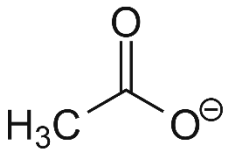
Acetate: Brief profile on systemic toxicological effects

For information on background, scope and use of this document, see accompanying cover-note!

1. Identification

Name: acetate (anion)
Chemical formula: $C_2H_3O_2^-$
Molecular mass: 59.04 g/mol



The name "acetate(s)" is used for anions of acetic acid, for salts containing such anion(s) and for esters of acetic acid. In this document, the term acetate usually refers to the anion (deprotonated acetic acid).

2. Introductory remarks

The aim of this summary on the systemic toxicity of "acetate" is to assist the assessor of health hazards of acetate-containing substances ("acetate as a counter-ion"), in determining whether the acetate moiety contributes to the overall toxicity of the substance. Ions such as acetate are not defined as a substance under REACH since they are always associated with a counterion to maintain electrical neutrality (formation of "salts"). The toxicology of such salts is always a combination of both ions, so that toxicological information is – in most cases - not available for the ion on its own. Toxicological data may be available for the salts as well as the acid itself. Acetic acid, depending on concentration, is an irritating or corrosive liquid that can cause local effects. Toxicological studies conducted with acetic acid as the test substance, can nevertheless be used to assess the systemic toxicity of the acetate ion if the dose/concentration is low enough to prevent a significant impact of the local effects of the acid. Acetic acid is a weak acid (pKa = 4.75), and at neutral conditions the predominant form is the dissociated one, i.e. the acetate ion. For the assessment of systemic toxicological effects, acetic acid and acetates are often grouped together.

The purpose of this document is not to discuss primary literature or studies in detail. Instead, reference is made to published authoritative reviews (e.g. European Food Safety Authority (EFSA), WHO or OECD).

Acetic acid and several acetate salts are authorised in the EU as food additives acc. to Regulation (EC) No. 1333/2008 (E260. E261, E262i, E262ii, E263). EFSA is currently in the process of re-evaluating various already authorised food additives, including these acetates[1]. However, as of today (25 May 2020), the re-evaluation has apparently not been concluded or at least not yet been published. EFSA (2012) on the use of acetates as preservatives in animal feed, refers to SCF (1990) as the most recent formal assessment of the safety for consumers of acetic acid and its salts. The joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted an initial review on acetates in 1974, while acetic acid was briefly re-considered by JECFA in 1998 as part of a group assessment of several "saturated aliphatic acyclic linear primary alcohols, aldehydes and acids". Likewise, acetic acid, sodium acetate and sodium diacetate are Generally Recognized As Safe (GRAS) food substances according to US FDA (1977, not considered further here as considered outdated).

Acetic acid and sodium acetate are also authorised in the EU as active substances in biocidal products according to Regulation (EU) No 528/2012. Both substances were eligible for a simplified authorisation procedure as biocidal active substances because they are already authorised as food additives. Therefore, a full assessment report is not available under the biocidal product regulation.

[1] See e.g. http://www.efsa.europa.eu/en/consultations/call/180122, Table 2 on "Remaining food additives to be re-evaluated according to Regulation (EU) No 257/2010"

In addition to being authorised as a food additive and biocidal active substance, acetic acid is also an approved active substance in plant protection products (Regulation (EC) 1107/2009). It was approved in 2009 and reviewed in 2017[2]. The corresponding 2008 Draft Assessment Report (DAR, 2008) on acetic acid is available and appears to be the most comprehensive, recent summary of reliable toxicological data on acetic acid and acetates. The formal EFSA conclusion following the DAR (EFSA, 2013) and the "Outcome of a consultation on confirmatory data" in 2017 (EFSA, 2017) did not provide new toxicological data in comparison to the 2008 DAR. Therefore, for the time being, this brief profile on systemic toxicological effects for acetate as a counter-ion refers mostly to the 2008 DAR on acetic acid. **It is suggested to update this document if/when the ongoing EFSA re-evaluation on acetates becomes available**.

3. Natural occurrence and dietary intake

Acetic acid is a natural substance occurring in foods as a result of the action of certain bacteria on sugars or ethanol. Acetic acid is also added deliberately to food as vinegar to acidify them and to add taste. Acetic acid and acetates are approved food additives (see above).

Recent information on the actual human intake of acetic acid/acetates via food (natural content or added) was not gathered for this brief profile (expected to be made available by EFSA as part of the ongoing re-evaluation).

4. Toxicokinetics

"Acetic acid is absorbed from the gastrointestinal tract and through the lung. It can be assumed that total absorption from the gastrointestinal tract after oral exposure will occur to 100 %. …The metabolic pathways of acetic acid in animals and humans are reasonably well-known and involve the formation of ketone bodies as intermediates. Isotope experiments have shown the various carbon atoms to be utilised in the formation of glycogen, intermediates of carbohydrate and fatty acid synthesis as well as cholesterol synthesis. In addition, acetic acid participates in the acetylation of amines and the formation of proteins. Acetic acid is utilised as an energy source in the body after being reacted with co-enzyme A by acetate-CoA ligase to form acetyl-CoA, which then enters the Krebs' citric acid cycle and combines with oxalacetate [sic] *to yield citrate. This process is active in the mitochondria of all animals and higher plants. Acetyl-CoA can either be used directly in the mitochondrial citrate cycle or channelled into other processes such as fatty acid synthesis"* (DAR, 2008).

5. Toxicological effects

5.1. Acute toxicity

Acetic acid (and acetates) show a low acute oral and inhalation toxicity. Oral LD50s in excess of 3300 mg/kg have been reported for rats and mice for acetic acid and sodium acetate (DAR, 2008).

5.2. Sensitisation

Although standard sensitisation studies such as GPMT or LLNA were not available for the DAR, it was concluded that new animal studies were not necessary since information on the (low) sensitisation potential of acetic acid can be derived from human data. Whereas skin *irritation* is considered a relevant effect for acetic acid based on human data, "the skin *sensitisation* potential appears to be low" (DAR, 2008). Only very few individual cases of hypersensitivity to acetic acid are reported in literature (e.g. in US FDA 1977).

[2] https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.detail&language=EN&selectedID=912

5.3. Repeated dose toxicity

The DAR (2008) summarised 10 sub-chronic toxicity studies on acetic acid or acetates that were conducted as early as 1919 and up to 2001. None of the studies met current guidelines or GLP requirements, but the DAR nevertheless concluded: *"Because acetic acid is a food acid and a naturally occurring substance, no new repeated dose toxicity studies that would conform to present test guidelines are considered necessary for the Annex I [of Council Directive 91/414/EEC] inclusion of this substance."* Based on the available animal studies, the best approximation for an unbounded NOAEL in rats can be derived from the study of Kondo et al. (2001) where dietary exposure for 8 weeks to a dose of 290 mg/kg bw/day (highest dose tested) did not induce adverse effects in the spontaneously hypertensive rat strain and was even found to be beneficial for the development of blood pressure (based on DAR, 2008).

5.4. Mutagenicity/genotoxicity

The DAR (2008) reviewed available studies, concluding as follows: *"The available data support the conclusion that the mutagenic effect of acetic acid in mammalian cells is mediated by a decrease of the pH to unphysiological values where the viability of the cells is compromised. …. Acetic acid, therefore, is considered to be not mutagenic for sufficiently buffered systems but such effects may become apparent when the capacity to maintain homeostasis is overwhelmed."* The same conclusion can be applied to the acetate ion.

5.5. Reproductive toxicity

Developmental toxicity studies on acetic acid were conducted by Morgareidge (1974) in rats, mice and rabbits. Each species was dosed orally with up to 1600 mg/kg/day. For details, see DAR (2008). In summary, *"mild reproductive effects of acetic acid were observed in parentally toxic doses in mice and rabbits."* There were no effects in rats. *"The findings in rabbits are considered to be a consequence of the bactericidal properties of acetic acid in the gastrointestinal tract of the females and not a direct effect of the test substance on embryonic implantation and development. As there was no similar effect in rats and mice it can be assumed that acetic acid probably interfered with the gut flora on which rabbits are strongly dependent. The finding is considered not relevant for humans."*
"The lowest NOAELs for parental and developmental toxicity which are considered relevant for risk assessment were established in mice at 74 and 345 mg/kg bw/day, respectively. Developmental toxicity studies in three species detected no evidence for a primary embryotoxic or teratogenic potential of acetic acid."
The DAR (2008) also concluded that *"Based on human exposure to orally ingested acetic acid from various foods and the lack of evidence that such exposure is related to fertility problems and developmental deficiencies in humans, neither a new multigeneration study nor any other postnatal evaluation or developmental toxicity study are required."*

5.6. Carcinogenicity

The DAR (2008) reviewed two non-guideline chronic/carcinogenicity studies with acetic acid. Both studies (one oral and one dermal) used acetic acid in such high concentrations that local irritation/corrosivity occurred in the forestomach and/or the oesophagus, or on the skin, respectively. DAR (2008) concluded that further *"long-term toxicity / carcinogenicity studies in animals with oral exposure are not necessary, considering that humans are exposed to orally ingested acetic acid from various food sources and there is no evidence that such exposure is causally related to toxic effects and an increased cancer incidence."* This conclusion can also be applied to acetates / the acetate ion.

6. Discussion and conclusions

Acetic acid is a natural substance occurring in foods as a result of the action of certain bacteria on sugars or ethanol. Acetic acid and acetates are approved food additives, and active substances in biocides and plant protection products (see above).

Various authorities have reviewed the safety of acetic acid and its salts as food additives but also in the context of its use as an active substance in plant protection products (JECFA, 1974&1998; SCF, 1990; DAR, 2008). JECFA and SCF have also been cited by EFSA as recently as 2012 when it assessed the safety of acetates in animal feeds. A re-evaluation by EFSA in the context of food additives for humans is anticipated to be currently on-going and was not available at the time of preparation of this report (May 2020).

None of these organisations has so far established a formal toxicological threshold value for systemic exposure to acetic acid or acetates, such as an ADI or DNEL, based on the considerations that the substances are natural components in foods, the established metabolic pathways, and/or the fact that acetic acid/vinegar has a long culinary use, without any apparent adverse effects on humans.

It is suggested to update this document if/when the ongoing EFSA re-evaluation on acetates becomes available.

Acetate "in a nutshell":

Key / leading adverse systemic effect on human health:	Acetates are not considered to cause relevant systemic toxicological effects in humans. Authoritative bodies have emphasised their natural occurrence in food and the long culinary use of vinegar (acetic acid) and have not established toxicological thresholds such as ADIs or DNELs.
Relevant (CLP) Hazard Classification(s) for systemic effects:	None
Numerical toxicological descriptor:	n/a

References

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EFSA (2017): Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for acetic acid in light of confirmatory data. EFSA Supporting publication 2017:EN-1194, doi:10.2903/sp.efsa.2017.EN-1194.

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Kondo, S. et al. (2001); Antihypertensive effects of acetic acid and vinegar on spontaneously hypertensive rats, Bioscience Biotechnology and Biochemistry 65: 2690-2694

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