Method Version: GreenScreen® Version 1.2

Verified or Non-Verified: VERIFIED

Date of Verification:	**October 22, 2013**
Expiration Date:	**October 22, 2016**
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GreenScreen® Verification Performed By:	Clean Production Action
	Date: October 22, 2013
	Verification Review Plan Prepared By: Dr. Eric Rosenblum
Verified GreenScreen® Prepared by Licensed Profiler:	Organization: ToxServices LLC
	Date: October 15, 2013

Acetic Acid (CAS# 64-19-7) GreenScreen® Assessment

Prepared for:

Clean Production Action

Date:

October 15, 2013

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GreenScreen® Executive Summary for Acetic Acid (CAS #64-19-7)

Acetic acid is a chemical that functions as an acidifier in food and pharmaceutical industries, and has been used in commercial organic synthesis, pesticides, as well as in a variety of other applications.

Acetic acid was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") based on a Very High (vH) score for Group II Human Toxicity. This corresponds to GreenScreen® benchmark classification 2f (Very High T) in CPA 2011. Data gaps (dg) exist for Reproductive Toxicity (R) and Endocrine Activity (E). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), acetic acid meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if acetic acid were assigned a High score for the data gaps Reproductive Toxicity (R) or Endocrine Toxicity (E), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
All exposure routes (oral, dermal and inhalation) were evaluated together, as a standard approach for GreenScreen® evaluations, so the GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Acetic Acid

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	DG	**L**	DG	**M**	**M**	**L**	**L**	**L**	**M**	**M**	***vH***	***vH***	**M**	**L**	***vL***	***vL***	**M**	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Acetic Acid (CAS #64-19-7)

GreenScreen® Version 1.2 Assessment

Chemical Name: Acetic Acid

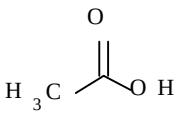
CAS Number: 64-19-7

GreenScreen® Assessment Prepared By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: February 13, 2013; September 27, 2013 (Revision #1)

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: February 21, 2013; October 15, 2013 (Revision #1)

Confirm application of the *de minimus* rule[1]: Not applicable for acetic acid; not a mixture.

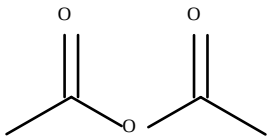
Chemical Structure(s):



Acetic Acid (CAS #64-19-7)

Also called: Acetic acid, glacial; Acetic acid, glacial [USP:JAN]; Ethanoic acid

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
Acetic anhydride (CAS #108-24-7) is used as a surrogate to fill the data gaps and support the confidence levels of hazard assignments. It is rapidly hydrolyzed to acetic acid with a half-life of 4.4 min in the hydrosphere and inside living organisms (UNEP 1997).



Acetic Anhydride (CAS #108-24-7)

Notes related to production specific attributes[2]: No information disclosed.

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

[2] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen™ assessment of the generic chemical by CAS #.

Identify Applications/Functional Uses:

1. Organic synthesis industry: widely used in commercial organic syntheses, such as in the manufacturing of various acetates, acetyl compounds, cellulose acetate, acetate rayon, plastics and rubber in tanning; as laundry sour (Merck & Co 1996)
2. Food industry: as an acidifier (pH control agent), flavor enhancer, carrier, formulating aid, curing agent, preservative in food processing, and solvent. House vinegar contains 5% acetic acid (Merck & Co 1996; Michael and Irene Ash 2004; HSDB 2005)
3. Pharmaceutical industry: acidifier, buffer and solvent (Merck & Co. 1996; Ash 2004)
4. Pesticide: fungicide, herbicide (10-20% proved 80 – 100% effective), microbiocide, pH adjus®ent (ODA 2002; PAN 2013)
4. Miscellaneous: textile printing; solvent for gums, resins, volatile oils and many other substances; laboratory reagent in chemical and biochemical analysis, constituent of photographic chemicals (fixing baths, hardeners, hypotest solutions and microfilm cements); dyeing auxiliary, etchant (semiconductor manufacture), aluminum brightening agent, laundry sour, deliming agent during leather tanning, oil well acidifier (Merck & Co. 1996; HSDB 2005).

GreenScreen® Summary Rating for Acetic Acid[3]: Acetic acid was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") based on a Very High (vH) score for Group II Human Toxicity. This corresponds to GreenScreen® benchmark classification 2f (Very High T) in CPA 2011. Data gaps (dg) exist for Reproductive Toxicity (R) and Endocrine Activity (E). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), acetic acid meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if acetic acid were assigned a High score for the data gaps Reproductive Toxicity (R) or Endocrine Toxicity (E), it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Acetic Acid

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	**L**	DG	**L**	DG	**M**	**M**	**L**	**L**	**L**	**M**	**M**	***vH***	***vH***	**M**	**L**	***vL***	***vL***	**M**	**M**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

[3] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:

Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[4]

Combustion of acetic acid can generate carbon monoxide and carbon dioxide. Although they are feasible environmental transformation products, they are not considered relevant to this GreenScreen® assessment, as they are naturally occurring in the environment, and are not persistent or bioaccumulative. In addition, combustion is not a likely transformation pathway for acetic acid-containing products, which are mainly food, pharmaceuticals, and pesticides.

Introduction

Acetic acid is a common chemical with wide applications in chemical industry, food and medicine. The largest use (33%) of acetic acid is as a chemical intermediate in the manufacture of vinyl acetate monomer, which is used to make emulsions as base resins for water-based paints, adhesive, paper coatings and textile finishes. Another use (17%) of acetic acid is as a process solvent in the manufacture of terephthalic acid which is used to make polyethylene terephthalate (PET) bottle resins and polyester fiber. Acetic acid is also used as a food and animal feed additive, a preservative in pickles, as a natural latex coagulant, and in textile dyeing and printing. Finally, dilute acetic acid solutions are used to treated microorganism infections and to remove lime scale (EC 2012).

ToxServices assessed Acetic Acid against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for acetic acid can be found in Appendix C and a summary of the results can be found below:

Respiratory –
- AOEC – Asthmagens: sensitizer-induced and irritant-induced
- GHS-Japan – Respiratory sensitizer category 1

Mammalian –
- GHS-Japan – Systemic toxicity single exposure category 1
- GHS-Japan – Acute toxicity (dermal) category 4
- GHS-Japan – Acute toxicity (oral) category 5

Eye irritation –
- GHS-Japan – Eye irritation category 1

Skin irritation –
- EU H314 – Causes severe skin burns and eye damage
- EU R35 – Causes severe burns
- GHS-Japan – Skin irritation category 1

Neurotoxicity –

[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

Boyes-N neurotoxic
Acute aquatic –
GHS-Japan – Hazardous to aquatic environment (acute) category 3
Flammable –
EU H226 – Flammable liquid and vapor
WHMIS – Class B3 – combustible liquids
GHS-Japan – Flammable liquids category 3
Reactive –
WHMIS Class E – Corrosive materials
Restricted list –
German FEA – Class 1 low hazard to waters

PhysioChemical Properties of Acetic Acid

Acetic acid is an organic acid with a molecular weight of 60. It is a clear colorless liquid at room temperature. It has a high vapor pressure (15.7 mmHg), and therefore is mostly in the vapor phase at ambient temperature. It is highly soluble in water (Log Kow < 1) and has similar density as water.

Table 1: Physical and Chemical Properties of Acetic Acid

Property	Value	Reference
Molecular formula	C_2-H_4-O_2	ChemIDplus 2013
SMILES Notation	C(=O)(C)O	ChemIDplus 2013
Molecular weight	60.0516	ChemIDplus 2013
Physical state	Liquid	HSDB 2005
Appearance	Clear, colorless	HSDB 2005
Melting point	16.6℃	HSDB 2005
Vapor pressure	15.7 mm Hg at 25℃ (Extrapolated)	HSDB 2005
Water solubility	Miscible with water	HSDB 2005
Dissociation constant	4.76 at 25℃	HSDB 2005
Density/specific gravity	1.0446 g/cm^3 at 25℃	HSDB 2005
Partition coefficient	-0.17	HSDB 2005

Hazard Classification Summary Section

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): L

Acetic acid was assigned a score of L for carcinogenicity based on negative findings in repeated dose toxicity studies (rather than standard carcinogenicity studies) in rats and rabbits. Although there is some evidence of its weak tumor promoting activity on the skin of mice, its long history of safe use indicates that it is unlikely to be a carcinogen in humans. GreenScreen® criteria classify chemicals as a low hazard for carcinogenicity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2012a)

- Authoritative and Screening Lists
  - Not listed as a known carcinogen by IARC, NTP, U.S. EPA or CA Prop 65.
  - Not on any authoritative or screening lists.
- EC 2012

  - Application of acetic acid to the skin of mice was reported to stimulate the occurrence of epidermal hyperplasia, indicating very weak tumor promoting activity
- ESIS 2000
  - Rabbits received acetic acid at 100 – 700 mg/kg/day in drinking water for 13 months and no tumors were found. No further details were provided for the study (GLP status not reported).
  - In a 5-month gavage study in rabbits (GLP status not reported), animals received 100 – 200 mg/kg acetic acid twice daily. No tumors were found. No further details were provided.
  - In a 135-day study in rats, animals received 350 mg/kg acetic acid orally (unspecified) 3 times per week for 63 days and then 140 mg/kg for 72 days. No histological evidence of tumors was found. No further details were provided
  - In a tumor promotion study in CD-1 mice (20 – 30/group), beta-propiolactone- or DMBA-initiated animals received acetic acid on the skin at the doses of 17, 33, 167, 333, 500, or 667 µmol for 1 – 3 times/week for 32 weeks. Animals in the highest dose group had an average of 0.73 papillomas/mouse, and these papillomas were noted in 41% of the high dose animals. Single dermal applications of 500 – 833 µmol acetic acid stimulated RNA, protein and DNA synthesis followed by epidermal hyperplasia. The study authors concluded that acetic acid is a weak tumor promoter.
  - In another tumor promotion study using the multistage mouse-skin model, mice were initiated with a topical dose of 7,12-dimethylbenzanthracene and two weeks later promoted with 12-O-tetradecanoylphosbol-13-acetate twice weekly for 16 weeks. Four weeks later, mice received topical trea®ent of 40 mg glacial acetic acid in 200 µl acetone twice weekly for 30 weeks. Prior to acetic acid administration, each group of mice had roughly the same number of papillomas at the site of exposure. After trea®ent of acetic acid, mice treated with the chemical had 55% more conversion of skin papillomas to carcinomas compared to control mice. Selective cytotoxicity to certain cells within the papilloma with a compensatory increase in cell proliferation was considered to be the most probably mechanism of tumor promotion for acetic acid.
- JECFA 1974
  - About 1g/day of acetic acid has been consumed by humans in vinegar and other items of food and drinks without known adverse effects at these consumption levels. However, continued ingestion of large doses has been regarded as a contributory factor in the development of Laennec type of liver cirrhosis.
- U.S. EPA 2005
  - An attempt was made to evaluate the carcinogenicity of acetic acid using the OncoLogic program, but it does not belong to any of the chemical classes in the program, so its carcinogenic potential could not be assessed.

The weight of evidence indicates that acetic acid by itself is not carcinogenic. Based on its long history of safe use as a food additive, acetic acid is unlikely to be carcinogenic in humans.

Mutagenicity/Genotoxicity (M) Score (H, M or L): L

Acetic acid was assigned a score of L for mutagenicity/genotoxicity based on negative findings for mutagenicity and clastogenicity in *in vivo* and/or *in vitro* studies for acetic acid and/or its surrogate acetic anhydride. GreenScreen® criteria classify chemicals as a low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both chromosomal

aberrations and gene mutations, there are no structural alerts, and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any of the relevant lists.
- EC 2012
  - *In vitro* - Acetic acid tested negative for mutagenicity in Ames assays using *Salmonella typhimurium* tester strains TA97, TA98, TA100 and TA1535 at concentrations of 100-6,666 µmol/place in the presence and absence of metabolic activation.
  - *In vitro* - Acetic acid was not mutagenic in *Saccharomyces cerevisiae.*
  - *In vitro* - Acetic acid was not clastogenic at concentrations close to cytotoxicity (up to 16 mM) in cultured Chinese hamster ovary K1 cells. Although induction of chromosome aberrations was observed, the effects were considered to be the result of pH effects.
  - *In vitro* - Acetic acid at concentrations of 250 – 1,500 µg/ml (LC_{50} = 1,000 µg/ml) did not initiate transformation in C3H/$10T_{1/2}$ cells.
  - *In vivo* - Acetic acid did not induce mutations or chromosomal recombination in *Drosophila melanogaster*.
- CCRIS 1995
  - *In vitro* - Acetic acid did not induce gene mutations in Ames assays using *S. typhimurium* tester strains TA97 and TA102 at concentrations of 0.1 – 10 mg/plate in the presence and absence of metabolic activation.
- ECHA 2013
  - *In vitro* – Acetic acid did not induce chromosomal aberrations in Chinese hamster lung fibroblasts at concentrations of up to 1 mg/ml without metabolic activation.
  - *In vivo* – The surrogate acetic anhydride did not substantially induce micronucleus formation in immature erythrocytes or decrease the proportion of immature erythrocytes following inhalation exposure at concentrations of 0, 1, 5 or 20 ppm for 6 hours/day, 5 days/week for 13 weeks in Sprague-Dawley rats. This study was conducted under GLP according to EU Method B.12.

The above data indicate that acetic acid was not mutagenic or clastogenic in vitro in bacterial and mammalian cells. In addition, it did not induce chromosomal aberrations in vivo in Drosophila melanogaster. The surrogate acetic anhydride which reacts with water to generate acetic acid did not induce chromosomal aberrations in vivo. Based on the available study and the long history of safe use in food, acetic acid is not likely to be genotoxic.

Reproductive Toxicity (R) Score (H, M, or L): DG
Acetic acid was assigned a score of DG for reproductive toxicity based on lack of data.

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists.
- No relevant data were identified.
- A literature search on the surrogate acetic anhydride did not identify any reproductive toxicity studies on it, either. In addition, no appropriate modeling tools are available to predict the reproductive toxicity of acetic acid.

Developmental Toxicity including Developmental Neurotoxicity (D) Score (H, M or L): L
Acetic acid was assigned a score of L for developmental toxicity based on negative findings in three *in vivo* developmental toxicity studies in rats, mice and rabbits. GreenScreen® criteria classify

chemicals as a low hazard for developmental toxicity when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
    - Acetic acid is not on any relevant lists.
- ECHA 2013
    - In a study similar to EU method B.31 (Prenatal Developmental Toxicity Study) (GLP status unknown), acetic acid in the form of apple cider vinegar (table strength 5%) was administered to female Wistar rats (25/dose) via daily gavage at doses of 0, 16, 76.3, 345, or 1,600 mg/kg during gestation Days 6 – 15. Body weights, appearance and behavior of the animals were monitored throughout the study. On gestation day 20, all dams were subjected to C-section and the numbers of implantation sites, resorption sites, and live and dead fetus were recorded. The urogenital tract of each dam was examined for anatomical normality. Body weights of the live pups were recorded and all fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter were examined using Wilson technique and the rest of the fetuses were examined for skeletal defects. No clearly discernible effect was noted on fetal survival and soft or skeletal tissue abnormalities. Therefore, an NOAEL of 1,600 mg/kg/day (highest dose tested) was established for developmental toxicity.
    - In a study similar to EU method B.31 (Prenatal Developmental Toxicity Study) (GLP status unknown), acetic acid in the form of apple cider vinegar (table strength 5%) was administered to female CD-1 mice (25/dose) via daily gavage at doses of 0, 16, 76.3, 345, or 1,600 mg/kg during gestation Days 6 – 15. Body weights, appearance and behavior of the animals were monitored throughout the study. On gestation day 17, all dams were subjected to C-section and the numbers of implantation sites, resorption sites, and live and dead fetus were recorded. The urogenital tract of each dam was examined for anatomical normality. Body weights of the live pups were recorded and all fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter were examined using Wilson technique and the rest of the fetuses were examined for skeletal defects. No clearly discernible effect was noted on fetal survival and soft or skeletal tissue abnormalities. Therefore, an NOAEL of 1,600 mg/kg/day (highest dose tested) was established for developmental toxicity.
    - In a study similar to EU method B.31 (Prenatal Developmental Toxicity Study) (GLP status unknown), acetic acid in the form of apple cider vinegar (table strength 5%) was administered to female Dutch rabbits (approx. 12/dose) via daily gavage at doses of 0, 16, 76.3, 345, or 1,600 mg/kg during gestation Days 6 – 18. Body weights, appearance and behavior of the animals were monitored throughout the study. On gestation day 29, all dams were subjected to C-section and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetus were recorded. The urogenital tract of each dam was examined for anatomical normality. Life fetuses of each litter were placed in an incubator for 24 hours to evaluate neonatal survival. Then all were sacrificed and examined for visceral abnormalities and skeletal defects. No clearly discernible effect was noted on fetal survival and soft or skeletal tissue abnormalities. Therefore, an NOAEL of 1,600 mg/kg/day (highest dose tested) was established for developmental toxicity.

- ESIS 2000
    - Male offspring from dams treated with acetic acid were exposed to acetic acid from parturition until 17 days of age. These animals had above normal preweaning body weights and were significantly less active than control rats in an open field by the age of 44 days old. No further details were provided for the study.

The weight of evidence indicates that acetic acid is not a developmental toxicant.

Endocrine Activity (E) Score (H, M or L): DG
Acetic acid was assigned a score of DG for endocrine disruption activity based on lack of data for multiple endocrine pathways.

- Authoritative and Screening Lists
    - Acetic acid is not on any relevant authoritative list.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- No relevant data were identified.
- ACD/I-Lab 2.0 2010
    - Acetic acid is predicted to have no binding potential with Estrogen Receptor alpha (Appendix D).
- A literature search of the surrogate acetic anhydride did not reveal any additional information on this endpoint.

Although predicted to be of low binding potential to estrogen receptor alpha, a low hazard rating for endocrine activity requires negative data for multiple endocrine pathways, including androgenicity, anti-androgenicity, thyroid effects, estrogenicity and antiestrogenicity. Insufficient data are available on acetic acid to fulfill the data requirement.

Group II and II* Human Health Effects (Group II and II* Human)
Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): M
Acetic acid was assigned a score of M for acute toxicity based on a dermal LD_{50} of between 1,000 and 2,000 mg/kg in rabbits. GreenScreen® criteria classify chemicals as a moderate hazard for acute toxicity when dermal LD_{50} values are between 1,000 and 2,000 mg/kg (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Acetic acid is not on any authoritative lists.
    - *Screening:* GHS-Japan: Acute toxicity (dermal) category 4.
    - *Screening:* GHS-Japan: Acute toxicity (oral) category 5.
- HSDB 2005
    - Immediately Dangerous to Life or Health: 50 ppm.

  - Acute exposure to acetic acid may cause bronchopneumonia and pulmonary edema in humans.
- EC 2012
  - Acute poisoning following incidental or accidental ingestion of concentrated acetic acid in humans has been reported. Doses of 25 – 50 g or 60 – 70 ml acetic acid have been calculated to be lethal.
  - Oral LD_{50} for acetic acid was 3,310 and 4,960 mg/kg in rats and mice, respectively
  - Inhalation LC_{50} in mice was 5,620 ppm for 1-hour exposure. Symptoms were mostly irritation of the upper respiratory tract and of the conjunctiva. Most of the surviving animals recovered quickly without abnormal condition after 30 – 35 hours.
- ECHA 2013
  - One out of 6 rats (strain not specified) exposed to 16,000 ppm (40 mg/l) acetic acid died within 14 days following a 4-hour inhalation exposure. LC_{50} is over 40 mg/l.
- ESIS 2000
  - Dermal LD_{50} = 1,060 mg/kg in rabbits

Systemic Toxicity/Organ Effects including Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M or L)**: **M**
Acetic acid was assigned a score of M for systemic toxicity (single dose) based on its classification to GHS category 3. GreenScreen® criteria classify chemicals as a moderate hazard for systemic toxicity (single dose) when the chemical belongs to GHS category 3 (CPA 2012a).

- Authoritative and Screening Lists
  - *Screening:* Acetic acid is listed by NITE 2006:
    - GHS Category 1 (blood) for single exposure systemic toxicity due to disseminated intravascular coagulations disorders and severe hemolysis.
    - GHS Category 2 (respiratory organs) for single exposure systemic toxicity due to stimulative effects to the nose, upper respiratory tract and lung in humans via inhalation exposure. In addition, inhalation of vapor by humans may cause respiratory tract corrosiveness and pulmonary edemas.
- HSDB 2005
  - As little as 1 ml glacial acetic acid (1,045 mg[5]) has resulted in perforation of the esophagus in humans.
  - Two patients ingested 80% acetic acid (amount ingested not specified) were described. One developed hemolysis, slight intravascular coagulation and oliguric kidney insufficiency. During the first week after admission, urinary excretion of beta 2-microglobulin, alanine-aminopeptidase and N-acetyl-glycosaminidase was significantly increased in both patients. They remained hemodynamically stable and did not develop fever. The urinary excretion abnormalities returned to normal after trea®ents and both patients showed similar patterns of tubular proteinuria. The observations in one of the patients suggest a direct toxic effect of acetic acid on the proximal tubule of the kidney.
  - The ototoxicity of an otic drop containing 2% acetic acid and 3% propylene glycol was investigated by measuring endocochlear potential and inner ear fluid pH. Both the otic drop and 2% acetic acid alone depressed endocochlear potential and lowered inner ear fluid pH in endolymph and perilymph. However, the application of a preparation of 2% acetic acid titrated with hydrochloric acid to pH of 4 did not cause any of the above-mentioned changes.

[5] Based on the density of 1.045 g/cm^3 for acetic acid, 1 ml acetic acid is equivalent to 1 ml x 1.045 g/ml x 1,000 mg/g = 1,045 mg.

  - Ingestion of glacial acetic acid, though not likely to occur in industry, may result in penetration of the esophagus, bloody vomiting, shock, hemolysis and hemoglobinuria.
- EC 2012
  - In the acute inhalation toxicity study in albino mice that established an LC_{50} of 5,620 ppm for 1 hour exposures, symptoms were mainly irritation of the upper respiratory tract of the conjunctiva. Most of the surviving animals recovered quickly without abnormal effects after 30 – 35 hours.
- ECHA 2013
  - In a whole body acute inhalation toxicity study in male Sprague-Dawley rats, animals were exposed to 0, 135, 450 or 598 ppm acetic acid for 4 hours. At the end of the exposure period, the animals were anesthetized and exsanguinated from the abdominal aorta. Red blood cell count, total white blood cell count and leucocyte differential count were examined. A dose-dependent reduction in the number of circulating leucocytes was found, which reached statistical significance at 450 and 598 ppm (1.1 and 1.5 mg/l, respectively).
  - In a 1-h inhalation study in albino mice, animals were exposed to 1,000 or 4,500 ppm (2.46 or 11.07 mg/l, respectively). Clinical signs during the exposure period were reddening of eyes, ears and nose, tachypnea and ruffled fur. Surviving mice recovered quickly and showed no abnormalities 3 days post exposure.

Based on available data, a 4-hour single inhalation exposure to 1.1 and 1.5 mg/l acetic acid induced transient changes in the number of leucocytes in the blood in rats. No signs of irreversible systemic toxicity were found in other inhalation studies in mice and rats, although symptoms of irritation occurred. Oral exposure to acetic acid at high concentrations resulted in severe signs of irritation. There is insufficient information available to quantify the dose-response in the human case reports. Therefore, based on the weight of evidence, the blood effects observed in rats after inhalation exposure is of questionable toxicological significance and acetic acid is classified to GHS category 3: transient target organ effects.

Group II* Score (repeated dose)**(H, M, or L): L**

Acetic acid was assigned a score of L for systemic toxicity (repeated dose) based on oral NOAELs greater than 100 mg/kg/day and a dermal NOAEL greater than 200 mg/kg./day. GreenScreen® criteria classify chemicals as a low hazard for systemic toxicity (repeated dose) when oral NOAELs are greater than 100 mg/kg/day and dermal NOAELs are greater than 200 mg/kg./day (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists
- HSDB 2005
  - Workers exposed to acetic acid at 60 ppm for 7 – 12 years, plus 1 hour daily at 100 – 200 ppm developed conjunctivitis, bronchitis, pharyngitis, and erosion of exposed teeth.
  - Six patients with frequent episodes of symptomatic hypotension during acetate dialysis were treated with bicarbonate dialysis. During acetate dialysis, the patients showed frequent onset of sudden hypotension and arrhythmia with concomitant symptoms of the so called disequilibrium syndrome. None of these syndromes were seen during bicarbonate dialysis.
  - Long term exposure to acetic acid in humans can lead to darkening of the skin, erosion of tooth enamel and chronic inflammation of the respiratory tract.
  - In 49 female workers in a Croatian vegetable pickling factory who were exposed to heated acetic acid at 4 – 10% during the work day at average concentrations of 19 - 40 mg/m^3,

respiratory function was assessed at the beginning and the end of a 2-year period. In the initial survey, occupational asthma symptoms were recorded including hoarseness and rhinitis and decreases in lung function. No progression or worsening of these conditions was found although they were still present at the end of the study period.

- Workers exposed to acetic acid at concentrations up to 200 ppm for a number of years suffered palpebral edema with hypertrophy of the lymph nodes, conjuctival hyperaemia, chronic pharyngitis, chronic catarrhal bronchitis and in some cases asthmatic bronchitis and traces of erosion on the vestibular surface of teeth. Some have reported symptoms such as digestive disorders with pyrosis and constipation, and dry, cracked and hyperkaratotic skin on palms of hands.
- Chronic exposure to acetic acid may result in pharyngitis and catarrhal bronchitis in humans.

- ECHA 2013
  - In a non-GLP study, groups of 6 male Spontaneous Hypertensive (SHR) rats were fed diets containing 6% (w/w) acetic acid (290 mg/kg/day), 6% (w/w) rice vinegar or the control diet for 8 weeks. Blood pressure, heart rate, body weight, food intake and water consumption were monitored weekly. Urine samples were analyzed every 2 weeks for volume, sodium calcium and catecholamine excretion. After 8 weeks animals were sacrificed and blood samples were collected. The heart, aorta, kidneys and lungs were removed and angiotensin I-converting enzyme (ACE) activity was measured. Although decreased blood pressure and reduced plasma renin activity were observed in all acetic acid- and vinegar-treated groups, and a NOAEL was established at 290 mg/kg/day for acetic acid based on no adverse effects observed at this dose.
  - In a non-GLP study, groups of 2 pigs were fed diets with addition of acetic acid. The dose level was raised every 10 – 30 days from approximately 155 mg/kg/day after being on a base diet without acetic acid for 30 days, to 3809 – 450 mg/kg/day after 60 days. Pigs were maintained on this dose for another 3 months except during a period when lactic acid was fed instead of acetic acid. Body weights and urine ammonia content were measured. At the end of the study, blood samples were taken for pH measurement. A NOAEL was established at 450 mg/kg/day based on no mortality or adverse effects on body weight or acid-base balance in pigs fed acetic acid at doses of up to 450 mg/kg/day for approximately 6 months.
  - In a non-GLP tumor promoting study, female CD-1 mice initiated with DMBA or β-PL received dermal application of acetic acid at doses of 1 – 40 mg/ animal 1 to 3 times per week for 32 weeks. A single dermal dose of 40 mg acetic acid in initiated mice did not induce excessive mortality. However, more than one weekly dermal application of 10 – 40 mg acetic acid caused excessive mortality. 33% of mice died when 10 mg acetic acid was administered dermally 3 times per week and 50% died when 20 mg was applied twice a week. A NOAEL was established at 30 mg/animal or 149 mg/kg/day[6] based on no mortality when applied dermally once per week for 32 weeks and a LOAEL was established at 10 mg/animal or 810 mg/kg/day[7] based on a 33% mortality when applied dermally 3 times per week.
- ESIS 2000
  - In a 35-day inhalation toxicity study in rats (GLP status unknown, strain not specified), acetic acid at a dose of 75 mg/m^3 caused damage to the spleen and kidney. No further details were provided.

[6] According to U.S. EPA (1988), NOAEL = 30 mg/week/animal ÷ 0.0288 kg/animal ÷ 7 days/week = 149 mg/kg/day
[7] According to U.S. EPA (1988), LOAEL = 10 mg/week/animal ÷ 0.0288 kg/animal ÷ 3 days/week = 810 mg/kg/day

  - In a 30-day oral study in rats (GLP status unknown), acetic acid was administered via the diet at 4,500 mg/kg/day. Thickening and inflammatory changes of the stomach were observed. No further details were provided.
  - In a repeated dose study (GLP status unknown, strain not specified), rats received oral (unspecified) doses of 0, 1,800, 2,400, 3,000 or 3,600 mg/kg acetic acid for 14 days. All animals were alive at the lowest dose. At higher doses (2400 – 3600 mg/kg), animals died within 2 – 5 days. The authors concluded that the deaths resulted from the strong corrosive effect on the gastrointestinal tract. No further details were provided.
  - Two additional studies were available from ESIS 2000, but as they were written in German, an accurate description of these studies could not be performed.
- JECFA 1974
  - Groups of 3 – 6 rats (strains unspecified) were administered acetic acid at 0.01, 0.1, 0.25 and 0.5% in drinking water for periods of 9 to 15 weeks (GLP status not reported). Fluid intake was the same in all groups. There was an immediate and progressive reduction in body weight gain, loss of appetite and a decrease in food consumption to 27% of controls at the highest dose level, although mortality was not affected. No further details were provided.
  - Approximately 1 g/day of acetic acid has been consumed by humans in vinegar and other food/drinks without known adverse effects at these consumption levels. However, continued ingestion of large doses has been regarded as a contributory factor in the development of Laennec type of liver cirrhosis.
- ICSC 1997
  - The substance may have effects on the gastrointestinal tract, resulting in digestive disorders including pyrosis and constipation.

Neurotoxicity (N)

Group II Score (single dose)**(vH, H, M or L): L**

Acetic acid was assigned a score of L for neurotoxicity (single dose) based on neurological effects observed only at very high concentrations. GreenScreen® criteria classify chemicals as a low hazard for neurotoxicity (single dose) when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Acetic acid is not on any authoritative lists.
  - *Screening:* Boyes-N: listed as neurotoxic.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- RTECS 2012
  - In humans, a Toxic Concentration Low (TCL_o)[8] of 816 ppm acetic acid over three months was established. Observations included changes in olfaction and eyes. No further details are provided.
  - In humans, a Toxic Dose Low (TDL_o)[9] of 10 ppm over 2 hours was established. Changes in olfaction were observed. No further details are provided.

[8] TCLo (Toxic Concentration Low) is the lowest concentration of a substance in air to which humans or animals have been exposed for any given period of time that has produced any toxic effect in humans or carcinogenic, neoplastigenic, or teratogenic effects in animals or humans.

[9] TDLo (Toxic Dose Low) is the lowest dose of a substance introduced by any route other than inhalation over any given period of time, and reported to produce any toxic effect in humans or carcinogenic, neoplastigenic or teratogenic effects in animals or humans.

- In a study using the intraperitoneal route of exposure in mice, a TDL_0 50 mg/kg was established. An analgesia effect was observed in the study.
- In a study using the intraperitoneal route of exposure in mice, a TDL_0 93.75 mg/kg was established, and convulsions or effect on seizure threshold were observed.
- In a study using the intravenous route of exposure in mice, a LD_{50} of 525 mg/kg was established, with convulsions or effect on seizure threshold observed

Group II* Score (repeated dose)**(H, M, or L): L**

Acetic acid was assigned a score of L for neurotoxicity (repeated dose) based on lack of behavioral abnormalities in three developmental studies. GreenScreen® criteria classify chemicals as a low hazard for neurotoxicity (repeated dose) when adequate data are available and negative, there are no structural alerts, and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Acetic acid is not on any authoritative lists.
  - *Screening:* Boyes-N: listed as neurotoxic.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- RTECS 2012
  - In a 22-day continuous inhalation exposure study in rats, a TCL_0 was established at 15 ppm. The behavioral effect of somnolence (general depressed activity) was observed.
  - In a 9-week continuous oral exposure study in rats, a TDL_0 of 22,680 mg/kg was established with observed behavioral change of decreased food intake.
- ECHA 2013
  - In the three developmental toxicity studies in Wistar rats as described in the developmental toxicity section, all the dams were observed daily for appearance and behavior, and no abnormal behavioral effects were reported.
  - No neurological effects were evaluated in the repeated dose toxicity studies for acetic acid.

Data identified in RTECS has limited value due to lack of experimental details. In the developmental toxicity studies identified in ECHA, no abnormal behaviors were observed in the dams after repeated exposure. Based on the weight of evidence, acetic acid is unlikely to be a repeated dose neurotoxicant.

Skin Sensitization (SnS) Group II* Score (H, M or L): M

Acetic acid was assigned a score of M for skin sensitization based on classification to GHS category 1B. GreenScreen® criteria classify chemicals as a moderate hazard for skin sensitization when they are classified to GHS category 1B (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists.
- VDH 1994
  - Skin sensitization to acetic acid is rare, but has occurred.
- EFSA 2013
  - Skin sensitization potential of acetic acid was judged to be low based on human experience, although no data were found.
- NIOSH 2011
  - Symptoms after exposure to acetic acid include skin sensitization.

The weight of evidence indicates that acetic acid has the potential to induce dermal sensitization, but the frequency of occurrence is expected to be low based on human experience. This classifies acetic acid to GHS category 1B (low to moderate frequency of occurrence).

Respiratory Sensitization (SnR) Group II* Score (H, M or L): M

Acetic acid was assigned a score of M for respiratory sensitization based on being listed by AOEC as an asthmagen. GreenScreen® criteria classify chemicals as a moderate or high hazard for respiratory sensitization when classified by AOEC as Rrs (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Listed as an asthmagen (ARrs) by AOEC.
  - *Screening:* GHS-Japan – respiratory sensitizer category 1.
- HSDB 2005
  - A patient with bronchial asthma reacted to acetic acid challenge. Some researchers consider acetic acid capable of causing reactive airways dysfunction (RAD), which resembles bronchial asthma but differs in that exposure to small doses does not cause a reaction a few weeks after onset. Symptoms include dyspnea, wheezing and cough.
- EC 2012
  - In a case report, a 68-year-old female showed type-1-hypersensitivity-like reactions following ingestion of alcoholic beverages, medication containing ethanol and salad dressing with acetic acid. Based on her history and the results of allergological tests, acetic acid was the likely causative agent for these reactions

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): vH

Acetic acid was assigned a score of vH for skin irritation/corrosivity based on known dermal irritation in animals and association of EU Hazard phrase H314 and Risk phrase R35. GreenScreen® criteria classify chemicals as a very high hazard for skin irritation/corrosivity when associated with EU phrases of H314 and R35 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* EU R-phrase: R35: Causes severe burns (ESIS 2013).
  - *Authoritative:* EU H314: Causes severe skin burns and eye damage.
  - *Screening:* GHS-Japan: skin irritation category 1.
- HSDB 2005
  - Repeated or prolonged contact of skin may cause dermatitis.
- ECHA 2013
  - In an *in vivo* study similar to OECD Guideline 404 (Acute Dermal Irritation/corrosion) (GLP unknown), acetic acid as 3.3% or 10% aqueous solutions were applied to shaved, intact rabbit skin using gauze pads for 4 hours. The Primary Irritation Indices (PII) were 0.5 for the 3.3% solution and 1.1 for the 10% solution. As a result, acetic acid at both concentrations was slightly irritating to rabbit skin.
  - In a GPL-compliant *in vivo* study similar to OECD Guideline 404, a 2.5% acetic acid was not irritating to rabbit skin. Concentrations of 10 – 25% were severely irritating and therefore 10% acetic acid was considered a skin irritant.
  - In an *in vivo*, non-GLP study similar to OECD Guideline 404, a 10% acetic acid solution was not irritating to intact rabbit skin and only slightly irritating to abraded skin.
  - In an *in vivo*, non-GLP study similar to OECD Guideline 404, a 10% solution of acetic acid was not irritating to intact guinea pig skin, and only of negligible irritancy to abraded skin of guinea pigs.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): vH
Acetic acid was assigned a score of vH for eye irritation/corrosivity based on severe ocular responses in the eyes of humans and rabbits. GreenScreen® criteria classify chemicals as a very high hazard for eye irritation/corrosivity when they are classified to GHS category 1 (irreversible) (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative lists:* Acetic acid is not on any authoritative lists.
  - *Screening lists:* GHS-Japan: eye irritation category 1.
- HSDB 2005
  - Unacclimatized humans experienced extreme eye and nasal irritation to acetic acid at concentrations in excess of 25 ppm. Conjunctivitis has been report when exposed to concentrations below 10 ppm. Glacial acetic acid has caused permanent corneal opacification in humans.
  - A splash of vinegar (4 – 10% acetic acid) in the human eye caused immediate pain and conjunctival hyperemia which are sometimes accompanied with injury of the corneal epithelium.
  - In two patients, accidental application of acetic acid to the eyes followed quickly by irrigation with water resulted in immediate corneal opacification. The corneas cleared sufficiently in a few days to reveal severe iritis and small pupils fixed by posterior synechiae. Although it took several months for the epithelium to regenerate, corneal anesthesia and opacity were permanent.
- ECHA 2013
  - In an *in vivo* non-GLP study similar to U.S. EPA OPP81-4 (Acute Eye Irritation), 5% acetic acid (pH 2.7) was instilled into the eyes of rabbits and produced opacities. The duration and the onset of corneal opacity were reduced after washing the eyes.
  - In an *in vivo* study (GLP status unknown) similar to OECD Guideline 405 (Acute Eye irritation/Corrosion), instillation of 10% acetic acid in the eyes of rabbits resulted in a mean erythema score of 2.67, which should be classified as an "eye irritant" according to EEC classification. In addition, the mean % corneal swelling reached 87%.
  - In an *in vivo* study (GLP status unknown) similar to OECD Guideline 405 (Acute Eye irritation/Corrosion), 3% and 10% acetic acid induced eye irritation in rabbits dose-dependently. At the lower concentration, damages to the eyes were of minimal to moderate severity and resolved by 2 weeks while at the higher concentration severe eye irritation was resulted and still present after 21 days.

Based on the weight of evidence, acetic acid at concentrations equivalent to or higher than 3% in the aqueous solution is likely to be a severe eye irritant.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): M
Acetic acid was assigned a score of M for acute aquatic toxicity based on the most conservative 48-h EC_{50} of 18.9 mg/l in daphnia. GreenScreen® criteria classify chemicals as a moderate hazard for acute aquatic toxicity when L/EC_{50} values are bigger than 10 but smaller than 100 mg/l (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists.
  - *Screening:* GHS-Japan: Hazardous to aquatic environment (acute) category 3.
- ECHA 2013
  - Fish: In a GLP-compliant acute toxicity test in *Oncorhynchus mykiss* (rainbow trout)

following SOP E257 guidelines modified from OECD Guideline 203 (Fish, Acute Toxicity Test), the 96 hour LC_{50} was greater than 1,000 mg/l for potassium acetate and therefore the 96-h LC_{50} for acetic acid was calculated to be greater than 300.82 mg/l based on the effect on the acetate ion in fresh water.

- Fish: In a GLP-compliant acute toxicity study in *Danio rerio* (zebra fish) following OECD Guideline 203, the 96 hour LC_{50} was greater than 1,000 mg/l for potassium acetate and therefore the 96-h LC_{50} for acetic acid was calculated to be greater than 300.82 mg/l based on the effect on the acetate ion in fresh water.
- Fish: In a GLP-compliant acute toxicity study in *Oncorhynchus mykiss* (rainbow trout) following OECD Guideline 203, the 96 hour LC_{50} was 108 mg/l for acetic acid in fresh water.
- Fish: In a GLP-compliant acute toxicity study in *Oncorhynchus mykiss* (rainbow trout) following OECD Guideline 203, the 96 hour LC_{50} was 45 mg/l for acetic acid in fresh water.
- Fish: In a GLP-compliant acute toxicity study in *Cyprinodon variegatus* (sheepshead minnow, saltwater fish) following OECD Guideline 203, the 96 hour LC_{50} was greater than 1,000 mg/l for potassium acetate and therefore the 96-h LC_{50} for acetic acid was calculated to be greater than 300.82 mg/l based on the effect on the acetate ion in saltwater.
- Aquatic invertebrates: In a GLP-compliant acute toxicity study in daphnia following OECD Guideline 202, the 48 hour EC_{50} was greater than 1,000 mg/l for a product containing 50% potassium acetate, 0.1% tolytriazole and 0.05% H3PO4 in fresh water. Therefore the 48-h EC_{50} for acetic acid was calculated to be greater than 300.82 mg/l in *Daphnia magna* based on the effect of acetate ion in freshwater.
- Aquatic invertebrates: In a GLP-compliant acute toxicity study in daphnia following OECD Guideline 202, the 48 hour EC_{50} was 39.6 mg/l (nominal) and 18.9 mg/l (measured) for 100% acetic acid in freshwater.
- Aquatic invertebrates: In a GLP-compliant acute toxicity study in daphnia following OECD Guideline 202, the 48 hour EC_{50} was 79.5 mg/l (measured) for acetic acid in freshwater.
- Aquatic invertebrates: In a GLP-compliant acute toxicity study in *Acartia tonsa* (calanoid copepod) following ISO 14669 (1999), the 48 hour LC_{50} was 4,966 mg/l for 50% potassium acetate in saltwater.
- Aquatic algae and cyanobacteria: In a GLP-compliant acute toxicity study in *Anabaena flos-aquae* (cyanobacteria) following OECD Guideline 201, the 72 hour EyC_{50} was 29.2 mg/l (biomass) and the 72-h ErC_{50} was 55.2 mg/l (growth rate) for acetic acid (99.85%) in freshwater.
- Aquatic algae and cyanobacteria: In a GLP-compliant acute toxicity study in *Desmodesmus subspicatus* (green algae) following OECD Guideline 201, the 72 hour ErC_{50} was 810.9 mg/l (nominal) for 60% acetic acid and the 72-h ErC_{50} (nominal, growth rate) was 486.5 mg/l (nominal, growth rate) for acetic acid (100%) in freshwater.
- Aquatic algae and cyanobacteria: In a GLP-compliant acute toxicity study in *Navicula pelliculosa* (marine algae) following OECD Guideline 201, the 72 hour EC_{50} for biomass was 87 mg/l and the 72-h EC_{50} for reproduction was 134 mg/l for acetic acid (60%) in saltwater.
- Aquatic algae and cyanobacteria: In a GLP-compliant acute toxicity study in *Skeletonema costatum*
- (marine algae) according to ISO 10253, the 72-h EC_{50} (growth rate) was over 1,000 mg/l for 50% potassium acetate and the 72-h EC_{50} for acetic acid was calculated to be greater

than 300.82 mg/l based on the effect of the acetate ion in saltwater.

Based on the weight of evidence, the most conservative acute aquatic toxicity value for acetic acid is the measured 48-h EC_{50} of 18.9 mg/l for 100% acetic acid in *Daphnia magna* in freshwater.

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L
Acetic acid was assigned a score of L for chronic aquatic toxicity based on the most conservative chronic aquatic toxicity value (21-day NOEC) of 22.7 mg/l in daphnia. GreenScreen® criteria classify chemicals as a low hazard for chronic aquatic toxicity when its chronic aquatic toxicity values are greater than 10 mg/l (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists.
- ECHA 2013
  - Fish: In a GLP-compliant study in freshwater *Oncorhynchus mykiss* (rainbow trout) conducted according to OCED Guideline 204, the mean measured 21-day LC_{50} and NOEC for 60% acetic acid was 87 and 57.2 mg/l, respectively. The mean measured 21-day LC_{50} and NOEC for 100% acetic acid was 52.2 and 34.3 mg/l, respectively.
  - Aquatic invertebrates: In a GLP-compliant study in freshwater *Daphnia magna* conducted according to OCED Guideline 202-II, the 21-day NOEC for reproduction based on measured concentrations was reported as 31.4 mg/l for 100% acetic acid.
  - Aquatic invertebrates: In a GLP-compliant study in freshwater *Daphnia magna* conducted according to OCED Guideline 202-II, the 21-day NOEC for reproduction based on measured concentrations was reported as 22.7 mg/l for 100% acetic acid.

Based on the weight of evidence, the most conservative chronic aquatic toxicity value for 100% acetic acid is the 21-day NOEC of 22.7 mg/l in daphnia.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL
Acetic acid was assigned a score of vL for persistence based on fast biodegradation in soil and water. GreenScreen® criteria classify chemicals as a very low hazard for persistence when the degradation half-life meets the 10-day window in ready biodegradation test (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists.
- ECHA 2013
  - In a non-GLP compliant aerobic ready biodegradability test conducted according to published BOD procedure – "Standard methods for examination of waste and wastewater" (APHA 1971), 96% biodegradation was reached in non-acclimated freshwater after 20 days, indicating that acetic acid was readily biodegradable.
  - In a non-GLP compliant, non-guideline, 4-week anaerobic ready biodegradability test using synthetic sewage, acetic acid was tested to be readily biodegradable. No further information was provided.
  - In a non-GLP compliant, nonstandard, aerobic study using activated sludge from wastewater trea®ent plants, acetic acid reached 40.2% of its theoretical oxygen demand in 24 hours. This suggested that acetic acid degrades rapidly.
  - In a non-GLP compliant, nonstandard biodegradation study in soil, 34.42 mg ^{14}C-labeled acetate was added to 100g of loamy sand or clay loam with 9 times the amount of

cellulose. The radioactivity in the form of CO2 was approximately 2 – 6% on day 2 which increased to approximately 20% on day 120. The rest of the radioactivity was incorporated into humic or fulvic acids. Mineralization amount was approximately 20% after 120 days and the non-extractable residues accounted for approximately 80% after 120 days. It was concluded that the primary degradation of acetate is fast and complete incorporation into organic substances occurred within 2 days in soil.

- ESIS 2000
  - In a ready biodegradability test according to OECD Guideline 302B (Inherent biodegradability) (GLP status unknown), over 70% degradation was reached after 5 days.
  - In a ready biodegradability test according to OECD Guideline 302B (GLP status unknown), 95% degradation was reached after 5 days.
  - In an aerobic biodegradation study (GLP status not reported), 76% biodegradation was reached within 5 days, 82% within 10days, 85% within 15 days and 96% within 20days.
  - In an aerobic biodegradation study (GLP status not reported), 66% biodegradation was reached within 5 days, 88% within 10days, 88% within 15 days and 100% within 20days.

Based on the weight of evidence, acetic acid is readily degradable and the degradation half-life meets the 10-day window in the soil and in water.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Acetic acid was assigned a score of *vL* for bioaccumulation based on the log Kow of -0.71 and a calculated BCF of 3.2. The level of confidence was low as this assignment was based on model predictions. GreenScreen® criteria classify chemicals as a very low hazard for bioaccumulation when Log Kow is below 4 and BCF is below 100 (CPA 2012a).

- Authoritative and Screening Lists
  - Acetic acid is not on any relevant lists.
- HSDB 2005
  - An estimated BCF of 3.2 was calculated for acetic acid based on a log Kow of -0.71 and a regression-derived equation.

<u>Physical Hazards (Physical)</u>

Reactivity (Rx) Score (vH, H, M or L): M
Acetic acid was assigned a score of M for reactivity based on well documented corrosiveness to metals. GreenScreen® criteria classify chemicals as a moderate hazard for reactivity when it is classified to GHS category 1 for corrosiveness to metal (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not on any authoritative lists.
  - *Screening:* WHMIS Class E – Corrosive materials.
- NIOSH 1992
  - Conditions contributing to instability: heat and freezing temperatures. The vapor of acetic acid forms explosive mixtures with air.
  - Incompatibilities: fires or explosions may result from contact with chromic acid, ammonium nitrate, sodium peroxide, nitric acid, phosphorus trichloride or other oxidizers
  - Highly corrosive in concentrated form to metals, some coatings and some forms of plastic and rubber.
- ICSC 1997
  - Explosive vapor/air mixtures may be formed above 39℃

    - NFPA rating for reactivity hazard: 0
- Sigma-Aldrich 2012
    - DOT (US) Class 8(3):corrosive materials
- NITE 2006
    - Although acetic acid is classified by the United Nations Recommendations on the Transport of Dangerous Goods (UNRTDG) as a class 8 (subsidiary risks category3) corrosive substance, it is thought that this classification is based on skin corrosiveness. Since there are no data about corrosiveness to metals, it cannot be classified.
    - There are no chemical groups associated with explosive or self-reactive properties present in the molecule
    - The chemical does not contain metals or metalloids and therefore not expected to emit flammable gases upon contact with water
    - Acetic acid is an organic compound without peroxide (-O-O-) structure.
- The Engineering Toolbox 2013
    - Acetic acid in aerosol, vapor or air free forms are mildly to moderately corrosive to metals used in pipes such as stainless steels, bronze, titanium, and cobalt base alloy 6.

Flammability (F) Score (vH, H, M or L): M

Acetic acid was assigned a score of M for flammability based on association with EU phrases H226 and R10 (liquid). GreenScreen® criteria classify chemicals as an M hazard for flammability when associated with EU H-statement of H226 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* EU H-statement: H226 (Flammable liquid and vapor).
    - *Authoritative:* EU R-phrase: R10 (Flammable) (ESIS 2013).
    - *Screening:* WHMIS Class B3: combustible liquids.
    - *Screening:* GHS-Japan: Flammable liquids category 3.
- NIOSH 1992
    - NFPA rating for flammability: 2
    - Flash point of 39℃ for concentrated solutions approaches that of acetic acid while dilute acetic acid solutions are not combustible
    - Autoignition temperature: 427℃
    - Flammable limits in air: 4.0 – 16.0 % by volume

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Acetic Acid

GreenScreen™ Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
									S	R *	S	R *	*	*								
Table 2: Chemical Details																						
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	Acetic Acid	64-19-7	**L**	**L**	DG	L	DG	**M**	**M**	**L**	**L**	**L**	**M**	**M**	**vH**	**vH**	**M**	**L**	**vL**	*vL*	**M**	**M**

Table 3a: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	No	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen™ Benchmark Score
Acetic Acid	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen™ Benchmark Score
Acetic Acid	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Acetic Acid (CAS #64-19-7)

ACETIC ACID, GLACIAL

CAS RN: 64-19-7

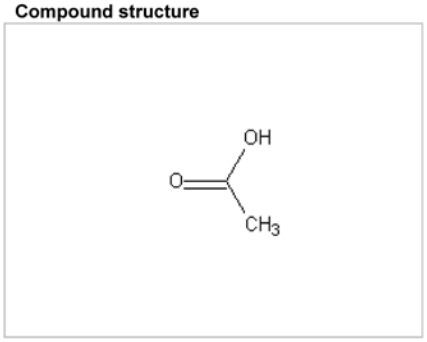
Detailed Direct Hazard Listings Quickscreen

RESPIRATORY	AOEC - Asthmagens (AOEC) Asthmagen (ARrs) - sensitizer-induced & irritant-induced - GreenScreen Benchmark Unspecified - HPD
RESPIRATORY	Japan METI/MOE - GHS Classifications (GHS-Japan) Respiratory sensitizer - Category 1 - GreenScreen Benchmark Unspecified
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following single exposure - Category 1 - GreenScreen Benchmark Unspecified
EYE IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Serious eye damage / eye irritation - Category 1 - GreenScreen Benchmark Unspecified
SKIN IRRITATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H314 Causes severe skin burns and eye damage - GreenScreen Benchmark Unspecified - HPD
SKIN IRRITATION	EC - Risk Phrases (EU R-Phrases) R35: Causes severe burns. - GreenScreen Benchmark Unspecified - HPD
SKIN IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Skin corrosion / irritation - Category 1 - GreenScreen Benchmark Unspecified
NEUROTOXICITY	Pattys Toxicology - Boyes Neurotoxicants (Boyes-N) Neurotoxic - GreenScreen Benchmark Unspecified
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (dermal) - Category 4 - GreenScreen Benchmark Unspecified
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (oral) - Category 5 - GreenScreen Benchmark Unspecified
ACUTE AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (acute) - Category 3 - GreenScreen Benchmark Unspecified
FLAMMABLE	EC - CLP/GHS Hazard Statements (EU H-Statements) H226 Flammable liquid and vapour - GreenScreen Benchmark Unspecified - occupational hazard only
FLAMMABLE	Québec CSST - WHMIS Classifications (WHMIS) Class B3 - Combustible liquids - GreenScreen Benchmark Unspecified
FLAMMABLE	Japan METI/MOE - GHS Classifications (GHS-Japan) Flammable liquids - Category 3 - GreenScreen Benchmark Unspecified
REACTIVE	Québec CSST - WHMIS Classifications (WHMIS) Class E - Corrosive materials - GreenScreen Benchmark Unspecified
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS) Class 1 Low Hazard to Waters - GreenScreen Benchmark Unspecified - occupational hazard only

APPENDIX D: ACD/I-Lab 2.0 Output for Acetic Acid (CAS #64-19-7)

ACD/Labs
I-Lab 2.0 - ilab.acdlabs.com
Monday 18th of March 2013 04:37:26 PM. Algorithm Version: v5.0.0.184

Compound structure



No binding to Estrogen Receptor alpha (LogRBA<-3)

Probability of Estrogen Receptor Binding:
LogRBA > -3: 0
LogRBA > 0: 0

Experimental Values for Similar Structures

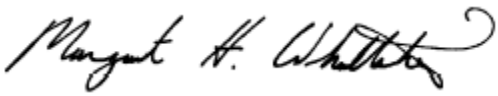
1 / 1

Authorized Reviewers

Acetic Acid GreenScreen® Evaluation Prepared By:

Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC

Acetic Acid GreenScreen® Evaluation QC'd By:



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