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# Acetic anhydride

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

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**Keywords:** acetic anhydride; MAK value; maximum workplace concentration; peak limitation; developmental toxicity; irritation

**Citation Note:** Hartwig A, MAK Commission. Acetic anhydride. MAK Value Documentation, addendum – Translation of the German version from 2018. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2019 Nov;4(4):1792-1801]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/mb10824e6519_w

**Republished (online):** 08 Aug 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb10824e6519

**Addendum completed:** 22 Mar 2017

**Published (online):** 13 Nov 2019

*The commission established rules and measures to avoid conflicts of interest.*

# Acetic anhydride / Acetyl acetate

## MAK Value Documentation

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DOI: 10.1002/3527600418.mb10824e6519


### Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group of acetic anhydride [108-24-7]. Furthermore genotoxicity and skin absorption have been evaluated.
Critical effects are irritation of mucous membranes in humans and inflammation reactions as well as hyper- and metaplasia in the upper respiration tract with a NOAEC of 1 ml/m³ in a 13-week-inhalation study with rats. Since 2014 the Commission uses an empirical approach to set MAK values for such substances. According to this, the MAK value for acetic anhydride has been lowered to 0.1 ml/m³. As local effects are critical, the assignment to Peak Limitation Category I is confirmed. As the LOAEC is fivefold as high as the NOAEC in the 13-week-inhalation study with rats, the true NAEC might be higher and the excursion factor of 2 is set. Taking into consideration the low systemic bioavailability and the data for the metabolite acetic acid, damage to the embryo and foetus is unlikely when the MAK value for acetic anhydride is not exceeded. Therefore, acetic anhydride is classified in Pregnancy Risk Group C. Absorption of acetic anhydride via the skin is unlikely, due to the rapid hydrolysis to acetic acid in aqueous solution. In addition, the irritation of undiluted acetic anhydride precludes a skin contact over a longer period. The substance is not genotoxic.



### Keywords

acetic anhydride; acetic oxide; acetyl oxide; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; reproductive toxicity; fertility; developmental toxicity; genotoxicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance



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# Acetic anhydride

**[108-24-7]**

**Supplement 2018**

| | |
|---|---|
| **MAK value (2017)** | **0.1 ml/m³ ≙ 0.42 mg/m³** |
| **Peak limitation (2017)** | **Category I, excursion factor 2** |
| **Absorption through the skin** | **–** |
| **Sensitization** | **–** |
| **Carcinogenicity** | **–** |
| **Prenatal toxicity (2017)** | **Pregnancy Risk Group C** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |

**1 ml/m³ (ppm) ≙ 4.24 mg/m³** **1 mg/m³ ≙ 0.236 ml/m³ (ppm)**

For acetic anhydride there is documentation available from 1997 (documentation "Acetic anhydride" 1999) and a supplement on peak limitation from 2000 (supplement "Essigsäureanhydrid" 2000, available in German only).

The previous MAK value for acetic anhydride of 5 ml/m³ was provisionally set in 1997. At the time, the threshold concentration for irritation of the mucous membranes, the critical end point in humans, was not considered as proven. According to the information then available, it was, however, assumed to be greater than 5 ml/m³. There were no valid animal experiments available which could have been used for the derivation of a MAK value (see documentation "Acetic anhydride" 1999). Another uncertainty arose after reviewing the original study. In the publication it was stated that irritation of the conjunctiva with erythema and lacrimation occurred at concentrations of more than 5 ml/m³. However, both the Italian and the English abstract stated that concentrations below 5 ml/m³ already have these effects (Baldi 1953).

In the meantime, inhalation studies in rats have been carried out, which make a re-evaluation of the MAK value necessary. Furthermore, germ cell mutagenicity is assessed and the pregnancy risk group re-examined.

## Mechanism of Action

It has been postulated that the irritant effects of acetic anhydride are due to the release of acetic acid (documentation "Acetic anhydride" 1999). After single inhalation exposures, acetic anhydride and acetic acid caused severe irritation of the respiratory tract and mortality. None of the six rats died after 4-hour exposure to 1000 ml acetic anhydride/m$^3$, however all six animals died after exposure to 2000 ml/m$^3$. On the other hand, 4-hour exposure to an acetic acid concentration of 16 000 ml/m$^3$ was lethal for only one of six animals (Smyth et al. 1951). These data for inhalation toxicity illustrate that acetic anhydride is far more toxic than acetic acid, which is not to be expected from its hydrolysis to two molecules of acetic acid. Therefore, it has to be assumed that the toxicity or the irritant effects are not dependent on the released acid alone.

This assumption is additionally supported by the comparison of the NOAEC (no observed adverse effect concentration) for acetic anhydride and formic acid as regards the findings in the nasal epithelium of rats obtained in the 13-week study. For acetic anhydride this NOAEC is 1 ml/m$^3$, for formic acid 32 ml/m$^3$ (documentation "Formic acid" 2003, available in German only). For acetic acid, there are no corresponding animal experiments available.

The higher toxicity of acetic anhydride is possibly due to different toxicokinetics. It is likely that acetic anhydride is absorbed into the cells and is hydrolysed there to acetic acid. Acetic anhydride is used for the acetylation of alcohols and amines. There are, however, no studies available for the metabolism of acetic anhydride which would confirm acetylating effects in the organism.

It is also conceivable that the deposition or retention of acetic anhydride in the respiratory tract is higher than that of acetic acid. There are also no studies available with regard to this aspect.

## Toxicokinetics and Metabolism

There are no data available. Acetic anhydride hydrolyses in aqueous solution (documentation "Acetic anhydride" 1999).

As the experimental half-life for the hydrolysis of acetic anhydride in aqueous solution is 4.4 minutes (ECHA 2016), calculating the skin penetration rates with the mathematical models does not yield meaningful results.

## Animal Experiments and in vitro Studies

### Subacute, subchronic and chronic toxicity

### Inhalation

Studies relevant for the evaluation are listed in Table 1.

In a pilot study to determine the appropriate concentrations for a subchronic and a developmental toxicity study, groups of 5 male Sprague Dawley rats were exposed

**Table 1** Effects of acetic anhydride after repeated inhalation exposure

| Species, strain, number per group | Exposure | Findings | References |
|---|---|---|---|
| **rat**,<br>Sprague Dawley,<br>5 ♂, 5 pregnant ♀ | ♂: **14 days**<br>6 hours/day, 5 days/week,<br>0, 25, 100, 400 ml/m³<br>♀: **gestation days 6–15**<br>6 hours/day<br>0, 25, 100 ml/m³<br>whole-body | **25 ml/m³**: ♂, ♀: closed eyes, licking of the mouth, loud breathing noises after the end of exposure, food and water consumption ↓, local irritation in the olfactory, respiratory and transitional epithelium, larynx, trachea and lungs, increased gas formation in the intestine; ♂: absolute lung weights ↑, absolute liver and kidney weights ↓, body weights ↓, enlarged lymph nodes (cervical, tracheobronchial), ♀: body weight gains ↓<br>**100 ml/m³**: ♂, ♀: lacrimation ↑, partly closed eyes, licking of the mouth, loud breathing noises after the end of exposure, food and water consumption ↓, enlarged lymph nodes (cervical, tracheobronchial), severe irritation in the respiratory tract, body weights ↓ (exposure terminated prematurely – ♂ after 6, ♀ after 7 exposures)<br>**400 ml/m³**: ♂: loud breathing noises after the end of exposure, lethargy, mortality ↑ (40%) after one exposure, exposure was aborted, severe irritation of the respiratory tract, almost no food and water consumption, body weights ↓, increased gas formation in the intestine | Hoechst Celanese Corporation 1994 |
| **rat**,<br>Sprague Dawley,<br>10 ♂, 10 ♀<br>satellite groups<br>5 ♂, 5 ♀ | **13 weeks**,<br>6 hours/day, 5 days/week,<br>0, 1, 5, 20 ml/m³<br>satellite groups: 13 weeks recovery period | **1 ml/m³: NOAEC**<br>**5 ml/m³**: gross-pathological changes of the cornea (reversible; lacklustre: 3 ♂, 3 ♀; opacity: 1 ♂), loud breathing sounds once (1 ♂, 3 ♀)<br>≥ **5 ml/m³**: irritation of the respiratory tract (see Table 2)<br>**20 ml/m³**: eyes half closed, loud breathing noises (reversible), gross-pathological changes of the cornea (reversible; lacklustre: 1 ♂, 1 ♀; opacity: 6 ♂, 9 ♀), reddish-coloured snouts; body weight gains and food consumption ↓; haematocrit ↑, haemoglobin level ↑, erythrocytes ↑, cholesterol ↓; relative lung weights ↑, lung emphysema, adipose tissue ↓ | Hoechst Celanese Corporation 1996 |

whole-body to acetic anhydride concentrations of 0, 25, 100 or 400 ml/m³ for 6 hours a day, on 5 days per week for 2 weeks. Five pregnant rats per group were treated between gestation days 6 and 15. After the first 6-hour exposure, 2 male animals of the high concentration group died, so that the treatment of this group was discontinued. Due to the mortality of the male animals, the female animals were not exposed to the concentration of 400 ml/m³. Irritation of the respiratory tract was observed in the treated animals of all groups; this was already very pronounced at the concentration of 100 ml/m³. In male rats, the lymph nodes were enlarged as a result of lymphoid proliferation. A NOAEC was not obtained (Hoechst Celanese Corporation 1994).

In a 13-week inhalation study carried out according to OECD Test Guideline 413, 15 Sprague Dawley rats per sex and group were exposed whole-body to acetic anhydride vapour concentrations of 0, 1, 5 or 20 ml/m³ (analysed concentrations: 0.98, 4.96 and 20.0 ml/m³; nominal concentrations: 0, 1.23, 6.5, 26.3 ml/m³) for 6 hours a day on 5 days per week. Of these, 5 animals per concentration and sex were examined as satellite groups at the end of a 13-week exposure-free period. In comparison with that of the control animals, the food intake and the body weight gains of the animals of the high concentration group were reduced and clinical signs (partly closed eyes, breathing noises) occurred due to the local irritation. Corneal changes were found in a few animals in the middle concentration group, and in almost all animals in the high concentration group. At concentrations of 5 ml/m³ and above, histopathological changes in the respiratory tract, such as local inflammatory reactions with epithelial hyperplasia and metaplasia in the nose, larynx and trachea were observed with a dose-dependent increase in severity. In addition, in the high concentration group, irritation of the lungs was observed. There were no lesions in the olfactory epithelium. An overview of the effects on the respiratory tract is found in Table 2. With the exception of one male animal, in which a slight lesion in the nose was found, damage to the respiratory tract was not seen in any of the animals of the satellite group exposed to the concentration 5 ml/m³. In the satellite groups of the animals exposed to high concentrations, both the incidence and the severity of the lesions were reduced. The NOAEC in this study is 1 ml/m³ (Hoechst Celanese Corporation 1996).

## Reproductive and developmental toxicity

### Fertility

In the 13-week inhalation study in male and female Sprague Dawley rats carried out according to OECD Test Guideline 413, which has already been described in Section "Subacute, subchronic and chronic toxicity", no histopathological lesions were found in the reproductive organs examined after exposure to an acetic anhydride concentration of 20 ml/m³. The two lower concentration groups were not examined due to the absence of effects in the high concentration group (Hoechst Celanese Corporation 1996).

**Table 2** Effects on the respiratory tract of rats after inhalation exposure to acetic anhydride (Hoechst Celanese Corporation 1996)

| | Number of male animals with findings | | | | Number of female animals with findings | | | |
|---|---|---|---|---|---|---|---|---|
| Target concentration [ml/m$^3$] | 0 | 1 | 5 | 20 | 0 | 1 | 5 | 20 |
| Analysed concentration [ml/m$^3$] | 0 | 0.98 | 4.96 | 20 | 0 | 0.98 | 4.96 | 20 |
| **Findings** | | | | | | | | |
| **Nose** | | | | | | | | |
| exudative inflammation | 0/10 | 0/10 | 1/10 | 9/10** | 0/10 | 0/10 | 0/10 | 8/10** |
| respiratory epithelium | | | | | | | | |
| inflammation | 0/10 | 0/10 | 1/10 | 9/10** | 0/10 | 0/10 | 0/10 | 8/10** |
| granular eosinophilic inclusions | 0/10 | 0/10 | 1/10 | 5/10* | 0/10 | 0/10 | 0/10 | 3/10 |
| hyperplasia / prominent goblet cells | 0/10 | 0/10 | 1/10 | 10/10** | 0/10 | 0/10 | 1/10 | 10/10** |
| squamous cell metaplasia | 0/10 | 0/10 | 0/10 | 6/10** | 0/10 | 0/10 | 0/10 | 4/10* |
| transitional epithelium | | | | | | | | |
| inflammation | 0/10 | 0/10 | 3/10 | 8/10** | 0/10 | 0/10 | 0/10 | 8/10** |
| erosion | 0/10 | 0/10 | 0/10 | 3/10 | 0/10 | 0/10 | 0/10 | 6/10** |
| granular eosinophilic inclusions | 0/10 | 0/10 | 7/10** | 1/10 | 0/10 | 0/10 | 9/10** | 3/10 |
| hyperplasia | 0/10 | 0/10 | 9/10** | 8/10** | 0/10 | 0/10 | 8/10** | 9/10** |
| squamous cell metaplasia | 0/10 | 0/10 | 1/10 | 9/10** | 0/10 | 0/10 | 0/10 | 9/10** |
| olfactory epithelium | | | | | | | | |
| hyperplasia | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 0/10 | 1/10 |
| **Larynx** | | | | | | | | |
| subepithelial infiltration of inflammatory cells | 0/10 | 0/10 | 1/10 | 9/10** | 0/10 | 0/10 | 3/10 | 4/10* |
| ventrolateral squamous cell metaplasia | 0/10 | 0/10 | 2/10 | 10/10** | 0/10 | 0/10 | 1/10 | 10/10** |
| hyperplasia of the epithelium surrounding the arytenoid cartilage | 0/10 | 1/10 | 5/10* | 10/10** | 0/10 | 0/10 | 0/10 | 10/10** |
| erosion/ulceration of the epithelium surrounding the arytenoid cartilage | 0/10 | 0/10 | 0/10 | 9/10** | 0/10 | 0/10 | 0/10 | 8/10** |

**Table 2** (continued)

| | Number of male animals with findings | | | | Number of female animals with findings | | | |
|---|---|---|---|---|---|---|---|---|
| Target concentration [ml/m³] | 0 | 1 | 5 | 20 | 0 | 1 | 5 | 20 |
| Analysed concentration [ml/m³] | 0 | 0.98 | 4.96 | 20 | 0 | 0.98 | 4.96 | 20 |
| **Trachea** | | | | | | | | |
| inflammation | 0/10 | 0/10 | 0/10 | 9/10** | 0/10 | 0/10 | 0/10 | 10/10** |
| epithelial hyperplasia | 0/10 | 0/10 | 1/10 | 9/10** | 0/10 | 0/10 | 0/10 | 10/10** |
| hyperplasia (carina) | 0/10 | 0/10 | 0/10 | 8/10** | 0/10 | 0/10 | 0/10 | 6/10** |
| squamous cell metaplasia (carina) | 0/10 | 0/10 | 0/10 | 6/10** | 0/10 | 0/10 | 1/10 | 4/10* |
| **Lungs** | | | | | | | | |
| perivascular inflammatory cells | 0/10 | 0/10 | 0/10 | 6/10** | 0/10 | 0/10 | 0/10 | 7/10** |
| prominent BALT | 0/10 | 0/10 | 0/10 | 4/10* | 0/10 | 0/10 | 0/10 | 2/10 |
| fibrosis of the alveolar duct | 0/10 | 0/10 | 0/10 | 5/10* | 0/10 | 0/10 | 0/10 | 9/10** |
| **Cervical lymph nodes** | | | | | | | | |
| plasmacytosis | 6/10 | 5/10 | 7/10 | 9/10 | 8/10 | 2/10 | 6/10 | 8/10 |
| moderate severity | 1/10 | 3/10 | 2/10 | 8/10** | 3/10 | 0/10 | 2/10 | 6/10 |

* : $p < 0.05$
** : $p < 0.01$ (Fisher's Exact Test)
BALT: bronchus-associated lymphoid tissue

## Developmental toxicity

In the pilot study already described in Section "Subacute, subchronic and chronic toxicity" with groups of five pregnant Sprague Dawley rats at concentrations of 0, 25 and 100 ml/m³, caesarian section was carried out prematurely in the rats of the 100 ml/m³ group on day 13 of gestation due to the severity of the local irritation in that group. This made closer examination of the foetuses impossible. Resorption of the litters occurred in two of four pregnant animals. In the dams, slight irritation of the respiratory tract, delayed body weight gains and reduced food and water consumption were found in both treated groups. At 25 ml/m³, no effects on the viability of the foetuses, litter size or foetal weights were found and gross-pathologically visible abnormalities in the foetuses were not observed. The NOAEC for foetotoxicity was 25 ml/m³, a concentration at which already marked maternal toxicity was observed (Hoechst Celanese Corporation 1994). As, due to the pronounced maternal toxicity, the 100 ml/m³ group had to be prematurely terminated on gestation day 13 and the visceral and skeletal examinations for teratogenicity could not be conducted in the insufficiently developed foetuses, this study is of limited meaningfulness.

## Genotoxicity

### In vitro

Acetic anhydride was not mutagenic in the Salmonella typhimurium strains TA97, TA98, TA100, TA1535, TA1537, TA1538, G46, C3076 and D3052, or in Escherichia coli WP2 and WP2uvrA, with and without the addition of a metabolic activation system. The cytotoxic range was covered where specified (documentation "Acetic anhydride" 1999; OECD 2002; Seifried et al. 2006). In the $TK^{+/-}$ mutation assay with L5178Y mouse lymphoma cells without the addition of a metabolic activation system, a slight increase in mutations was observed. In the presence of the metabolic activation system, the test result was negative. The concentration range tested was between 0.04 and 0.3 µl/ml (Seifried et al. 2006, 2008). The questionable result might be explained by a change in the pH value of the medium. It is known that such results can occur in the $TK^{+/-}$ mutation test with organic acids (OECD 2002).

### In vivo

In the 13-week inhalation study with Sprague Dawley rats, already described in more detail, exposure to a concentration of 20 ml/m³ did not increase the frequency of micronuclei in the bone marrow of the animals. The ratio of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) remained unaffected. Examinations were carried out 24 hours after the last exposure in 10 animals per sex and group. The positive control consisted of 5 male and 5 female animals which were given oral doses of cyclophosphamide. As the result of the evaluation was negative, the animals of the two lower concentration groups were not examined (Hoechst Celanese Corporation 1996).

## Manifesto (MAK value/classification)

The critical effects of acetic anhydride are irritation of the mucous membranes in humans and inflammatory reactions, hyperplasia and metaplasia in the upper respiratory tract of rats exposed by inhalation.

**MAK value.** The threshold concentration for the irritant effects on mucous membranes in humans remains uncertain (documentation "Acetic anhydride" 1999). The derivation of the MAK value is therefore based on more recent studies with animals, which were not yet available when the previous documentation was drawn up.

The NOAEC in a 13-week inhalation study, in which Sprague Dawley rats were exposed for six hours a day, on five days a week, was 1 ml/m³. At the next-higher concentration of 5 ml/m³ and above, inflammation, hyperplasia and metaplasia occurred in various regions of the nose (particularly in the transitional epithelium, but not in the olfactory epithelium), larynx and trachea; the incidence and severity of these effects were concentration-dependent. On the basis of the NOAEC for rats of 1 ml/m³ a NOAEC for humans can be estimated (1:3) using the procedure described in Brüning et al. (2014) for substances which cause local irritation with effects on the upper respiratory tract of rats. Taking into consideration a possible amplification of

the effects with chronic exposure (1:2) and the Preferred Value Approach, a MAK value of 0.1 ml/m³ has been established.

**Peak limitation.** Due to its local irritating property, acetic anhydride remains in Peak Limitation Category I. The excursion factor is 2, as the LOAEC in the 13-week study was five times as high as the NOAEC.

**Prenatal toxicity.** In a pilot study with pregnant Sprague Dawley rats, resorption of the litters of two of four pregnant animals occurred at 100 ml/m³. At 25 ml/m³, no effects on the loss of foetuses, litter size, foetal weights or gross-pathological abnormalities of the foetuses were observed. At 100 ml/m³, however, as a result of the poor general condition of the dams, caesarian section was carried out prematurely on day 13 of gestation, and visceral or skeletal examination of the foetuses was not carried out; it is therefore not possible to make any statement about the developmental toxicity of acetic anhydride. Taking into consideration the increased respiratory volume (1:2), there is a 125-fold difference between the NOAEC for foetotoxicity of 25 ml/m³ and the MAK value of 0.1 ml/m³. The systemic toxicity is limited by the high local toxicity in the respiratory tract. The first systemic effects occurred in the adult animals of the 13-week study at 20 ml/m³ in the form of reduced body weights and food consumption (Hoechst Celanese Corporation 1996). The difference between the concentration at which systemic effects were first observed and the MAK value is therefore 200-fold and demonstrates the low systemic availability of acetic anhydride. The pronounced local irritant effect of the substance, which is stronger than that of acetic acid, and the very low MAK value of 0.1 ml/m³ together with the hardly present systemic availability of acetic anhydride speak for classification of the substance in Pregnancy Risk Group C. In addition, acetic acid is formed during the hydrolysis of acetic anhydride, which can cause acidosis. As acetic acid, with a MAK value of 10 ml/m³, is classified in Pregnancy Risk Group C and acetic anhydride is hardly available systemically, acidosis is not to be expected at the level of the 100 times lower MAK value for acetic anhydride of 0.1 ml/m³. Despite the lack of investigations regarding its teratogenicity, acetic anhydride is therefore classified in Pregnancy Risk Group C.

**Germ cell mutagenicity.** Studies in germ cells are not available. Acetic anhydride is not mutagenic in bacteria. A $TK^{+/-}$ mutation test yielded questionably positive results without the presence of a metabolic activation system and negative results in the presence of a metabolic activation system. The questionably positive result was possibly caused by acidification of the culture medium, which is known for other organic acids. In a 13-week inhalation study with Sprague Dawley rats, no micronuclei were induced up to the highest concentration tested of 20 ml/m³. There are therefore no data available that would justify the classification of acetic anhydride in one of the categories for germ cell mutagens.

**Absorption through the skin.** Studies of dermal absorption are not available. Acetic anhydride causes marked skin irritation and is hydrolysed in the organism and already in aqueous solution to acetic acid.

In view of its rapid hydrolysis to acetic acid, exposure to aqueous acetic anhydride is unlikely. As a result of the irritant effects on the skin, longer-term exposure to undiluted acetic anhydride is unlikely. Acetic anhydride is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

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completed 22 March 2017