand, the half-life in blood is short (about 5 minutes), and to date no systemic availability has been demonstrated in genotoxicity studies, except at concentrations that were damaging to the skin (40%). Overall, the systemic toxicity

of peracetic acid resulting from dermal contact is considered to be low, so that it remains not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no positive findings for skin sensitization in humans and no reliable positive findings in animals. The respiratory symptoms experienced by exposed workers are to be regarded as the result of irritation. Peracetic acid remains therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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