

**U.S. HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM**

ASSESSMENT PLAN

For

ACETIC ACID AND SALTS CATEGORY

**Prepared by
American Chemistry Council
Acetic Acid and Salts Panel**

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Appendix 1. SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

I. INTRODUCTION

The High Production Volume (HPV) Challenge Program is a voluntary initiative with an objective of completing screening level hazard data profiles for approximately 2800 HPV chemicals as identified on the US Environmental Protection Agency's (USEPA) 1990 Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR). In the US, HPV chemicals are those that are manufactured or imported in quantities greater than 1 million pounds per year. The hazard data to be provided in the program are those that meet the requirements of the Screening Information Data Set (SIDS) Program (OECD 1997a). SIDS, which has been internationally agreed to by member countries of the Organization for Economic Cooperation and Development (OECD), provides the basic screening data needed for an initial assessment of the physical-chemical properties, environmental fate, and human and environmental effects of chemicals. The information for completing the SIDS can come from existing data, may be generated as part of the HPV Challenge Program or may be provided through structure activity or category-based analyses. Once the available studies are identified or conducted, "robust summaries" are prepared.

The USEPA, Industry, and Non-Governmental Organizations (NGOs) are unified in their commitment to minimize the numbers of animals tested in the HPV Challenge Program whenever it is scientifically justifiable (USEPA 1999a, 1999b). Evaluating closely related chemicals as a group, or category, rather than solely as individual chemicals is one way to accomplish this goal. The use of categories is encouraged by USEPA in the HPV Challenge Program. Appropriately constructed categories allow for a more efficient evaluation while reducing the number of animals required for testing.

In accordance with the HPV Challenge Program, the Acetic Acid and Salts Panel (Panel), housed at the American Chemistry Council, is sponsoring a category that includes acetic acid and its salts as well as related acids and their salts. The Panel is comprised of the following companies:

A.E. Staley Manufacturing Company
Millennium Chemicals Incorporated
Cargill, Inc.
Archer Daniel Midland Company
The Procter and Gamble Company
Vulcan Chemicals
W.R. Grace & Company
Mallinckrodt Inc.
Eastman Kodak Company
Eastman Chemical Company
Sterling Chemicals
Celanese Ltd
OMG Americas, Inc.
The Shepherd Chemical Company

This assessment plan provides a summary and analysis of the available data, and identifies areas where additional data may be needed. Section II of this assessment plan provides a rationale and justification for the development of the Acetic Acid and Salts category. Section III reviews the methods used in the collection of published and unpublished data. Section IV reviews the evaluation of data quality. Section V reviews the preparation of the robust summaries and the construction of a data matrix. Section VI is an in-depth evaluation of data matrix patterns for each of the four data endpoint categories (i.e., physical-chemical properties, environmental fate, ecotoxicity and toxicity). Section VII is a summary of the Acetic Acid and Salts category and its properties. Section VIII presents the conclusions regarding data availability and the need for additional testing to complete the SIDS profiles for the sponsored compounds.

II. IDENTIFICATION OF THE STRUCTURE BASED CATEGORY

The Panel is sponsoring a total of 13 individual compounds, the structures of which are shown in Appendix 1. The category includes several food acids and their corresponding salts, specifically acetic acid and its ammonium, calcium, potassium, sodium, magnesium, and manganese salts; citric acid and its sodium, tripotassium and trisodium salts; fumaric acid; and malic acid¹. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the citric acid or Krebs's cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. As shown in Appendix 1, acetic acid has one, fumaric acid and malic acid have two, and citric acid has three carboxylic acid functional groups. Malic acid and citric acid also have an additional alcohol group.

Role in the Citric Acid Cycle

Food acids, such as acetic acid, citric acid, fumaric acid, and malic acid (and citrate, fumarate and malate), are found in a wide variety of unprocessed foods. The last three acids play key roles in the metabolic energy system called the Citric Acid Cycle or Krebs's Cycle (Gardner 1966). The cycle consists of a series of chemical reactions occurring within the cell that are responsible for the final breakdown of food molecules to form carbon dioxide, water, and energy. This process is active in all animals and higher plants and is carried out in the mitochondria.

The cycle is the major pathway by which animals obtain their required energy, and three of these food acids (citric, fumaric and malic) are integral components in this series of enzymatic reactions. A key feature of the cycle is that the citric, fumaric and malic acids are used over and over again in the production of energy. Furthermore, these acids catalytically accelerate oxygen uptake and the production of carbon dioxide by muscle and other tissues. They are not found in appreciable

¹ Note that the salts may be referred to by synonyms in some sources. For example, acetic acid ammonium salt is commonly called ammonium acetate. Similarly, citric acid tripotassium salt is commonly called potassium citrate (or tripotassium citrate).

quantities among the waste products, as elimination by animal kidneys tends to increase their consumption by the respiratory reactions, thus maintaining an “acid-base” balance within the animal system (Gardner 1966).

In summary, the compounds in this category are naturally occurring in foods and essential to normal metabolic processes. They are also commonly used as flavor and texture enhancers in a wide variety of foods. The compounds in this category can be viewed as biochemically and toxicologically equivalent to their naturally occurring counterparts.

III. COLLECTION OF PUBLISHED AND UNPUBLISHED DATA

Panel members contributed in-house studies of physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity for the compounds in the category. To supplement the industry data, literature searches were conducted of on-line databases and CD-ROMs (e.g., Hazardous Substance Data Bank [HSDB], Registry of Toxic Effects of Chemical Substances [RTECS], Aquatic Toxicity Information Retrieval [AQUIRE]), standard scientific compendia (e.g., *CRC Handbook of Chemistry and Physics*, *The Merck Index*, *Patty's Industrial Hygiene and Toxicology*, *Handbook of Environmental Data on Organic Chemicals*, BIBRA toxicology profiles), and other published sources (e.g., International Uniform Chemical Information Database [IUCLID]). The literature search was augmented by investigating the web sites of a variety of government and regulatory organizations, such as the Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Food and Drug Administration (FDA), and World Health Organization (WHO). The USEPA ECOTOX database was also searched. A number of primary references from peer reviewed published journals were also reviewed. The Syracuse Research Corporation EPIWIN v.2.2 model, which is accepted by the U.S. Environmental Protection Agency (USEPA) for organic compounds, was used to provide estimates of key physical-chemical properties for some of the compounds.

IV. EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general USEPA and OECD SIDS guidance (USEPA 1999c; OECD 1997b) and the systematic approach described by Klimisch et al. (1997). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. The Klimisch et al. (1997) approach specifies four categories of reliability for describing data adequacy. These are:

- 1 Reliable without Restriction:** Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

- 2 **Reliable with Restrictions:** Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.
- 3 **Not Reliable:** Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.
- 4 **Not Assignable:** Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

Only those studies which are deemed reliable for the current HPV Challenge Program purposes are included in the data set for this assessment plan. Reliable studies include both categories rated 1 (Reliable without restriction) and 2 (Reliable with restrictions). Studies rated 3 (Not reliable) were not used. Studies rated 4 (Not assignable) were used when professional judgment deemed it appropriate as part of a weight-of-evidence approach. Finally, some older studies were not included if they had been superceded by more recent studies rated 1.

V. ROBUST SUMMARIES AND CONSTRUCTION OF DATA MATRIX

Robust summaries were prepared according to the format recommended by the USEPA (1999d) and OECD (1997a) and constructed using Microsoft Word software. These summaries present the salient information from each of the reliable studies. All of the summaries are collected into a dossier that includes all of the individual acids and salts for the category. The dossier for the Acetic Acid and Salts category is a separate document that should be used in conjunction with this assessment plan.

The data in the robust summaries are used to construct a data matrix table. This table (Appendix 1 to this assessment plan) is a matrix of SIDS/HPV endpoints and the available data for each of the sponsored compounds in the Acetic Acid and Salts category. To facilitate the connection between data in the table and the corresponding robust summaries, reference sources have been included with each data point.

VI. EVALUATION OF MATRIX DATA PATTERNS

The data matrix table (Appendix 1) identifies where data for specific compounds and data endpoints are available (data provided) and not available (indicated by "--" in the table). The available data were evaluated for patterns and trends among the 13 compounds that could be used to predict values for a particular endpoint (e.g., acute oral toxicity) where adequate data are not available for a given compound (i.e., "Read Across"). In addition, the data were evaluated to determine to what extent the SIDS/HPV data endpoints were covered by available data for each compound in the category (i.e., "Read Down").

A. *Evaluation of “Read Across” Patterns*

The following discussion reviews the “Read Across” patterns among the 13 compounds for each of the four major data areas: physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity. The primary patterns to look for in the physical-chemical property data are similarities in the parameters that affect dissociation and partitioning between aqueous and organic phases. In reviewing the environmental fate data, the important information to look for is the primary mechanism of degradation or dissociation of the compounds. These factors also affect the bioavailability and aquatic toxicity of the compounds. Similarly, it is important to look for any trends or similarities in the mammalian toxicity data, which are important surrogates for potential human effects. Each of the four acids (acetic, fumaric, malic, and citric), along with their corresponding salts, are reviewed separately in the following sections.

Acetic Acid and its Salts

Acetic acid and its salts are comprised of seven compounds that include acetic acid ($\text{H}_4\text{C}_2\text{O}_2$), ammonium acetate ($\text{H}_7\text{C}_2\text{NO}_2$), calcium acetate ($\text{H}_6\text{CaC}_4\text{O}_4$), magnesium acetate ($\text{H}_6\text{C}_4\text{MgO}_4$), manganese acetate ($\text{H}_6\text{C}_4\text{MnO}_4$), potassium acetate ($\text{H}_3\text{KC}_2\text{O}_2$), and sodium acetate ($\text{H}_3\text{NaC}_2\text{O}_2$). The chemical structures, physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these seven compounds are similar. Acetic acid and its salts undergo dissociation in aqueous media into the acetate anion ($\text{H}_3\text{C}_2\text{O}_2^-$) and the respective cations (H^+ , NH_4^+ , Ca^{2+} , Mg^{2+} , Mn^{2+} , K^+ , Na^+). The toxicity of each compound is driven by acetate, with the cations playing a minor role.

Physical-chemical Properties

Reliable data exist for melting and boiling points, water solubility and pH for most of the seven compounds (see Appendix 1). With the exception of acetic acid, for which actual experimental data exist, octanol-water partition coefficient (K_{ow}) and vapor pressure data are largely available as estimated values using the standard chemical property estimation software, EPIWIN v.2.2 (Syracuse Research Corporation 1993). All seven compounds are highly water soluble and of moderate to low volatility. Based on such information, the Panel believes that the available data adequately characterizes the physical-chemical properties of acetic acid and its salts.

Environmental Fate and Transport

Reliable data for environmental fate and transport behavior are available for acetic acid and its salts (see Appendix 1). Biodegradation appears to be the most significant removal mechanism. These compounds readily dissociate into their respective cations and the acetate anion; the anion is subsequently biodegraded. Data indicate that acetic acid and sodium acetate (acetic acid, sodium salt) photodegrade, although the rate is substantially slower than that of biodegradation. Level I fugacity modeling predicts that about 73% of any acetic acid

released to the environment would partition to water, with the remainder partitioning into the air. These data demonstrate that acetic acid and its salts are not persistent in the environment. The Panel believes that the available data and analogous behavior of the compounds can be used to adequately characterize the environmental fate and transport properties of acetic acid and its salts.

Ecotoxicity

Reliable ecotoxicity data for aquatic animals are available for four of the seven compounds (see Appendix 1). The ecotoxicity data indicate that these compounds are practically nontoxic to only slightly toxic. The three remaining salts (calcium, magnesium and manganese) are closely related to the other salts in structure and behavior and so would be expected to have low toxicity as well. Of the seven compounds, acetic acid appears more toxic, which is attributable to its relatively low pH. Toxicity data for algae are available for acetic acid and its sodium salt, and also indicate generally low toxicity. While some of these compounds lack actual data, the Panel believes that the available aquatic toxicity data and the generally low to moderate toxicity of acetic acid and its salts adequately characterize the ecotoxicity of these compounds.

Mammalian Toxicity

Several aspects of mammalian toxicity are evaluated. Acute testing provides information on gross effects, such as mortality, from exposure to high doses. Repeated dose testing provides information on toxicity associated with multiple doses over time. Genetic testing is conducted to evaluate the potential for mutagenic effects by using bacterial systems (e.g., the Ames test), non-bacterial systems (e.g., chromosomal aberrations), and *in vivo* (i.e., live animal) systems. Reproductive and developmental/teratogenic testing provides information on the potential effects of long-term exposure to lower doses, especially as related to possible effects in developing embryos and young animals. It is important to note that the lack of significant exposure may obviate the need to fill apparent data gaps with mammalian testing.

The available data indicate that acetic acid and its salts have generally low acute mammalian toxicity (see Appendix 1). Acute oral toxicity data for mammals are available for all compounds with the exception of the ammonium salt. Acute inhalation data are available for acetic acid and the sodium salt. Inhalation is not expected to be a primary route of exposure given that acetic acid and its salts have generally low volatility and are highly soluble. Dermal toxicity data are available only for acetic acid, but the level of toxicity is low and the salts are expected to exhibit a comparable dermal safety profile. Several studies indicate that the acute toxicity via other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) is also low. Thus, additional acute testing on the other compounds is not deemed by the Panel to be necessary to characterize this category.

There are repeated dose, genetic, and developmental/teratogenic toxicity test endpoints for acetic acid. An essentially complete set of data for the sodium salt of acetic acid also is available. Less data are available for the other salts, but the data that are available show similar responses to the sodium salt. The dissociative nature of salts suggests that additional testing would provide no information useful for assessing the hazard of this category. Of note, none of the counter ions is expected to impact the overall safety profile of the salts within this chemical category.

In addition, acetic acid is naturally occurring as the acid in apple cider vinegar and other fruit-derived products. It and several of its salts are commonly used as food additives (e.g., as flavor enhancers) and are listed as Generally Recognized as Safe (GRAS) by the USFDA. Given the lack of significant toxicity, the natural occurrence in both plants and animals, and the common use in foods, the Panel believes that no additional mammalian toxicity testing is necessary.

Fumaric Acid

While acetic acid is the simplest form and contains only a single carboxylic acid unit, fumaric acid ($\text{H}_4\text{C}_4\text{O}_4$) contains two carboxylic acid units connected by a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS/HPV data elements and indicate that fumaric acid is highly soluble in water and has low volatility. Level I fugacity modeling predicts that virtually all (99.8%) of any fumaric acid released to the environment would partition to water. The Panel believes that the available data adequately characterize the physical-chemical properties of fumaric acid.

Environmental Fate and Transport

Reliable data are available for all the SIDS/HPV data elements. Fumaric acid dissociates into H^+ and fumate ($\text{H}_3\text{C}_4\text{O}_4^-$) and fumate undergoes significant degradation by both biotic and abiotic mechanisms and is therefore not persistent. Nearly complete biodegradation was observed after 21 days under aerobic conditions. The Panel believes that the available data adequately characterize the environmental fate and transport properties of fumaric acid.

Ecotoxicity

Likewise, complete data are available for all the SIDS/HPV aquatic toxicity data elements. LC_{50} values for fish and *Daphnia* were greater than 200 mg/L. The value for the more sensitive algae was 41 mg/L. These data indicate that fumaric acid has low toxicity to aquatic animals and plants.

Mammalian Toxicity

Acute oral and dermal toxicity data indicate that fumaric acid is of low acute toxicity, with LD50 values from approximately 10 g/kg bw (oral) to greater than 20 g/kg bw (dermal). *In vitro* and *in vivo* studies were negative with regards to genetic toxicity. Reproductive and developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to fumaric acid. The Panel believes that the large amount of available data and the low toxicity indicated are adequate to characterize the mammalian toxicity of fumaric acid.

In addition, fumaric acid is naturally occurring in apples, beans, carrots and other fruits and vegetables. It is also commonly used to control pH and produce light textures in such foods as cake, cookies and soft drinks. Fumaric acid is listed as GRAS by the USFDA.

Malic Acid

Malic acid ($H_6C_4O_5$) is very similar to fumaric acid, with the difference being the addition of a hydroxyl group (OH) and removal of a double bond.

Physical-chemical Properties

Reliable data are available for all of the SIDS data elements and indicate that malic acid is highly soluble in water and has a low volatility. Based on such information, the Panel believes that the available data adequately characterize the physical-chemical properties of malic acid.

Environmental Fate and Transport

Photodegradation and biodegradation data are available for malic acid and show that it dissociates into H^+ and malate ($H_5C_4O_5^-$). Malate has been shown in a series of screening tests to biodegrade readily in soil and water. Level I fugacity modeling predicts that 100% of any malic acid released to the environment would partition to water. Based on such information, the Panel believes that malic acid is not persistent in the environment and is adequately characterized.

Ecotoxicity

Data on the aquatic toxicity of malic acid to daphnids are available. No data on toxicity to fish and algae were available, but the 48 hour LC_{50} for *Daphnia magna* was 240 mg/L, indicating a low level of aquatic toxicity. Given this data and the considerable aquatic toxicity data for the structurally related compounds in this category (e.g. acetic, fumaric and citric acids), no further aquatic tests are deemed by the Panel to be necessary.

Mammalian Toxicity

Acute data for the oral and intraperitoneal exposure routes are available for malic acid and indicate a low to moderate toxicity. Dermal toxicity data are not available for malic acid, but are expected to be comparable to the relatively low order of dermal toxicity associated with fumaric acid. *Both in vitro* and *in vivo* studies demonstrated no evidence of genetic toxicity. Developmental/teratogenic toxicity studies also resulted in no indication of these effects after exposure to malic acid. The Panel believes that the large amount of available data, combined with the low toxicity, are adequate to characterize the mammalian toxicity of malic acid.

In addition, malic acid occurs naturally as the major acid in apples, apricots, cherries, broccoli, carrots, potatoes, and many other fruits and vegetables. It is also commonly used as a flavor booster in candy, jelly, fruit drinks and ice cream. It is listed as GRAS by the USFDA.

Citric Acid and its Salts

Citric acid and its salts are comprised of four compounds, which include citric acid ($H_8C_6O_7$), sodium citrate ($H_7NaC_6O_7$), tripotassium citrate ($H_5K_3C_6O_7$), and trisodium citrate ($H_5Na_3C_6O_7$). The chemical structures and available data indicate that the physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these four compounds are similar. As in the case of the other acids and salts in this category, citric acid and its salts undergo dissociation in aqueous media into the citrate anion ($H_7C_6O_7^-$) and the respective cations (K^+ , Na^+). The toxicity of each compound is driven by citrate, with the cations playing a minor role. Therefore, where data are available for any of the compounds within this sub-category, they are considered by the Panel to be adequate to represent the entire group.

Physical-chemical Properties

Reliable data exist for all relevant physical-chemical properties for citric acid and its tripotassium and trisodium salts. These compounds are all highly water soluble and of moderate to low volatility. The Panel believes that the available data adequately characterizes the physical-chemical properties of citric acid and its salts.

Environmental Fate and Transport

Data on the environmental fate of citric acid and its trisodium salt are available. These data indicate that citric acid and its salts dissociate into their respective cations and the citrate anion, which is subsequently biodegraded. Studies indicate that citric acid and its trisodium salt are readily biodegraded (90-98% degradation after 48 hours). Level I fugacity modeling predicts that 100% of any citric acid released to the environment would partition to water.

Therefore, the existing data indicates that citric acid and its salts are not persistent in the environment. Collectively, these data are adequate, in the Panel's opinion, to characterize the environmental fate and transport properties of the group.

Ecotoxicity

Aquatic toxicity data for fish, *Daphnia* and algae are available for citric acid and its trisodium salt and indicate that these compounds have very low toxicity. With LC₅₀ values ranging from 120 to 1,526 mg/L, citric acid is considered to be of low aquatic toxicity. The toxicity that is exhibited is most likely attributed to pH. The salts exhibit even less toxicity. The Panel believes that the available data and the structural similarities adequately characterize the ecotoxicity of citric acid and its salts.

Mammalian Toxicity

The available data indicate that citric acid and its salts have generally low mammalian toxicity. Oral toxicity data for mammals are available for citric acid and its sodium salt and demonstrate low toxicity. Dermal toxicity studies indicate that these compounds are moderate contact irritants. Acute toxicity from other routes of exposure (i.e., intravenous, subcutaneous, intraperitoneal, etc.) are available for all four of the citric acid and salts and confirm the low toxicity. Repeated dose studies available for citric acid and its sodium salt resulted in no adverse effects. *In vitro* bacterial studies were negative for genotoxicity for citric acid and its sodium and tripotassium salts. An *in vivo* cytogenetics study with citric acid also indicated no genetic toxicity. Finally, reproductive and developmental/teratogenic data are available for citric acid and its sodium salt. While body weight and survival time were effected at high doses of citric acid, no reproductive, developmental or teratogenic effects were observed in tests with either the citric acid or its sodium salt. The Panel believes that the available data and analogous structures and behaviors are adequate to characterize the toxicity for citric acid and its salts.

In addition, citric acid occurs naturally in all citric fruits, beans, tomatoes, and many other fruits and vegetables. It is also listed as GRAS by the USFDA and is one of the most widely used food additives, with uses in everything from soft drinks to cheese. A SIDS Initial Assessment Report (SIAR) for citric acid was presented at SIDS Initial Assessment Meeting (SIAM) 11 in January 2001 and its status was determined to be, "currently of low priority for further work."

B. Evaluation of "Read Down" Patterns

The "Read Down" patterns were considered among the four major data areas (physical-chemical properties, environmental fate and transport, ecotoxicity, and mammalian toxicity) for each of the 13 compounds. Complete data sets are available for the acetic, fumaric, malic and citric acids. Several of the salts of these acids also have relatively complete data sets. The category is characterized by

acids and their salts, all of which readily dissociate in solution. This dissociation is followed by relatively rapid biodegradation and/or utilization in living organisms. The available data suggest that the cationic portion of the salt (e.g., Ca^{2+} , Mg^{2+} , K^+ , Na^+) does not significantly affect the relative toxicity of these compounds. Based on the similarities in structure and behavior, the widespread natural occurrence in many fruits and vegetables, and the long history of use as food additives, the Panel believes that no further testing is necessary to predict the environmental fate, ecotoxicity or mammalian toxicity of these compounds.

VII. SUMMARY OF ACETIC ACID AND SALTS CATEGORY

The 13 compounds in the category are acetic acid, its salts, and three structurally related acids (fumaric, malic, citric), as well as the salts of the citric acid. These compounds are grouped together because of their close structural relationships, their natural occurrence in plants and animals, and their fundamental role in cell metabolism, particularly in the tricarboxylic acid cycle (also known as the Citric Acid Cycle or Krebs's Cycle), which is where humans get their energy. These compounds are all carboxylic acids or their respective salts. They are all listed as GRAS by the USFDA and have widespread use as food additives.

The Panel believes the available information supports the following conclusions. All of these acids and salts are highly water soluble and have low to moderate volatility. They dissociate readily in solution and biodegrade rapidly or are utilized in the body. They are not persistent in the environment.

These compounds all exhibit relatively low toxicity to aquatic organisms, with any toxicity observed related to the effect of lowered pH. Likewise, these compounds all exhibit relatively low acute mammalian toxicity. Similarly, no significant effects were observed in genotoxicity, reproductive, and developmental/teratogenic testing.

VIII. CONCLUSIONS

The similarities in chemical structure and behavior of these 13 compounds, as well as the similarities found in the available testing data, support assessing these compounds under a single Acetic Acid and Salts category. The Panel believes that the available data sufficiently characterize the physical-chemical properties, environmental fate, ecotoxicity and mammalian toxicity of the group. Where reliable study data do not appear to exist, the missing values can be estimated using the available data of related chemicals within the group. In addition, these compounds have enjoyed widespread use as additives in a multitude of foods over many years. Therefore, based on the available data, the structural similarities, the natural occurrence, and the lack of significant toxicity, the Panel believes that no further testing is necessary to characterize the compounds included in this category. Support for this conclusion was provided in a review of the SIAR for citric acid at SIAM 11 in January 2001, where its status was determined to be, "currently of low priority for further work."

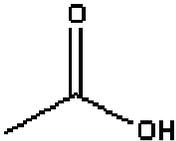
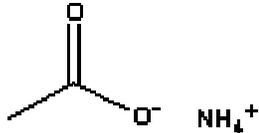
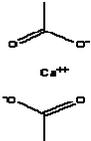
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APPENDIX 1

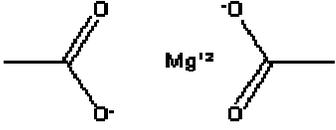
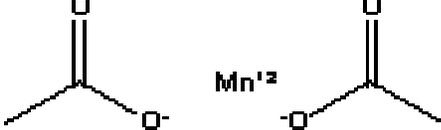
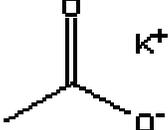
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

**APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY**

Description	Acetic Acid	Source	Acetic Acid, Ammonium Salt	Source	Acetic Acid, Calcium Salt	Source
Structure						
CAS Number	64-19-7		631-61-8		62-54-4	
Physical-Chemical Properties						
Structural Formula	H ₄ C ₂ O ₂		H ₇ C ₂ NO ₂		H ₆ Ca ₂ O ₄	
Melting Point	16.7°C	Verschueren 1996	114°C	Verschueren 1996	--	
Boiling Point	118.1°C	Verschueren 1996	--		Decomposes above 160°C	Budavari 1996
Vapour Pressure	11.4 mm Hg @ 20°C	Verschueren 1996	0.00014 mm Hg @ 25°C	EPIWIN (calculated)	14.7 mm Hg @ 25°C	EPIWIN (calculated)
Octanol/Water Partition Coefficient (log)	-0.17	Verschueren 1996	-2.79	EPIWIN (calculated)	-0.97	EPIWIN (calculated)
Water Solubility	50 g/L @ 20°C	Verschueren 1996	1,480 g/L @ 4°C	Lide 1999	430 g/L @ 25°C	Verdugt 1992
pH Value, pKa Value	pH: 2.5 at 50 g/L and 20°C pKa: 4.76 @ 25°C	Hoescht Serjeant and Dempsey 1979	pH: 7.0 @ 5 M aqueous solution	Budavari 1996	pH: 7.6 @ 0.2 M aqueous solution	Budavari 1996
Fate and Transport						
Photodegradation	5.1x10 ⁻¹³ cm ³ /molecule*sec 50% degradation after 21 days	Hoechst	--		--	
Stability in Water	Acids dissociate in water		Salts dissociate in water		Salts dissociate in water	
Biodegradation	Readily biodegradable: 99% after 7 days under anaerobic conditions using activated sludge	Kameya T. et al. 1995	Biodegrades in days to weeks	EPIWIN (calculated)	Readily biodegrades under aerobic conditions using activated sludge	European Commission 1996
Ecotoxicology						
Acute/Prolonged Toxicity to Fish	96-h LC ₅₀ (bluegill sunfish): 75 mg/L 96-h LC ₅₀ (mosquito fish): 251 mg/L 96-h LC50 (fathead minnow): 79-88 mg/L	Price et al. 1974 Wallen et al. 1957 Mattson et al. 1976	96-h LC ₅₀ (mosquito fish): 238 mg/L	Jones 1971	--	
Acute Toxicity to Daphnia	24-h LC ₅₀ : 47 mg/L 24-h EC ₅₀ (@ pH 7): 6,000 mg/L 48-h EC ₅₀ : 65 mg/L	Elkins et al. 1956 Bringmann and Kuhn 1982 Janssen et al. 1993	--		--	
Toxicity to Aquatic Plants (e.g., algae)	8-day, growth inhibition test; toxicity threshold = 4,000 mg/L	Bringmann and Kuhn 1980	--		--	
Toxicology						
Acute Oral Toxicity	LD ₅₀ (mouse): 4,960 mg/kg bw	Woodward et al. 1941	--		LD ₅₀ (rat): 4,280 mg/kg bw	Smyth et al. 1969
Acute Inhalation Toxicity	4-h LC ₅₀ (rat): 11.4 mg/L	BASF 1989 Ghiringhelli and DiFabio 1957	--		--	
Acute Dermal Toxicity	LD ₅₀ (rabbit): 1,060 mg/kg bw	Union Carbide 1963	--		--	
Acute Toxicity by Other Routes	LD ₅₀ (i.v.; mouse): 525 mg/kg bw	Oro and Wretling 1961	LD ₅₀ (i.p.; rat): 632 mg/kg LD ₅₀ (i.v. mouse): 98 mg/kg	Lewis 1994	LD ₅₀ (i.v.; mouse): 52 mg/kg bw	Lewis 1994
Repeated Dose Toxicity	Induced hyperplasia in rats @ 60 mg/kg bw Increased spleen and kidney weights, kidney damage @ 23-31 mg/kg bw	Alexandrov et al. 1989 Savina and Anisimov 1987	--		--	
Genetic Toxicity <i>in vitro</i> (Bacterial test)	Negative	McMahon et al. 1979 Zeiger et al. 1992 BIBRA 1993	--		--	
Genetic Toxicity <i>in vitro</i> (Non-bacterial test)	Cytotoxic, not clastogenic	Morita et al. 1990	--		--	
Genetic Toxicity <i>in vivo</i>	--	--	--		--	
Toxicity to Reproduction	--	--	--		--	
Developmental Toxicity/Teratogenicity	No effects on nidation or on maternal or fetal survival in mice, rats, and rabbits at doses up to 1600 mg/kg bw/day	FDRL 1974	--		--	

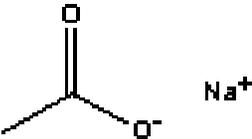
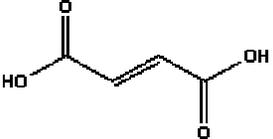
Notes: i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous; -- = Data unavailable

APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY

Description	Acetic Acid, Magnesium Salt	Source	Acetic Acid, Manganese Salt	Source	Acetic Acid, Potassium Salt	Source
Structure						
CAS Number	142-72-3		638-38-0		127-08-2	
Physical-Chemical Properties						
Structural Formula	C ₂ H ₃ MgO ₄		C ₂ H ₃ MnO ₄		H ₃ KC ₂ O ₂	
Melting Point	80°C	Budavari 1996	--		292°C	Lewis 1994
Boiling Point	--		--		--	
Vapour Pressure	--		--		7.08x10 ⁻⁷ mm Hg @ 25°C	EPIWIN (calculated)
Octanol/Water Partition Coefficient (log)	--		--		-3.72	EPIWIN (calculated)
Water Solubility	Very soluble in water or alcohol	Budavari 1996	Soluble in water or alcohol	Budavari 1996	2,530 g/L	Lewis 1994
pH Value, pKa Value	--		--		pH: 9.7 @ 1 M aqueous solution	Budavari 1996
Fate and Transport						
Photodegradation	--		--		--	
Stability in Water	Salts dissociate in water		Salts dissociate in water		Salts dissociate in water	
Biodegradation	--		--		--	
Ecotoxicology						
Acute/Prolonged Toxicity to Fish	--		--		96-h LC50 (rainbow trout): > 6,100 mg/L	Huntingdon Research Center 1992
Acute Toxicity to Daphnia	--		--		24-h LC ₅₀ : 7,170 mg/L	Bringmann and Kuhn 1977
Toxicity to Aquatic Plants (e.g., algae)	--		--		--	
Toxicology						
Acute Oral Toxicity	LD50 (rat): 8,610 mg/kg bw	Green 1977	LD ₅₀ (rat): 3,730 mg/kg bw	Smyth et al. 1969	LD ₅₀ (rat): 3,250 mg/kg bw	Smyth et al. 1969
Acute Inhalation Toxicity	--		--		--	
Acute Dermal Toxicity	--		--		--	
Acute Toxicity by Other Routes	LD ₅₀ (i.v., mouse): 111 mg/kg bw	RTECS 2000	--		--	
Repeated Dose Toxicity	--		Body weight gain suppressed, changes in spontaneous motor activity, and decrease in dopamine in the hypothalamus of young male mice fed 2 g Mn/kg of food for 1 year	Komura and Sakamoto 1992	--	
Genetic Toxicity <i>in vitro</i> (Bacterial test)	--		Weakly positive (rec-assay using <i>Bacillus subtilis</i>)	Nishioka 1975	--	
Genetic Toxicity <i>in vitro</i> (Non-bacterial test)	--		--		--	
Genetic Toxicity <i>in vivo</i>	--		--		--	
Toxicity to Reproduction	--		--		--	
Developmental Toxicity/Teratogenicity	--		Abnormalities occurred in birds when injected into the air cell of eggs at 96 hrs	Verret et al. 1980	--	

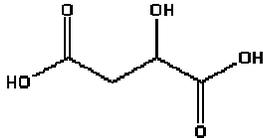
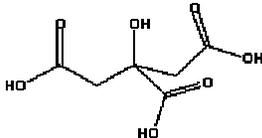
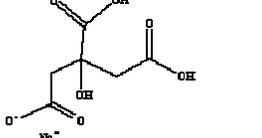
Notes: i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous; -- = Data unavailable

**APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY**

Description	Acetic Acid, Sodium Salt	Source	Fumaric Acid	Source
Structure				
CAS Number	127-09-3		110-17-8	
Physical-Chemical Properties				
Structural Formula	H ₃ NaC ₂ O ₂		H ₄ C ₄ O ₄	
Melting Point	58°C	Lewis 1994	287°C	Verschuieren 1996
Boiling Point	Decomposes at > 400°C	Hoechst 1993	290°C (sublimes)	Verschuieren 1996
Vapour Pressure	7.08x10 ⁻⁷ mm Hg @ 25°C	EPIWIN (calculated)	1.54x10 ⁻⁴ mm Hg @ 25°C	Verschuieren 1996
Octanol/Water Partition Coefficient (log)	-3.72	EPIWIN (calculated)	0.33 @ 23°C	Verschuieren 1996
Water Solubility	365 g/L @ 20°C	Hoechst 1993	7 g/l @ 25°C	Verschuieren 1996
pH Value, pKa Value	pH: 7.5-9 @ 50 g/L, 20°C	Hoechst 1993	pH: 2.1 @ 5 g/L; 20°C pK1: 3.02; pK2: 4.46 @ 18°C	Weast 1988
Fate and Transport				
Photodegradation	6.6% photomineralization after 17-h UV irradiation (> 290 nm)	Freitag et al. 1985	5.3x10 ⁻¹² cm ³ /molecule*sec 50% after 7.3 hours	Atkinson 1987
Stability in Water	Salts dissociate in water		Half-life in natural waters was 1-15 days	Saito et al. 1978
Biodegradation	Inherently biodegradable: 100% after 5 days @ 160 mg/L under aerobic conditions using activated sludge	Huels unpublished	Readily biodegradable: 98% after 21 days under aerobic conditions using predominantly domestic sewage	Huels 1992
Ecotoxicology				
Acute/Prolonged Toxicity to Fish	96-h LC ₀ (zebra fish): 100 mg/L 5-d LC ₅₀ (fathead minnow embryos): 13.33 mg/L	Huels 1993 DeYoung et al. 1996	48-h LC ₅₀ (zebra fish): 245 mg/L	Huels 1992
Acute Toxicity to Daphnia	48-h EC ₅₀ : > 1,000 mg/L 24-h LC ₅₀ : 7130 mg/L	Huels 1993 Bringmann and Kuhn 1977	48-h EC ₅₀ : 212 mg/L	Randall and Knopp 1980
Toxicity to Aquatic Plants (e.g., algae)	Growth inhibition in photoautotrophic algae @ 2,460 mg/L after 60-h	Hoare 1967	72-h EC ₅₀ (green algae): 41 mg/L	AIDA 1988
Toxicology				
Acute Oral Toxicity	LD ₅₀ (rat): 3,530 mg/kg bw	Lewis 1994	LD ₅₀ (rat): 9,300 mg/kg bw (female); 10,700 mg/kg bw (male) LD ₅₀ (rat): 10,000 mg/kg bw	Vernot et al. 1977 Ullman's
Acute Inhalation Toxicity	LC ₅₀ (rat): > 30 g/m ³	BIOFAX 1971	--	
Acute Dermal Toxicity	--		LD ₅₀ (rabbit): >20,000 mg/kg bw	Vernot et al. 1977
Acute Toxicity by Other Routes	s.c. LD ₅₀ (mouse): 3,200 mg/kg bw	Allen et al. 1986	LD ₅₀ (i.p., mouse): 200 mg/kg bw Hepatotoxicity in rats @ 10 mg/kg via i.p.	Smith et al. 1963 Mileski 1965
Repeated Dose Toxicity	NOAEL (drinking water; rat): 500 mg/L Normal growth and survival in rats @ 3.6 g/kg bw/day No cognitive impairment in young rats @ 50 mg/kg bw/day Altered thyroid function, decreased growth	Cory-Slechta 198 Dryden and Hartman 1971 Massaro and Massaro 1987 Goldman 1981	Slightly increased mortality and increased incidence of testes degeneration in rats fed diet @ 750 mg/kg bw	Fitzhugh and Nelson 1947
Genetic Toxicity <i>in vitro</i> (Bacterial test)	Negative	BIBRA 1993 Ishidate et al. 1984	Negative (up to 10 mg/plate)	Zeiger et al. 1988 Rapson et al. 1980
Genetic Toxicity <i>in vitro</i> (Non-bacterial test)	Negative	Ishidate et al. 1984	Negative (up to 0.5 mg/mL)	Ishidate et al. 1984
Genetic Toxicity <i>in vivo</i>	No inhibitory effect on DNA-replication detectable	Seiler 1981	--	
Toxicity to Reproduction	--	--	No evidence of reproductive toxicity @ 400 mg/kg bw	Levey et al. 1946
Developmental Toxicity/Teratogenicity	No maternal or neonatal effects in mice @ 1,000 mg/kg bw Nonteratogenic to chick embryos	Kavlock et al. 1987 Verret et al. 1980	No apparent teratogenic effect	Bournias-Vardiabasis 1983

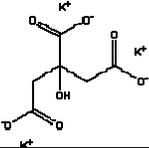
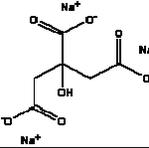
Notes: i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous; -- = Data unavailable

**APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY**

Description	Malic Acid	Source	Citric Acid	Source	Citric Acid, Sodium Salt	Source
Structure						
CAS Number	6915-15-7		77-92-9		994-36-5	
Physical-Chemical Properties						
Structural Formula	H ₆ C ₄ O ₅		H ₆ C ₆ O ₇		H ₇ NaC ₆ O ₇	
Melting Point	128°C	Lewis 1994	153°C	Verschueren 1996	--	
Boiling Point	Decomposes above 140°C	Lewis 1994	Decomposes	Verschueren 1996	--	
Vapour Pressure	4.6x10 ⁻⁶ mm Hg @ 25°C	EPIWIN (calculated)	3.7x10 ⁻⁹ mm Hg @25°C	EPIWIN (calculated)	--	
Octanol/Water Partition Coefficient (log)	-1.26	Hansch and Leo 1987	-1.72	Verschueren 1996	--	
Water Solubility	592 g/L @25°C	Yalkowsky 1989	1,330 g/L @ 20°C	Verschueren 1996	--	
pH Value, pKa Value	pK1: 3.40; pK2: 5.05	Clayton and Clayton 1994	pH: 2.2 at 0.1 N solution pK1: 3.13; pK2: 4.76; pK3: 6.40	Budavari 1996	--	
Fate and Transport						
Photodegradation	Photolysis rate of 7.76x10 ⁻¹² cm ³ /mole*sec at 25C; 50% after 2 days	Meylan and Howard 1993	--		--	
Stability in Water	Biodegrades readily in water	Fournier et al. 1992	Acids dissociate in water		Salts dissociate in water	
Biodegradation	--	--	Readily biodegradable: 98% after 48-h under aerobic conditions using domestic sewage	European Commission 1996	--	
Ecotoxicology						
Acute/Prolonged Toxicity to Fish	--		96-h LC ₅₀ (bluegill sunfish): 1,516 mg/L	Schwartz 1973	--	
Acute Toxicity to Daphnia	48-h LC ₅₀ : 240 mg/L	ABC Laboratories 1989	72-h EC ₅₀ : 120 mg/L 24-h EC ₅₀ : 1535 mg/L	Ellis 1937 Bringmann and Kuhn 1982	--	
Toxicity to Aquatic Plants (e.g., algae)	--		8-day growth inhibition test, toxicity threshold: 640 mg/L	Bringmann and Kuhn 1980	--	
Toxicology						
Acute Oral Toxicity	LD ₅₀ (mouse, rat): 1,600-3,200 mg/kg bw	Eastman Kodak 1981	LD ₅₀ (rat): 11,700 mg/kg bw LD ₅₀ (mouse): 5,790 mg/kg bw	Yokotani et al. 1971	LD ₅₀ (mouse): 7,100 mg/kg bw	Oelkers 1965
Acute Inhalation Toxicity	--		--		--	
Acute Dermal Toxicity	--		4-h exposure caused erythema and edema in rabbits.	Hill Top Biolabs, Inc. 1992	--	
Acute Toxicity by Other Routes	LD ₅₀ (i.p., mouse): 50-200 mg/kg	Eastman Kodak 1981	LD ₅₀ (s.c., rat): 5,500 mg/kg bw LD ₅₀ (s.c., mouse): 2,700 mg/kg bw	Yokotani et al. 1971	iv. infusion in rats increased calcium excretion No cardiovascular effects in horses given i.v. LD ₅₀ (i.p.; rat): 1,348 mg/kg bw LD ₅₀ (i.p.; mouse): 1,635 mg/kg bw	Borensztein et al. 1989 Hubbell et al. 1987 Lewis 1994
Repeated Dose Toxicity	Changes in organ weights, decreased growth, hunched appearance in rats @ 200 mg/kg bw	Hazleton Laboratories 1971	Citric acid (sodium salt) produced no gross or histopathological changes or effected growth or survival NOEL (oral feed; rat): 2,260 mg/kg bw LOAEL (oral feed; rat): 4,670 mg/kg bw	Packman et al. 1963 Yokotani et al. 1971	No adverse effects in 2 generations of rats fed sodium citrate as 0.1% of diet No adverse effects in male rats over 32 week exposure @ 2,500 mg/kg bw	Bonting and Jansen 1956 Fukushima et al. 1986
Genetic Toxicity <i>in vitro</i> (Bacterial test)	Negative	Al-Ani and Al-Lami 1988	Negative	Al-Ani and Al-Lami 1988	Negative	Ishidate et al. 1984
Genetic Toxicity <i>in vitro</i> (Non-bacterial test)	Negative	Ishidate et al. 1984	--		--	
Genetic Toxicity <i>in vivo</i>	--		Not mutagenic	Litton Bionetics 1975	--	
Toxicity to Reproduction			Effected body weight gain and survival time NOAEL (parent; oral feed; rat): > 600 mg/kg bw LOAEL (F1; oral feed; rat): > 600 mg/kg bw	Wright and Hughes 1976 Bonting and Jansen 1956	No reproductive effects in rats fed 0.1% sodium citrate in diet	Bonting and Jansen 1956
Developmental Toxicity/Teratogenicity	Nonteratogenic to chick embryos at up to 10 mg/egg No treatment-related fetal or maternal toxic effects observed @ up to 350 mg/kg bw	Verrett et al. 1980 FDRL 1974	No maternal or fetal effects NOAEL (maternal; rat): >241 mg/kg bw NOAEL (teratogenic; rat): > 241 mg/kg bw	FDRL 1973	Nonteratogenic to chick embryos	Verrett et al. 1980

Notes: i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous; -- = Data unavailable

**APPENDIX 1
SUMMARY DATA TABLE FOR ACETIC ACID AND SALTS CATEGORY**

Description	Citric Acid, Tripotassium Salt	Source	Citric Acid, Trisodium Salt	Source
Structure				
CAS Number	866-84-2		68-04-2	
Physical-Chemical Properties				
Structural Formula	H ₅ K ₃ C ₆ O ₇		H ₅ Na ₃ C ₆ O ₇	
Melting Point	211°C	EPIWIN (calculated)	150°C	European Commission 1996
Boiling Point	Decomposes when heated to 230°C	Lewis 1994	Decomposes at red heat	Lewis 1994
Vapour Pressure	2.09x10 ⁻¹² mm Hg @ 25°C	EPIWIN (calculated)	2.09x10 ⁻¹² mm Hg @ 25°C	EPIWIN (calculated)
Octanol/Water Partition Coefficient (log)	-0.28	EPIWIN (calculated)	-0.28	EPIWIN (calculated)
Water Solubility	63 g/L	EPIWIN (calculated)	~425 g/L @ 25°C	European Commission 1996
pH Value, pKa Value	--		pH: -8	Budavari 1996
Fate and Transport				
Photodegradation	--		--	
Stability in Water	Salts dissociate in water		Salts dissociate in water	
Biodegradation	--		Readily biodegradable: 90% after 48-h under aerobic conditions using activated sludge	European Commission 1996
Ecotoxicology				
Acute/Prolonged Toxicity to Fish	--		96-h LC50 (guppy): > 18,000- 32,000 mg/L	Sloof and Kappers 1982
Acute Toxicity to Daphnia	--		48-h EC ₅₀ : 5,600-10,000 mg/L 24-h EC ₅₀ : 3330 mg/L	Sloof and Kappers 1982 Bringmann and Kuhn 1977
Toxicity to Aquatic Plants (e.g., algae)	--		96-h EC ₅₀ (algae): > 18,000-32,000 mg/L	Sloof and Kappers 1982
Toxicology				
Acute Oral Toxicity	--		--	
Acute Inhalation Toxicity	--		--	
Acute Dermal Toxicity	--		--	
Acute Toxicity by Other Routes	LD ₅₀ (i.v. dog): 167 mg/kg bw	Lewis 1994	LD ₅₀ (i.p., rat): 1,548 mg/kg bw LD ₅₀ (i.p., mouse): 1,364 mg/kg bw LD ₅₀ (i.v., mouse): 170 mg/kg bw LD ₅₀ (i.v., rabbit): 449 mg/kg bw	RTECS 1999
Repeated Dose Toxicity	--		--	
Genetic Toxicity <i>in vitro</i> (Bacterial test)	Negative	Litton Bionetics Inc. 1975 Ishidate et al. 1984	--	
Genetic Toxicity <i>in vitro</i> (Non-bacterial test)	--		--	
Genetic Toxicity <i>in vivo</i>	--		--	
Toxicity to Reproduction	--		--	
Developmental Toxicity/Teratogenicity	--		--	

Notes: i.v. = intravenous; i.p. = intraperitoneal; s.c. = subcutaneous; -- = Data unavailable