UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 28, 2004

MEMORANDUM

SUBJECT: Tolerance Reassessment Decisions Completed by the Lower Toxicity Pesticide Chemical Focus Group

FROM: Betty Shackleford, Associate Director
Registration Division

TO: Peter Caulkins, Associate Director
Special Review and Reregistration Division

Please find attached the Focus Group Decision Document for ethylenediaminetetraacetic acid (EDTA) and its salts. The three tolerance exemptions for these chemicals in 40 CFR 180.1001(c) are reassessed. List reclassifications for ethylenediaminetetraacetic acid (EDTA) and 24 various ammonium, calcium, copper, iron, potassium, manganese, sodium and zinc salts of EDTA have been completed. These chemicals are now classified as List 4B.

If you have any comments or questions, please contact Kathryn Boyle at 703-305-6304.

Attachment (1)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 28, 2004

MEMORANDUM

FROM: Kathryn Boyle, Chair
Lower Toxicity Pesticide Chemical Focus Group
Registration Division

TO: Betty Shackleford, Associate Director
Registration Division

SUBJECT: Recommendation for Tolerance Reassessment

The attached science assessment discusses the toxicity of ethylenediaminetetraacetic acid (EDTA) and various ammonium, calcium, copper, iron, potassium, manganese, sodium and zinc salts of EDTA. EDTA is a chelating agent. Its ability to bind heavy metal ions can be used to sequester these trace metals. However, trace amounts of various metals are necessary for the proper functioning of the body. If instead, these minerals were bound to the EDTA, then deficiencies of these trace metals could result.

In fact, the toxic effects of EDTA are considered to be related to metal deficiencies, especially a deficiency of zinc. However, two critical pieces of information informed the Agency's evaluation of EDTA. Two developmental toxicity studies were performed using disodium EDTA. The Agency has reviewed the toxicological literature on both of these studies. In one study, rats were maintained on de-ionized water (water containing no trace minerals). The test animals displayed both maternal and developmental effects. In another very similar study, rats that were maintained on tap water displayed no such effects. Thus, the availability of trace metals, particularly zinc, in the diet and drinking water work to prevent deficiencies.

Additionally, EDTA and its salts have inherent limitations of percent in the formulation, due to the nature of the chemical interactions during manufacture, on the amount of EDTA that would be incorporated in a pesticide product. The information available to the Agency indicates that EDTA concentrations in agricultural products do not exceed 5% (by weight) of a formulated product and concentrations in products that could be used in and around the home do not exceed 1% (by weight) of a formulated product.

Based on its review and evaluation of the available information, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to residues of EDTA and its various salts from their uses as ingredients in pesticide products. The following three exemptions from the requirement of a tolerance as established in 40 CFR 180.1001 (c) are reassessed: disodium zinc ethylenediaminetetraacetate dihydride, ethylenediaminetetraacetic acid, and ethylenediaminetetraacetic acid tetrasodium salt.

Based on the chelating ability of EDTA and the various ammonium, calcium, copper, iron, potassium, manganese, sodium and zinc salts of EDTA, and the inherent limitations during manufacture of a pesticide product, the Agency will limit the percent of EDTA or any EDTA salt in a formulated pesticide product to 5% by weight. Based on this limitation, classification as List 4B is appropriate for the following chemicals:

Chemical Substance (Common Name)	**CAS Reg. No.**
Ethylenediaminetetraacetic acid (EDTA)	60-00-4
Ethylenediaminetetraacetic acid (EDTA) calcium disodium salt	62-33-9
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt	64-02-8
Ethylenediaminetetraacetic acid (EDTA) disodium salt	139-33-3
Ethylenediaminetetraacetic acid (EDTA) trisodium salt	150-38-9
Ethylenediaminetetraacetic acid (EDTA) tetrapotassium salt	5964-35-2
Ethylenediaminetetraacetic acid (EDTA) disodium salt, dihydrate	6381-92-6
Ethylenediaminetetraacetic acid (EDTA) potassium salt	7379-27-3
Ethylenediaminetetraacetic acid (EDTA) sodium salt	7379-28-4
Ethylenediaminetetraacetic acid (EDTA) copper (II) salt	12276-01-6
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt	14025-15-1

Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt	14025-21-9
Ethylenediaminetetraacetic acid (EDTA) disodium iron (II) salt	14729-89-6
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt	15375-84-5
Ethylenediaminetetraacetic acid (EDTA) sodium iron (III) salt	15708-41-5
Ethylenediaminetetraacetic acid (EDTA) iron (III) salt	17099-81-9
Ethylenediaminetetraacetic acid (EDTA) monosodium salt	17421-79-3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt	17572-97-3
Ethylenediaminetetraacetic acid (EDTA) diammonium salt	20824-56-0
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, dihydrate	61916-40-3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt, dihydrate	65501-24-8
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt, trihydrate	67401-50-7
Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt, dihydrate	73513-47-0
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, trihydrate	73637-19-1
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt, dihydrate	73637-20-4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 28, 2004

MEMORANDUM

FROM: Kathryn Boyle, Chair
Lower Toxicity Pesticide Chemical Focus Group
Registration Division

TO: Betty Shackleford, Associate Director
Registration Division

SUBJECT: Recommendation for Tolerance Reassessment

The attached science assessment discusses the toxicity of ethylenediaminetetraacetic acid (EDTA) and various ammonium, calcium, copper, iron, potassium, manganese, sodium and zinc salts of EDTA. EDTA is a chelating agent. Its ability to bind heavy metal ions can be used to sequester these trace metals. However, trace amounts of various metals are necessary for the proper functioning of the body. If instead, these minerals were bound to the EDTA, then deficiencies of these trace metals could result.

In fact, the toxic effects of EDTA are considered to be related to metal deficiencies, especially a deficiency of zinc. However, two critical pieces of information informed the Agency's evaluation of EDTA. Two developmental toxicity studies were performed using disodium EDTA. The Agency has reviewed the toxicological literature on both of these studies. In one study, rats were maintained on de-ionized water (water containing no trace minerals). The test animals displayed both maternal and developmental effects. In another very similar study, rats that were maintained on tap water displayed no such effects. Thus, the availability of trace metals, particularly zinc, in the diet and drinking water work to prevent deficiencies.

Additionally, EDTA and its salts have inherent limitations of percent in the formulation, due to the nature of the chemical interactions during manufacture, on the amount of EDTA that would be incorporated in a pesticide product. The information available to the Agency indicates that EDTA concentrations in agricultural products do not exceed 5% (by weight) of a formulated product and concentrations in products that could be used in and around the home do not exceed 1% (by weight) of a formulated product.

Based on its review and evaluation of the available information, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to residues of EDTA and its various salts from their uses as ingredients in pesticide products. The following three exemptions from the requirement of a tolerance as established in 40 CFR 180.1001 (c) are reassessed: disodium zinc ethylenediaminetetraacetate dihydride, ethylenediaminetetraacetic acid, and ethylenediaminetetraacetic acid tetrasodium salt.

Based on the chelating ability of EDTA and the various ammonium, calcium, copper, iron, potassium, manganese, sodium and zinc salts of EDTA, and the inherent limitations during manufacture of a pesticide product, the Agency will limit the percent of EDTA or any EDTA salt in a formulated pesticide product to 5% by weight. Based on this limitation, classification as List 4B is appropriate for the following chemicals:

Chemical Substance (Common Name)	**CAS Reg. No.**
Ethylenediaminetetraacetic acid (EDTA)	60-00-4
Ethylenediaminetetraacetic acid (EDTA) calcium disodium salt	62-33-9
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt	64-02-8
Ethylenediaminetetraacetic acid (EDTA) disodium salt	139-33-3
Ethylenediaminetetraacetic acid (EDTA) trisodium salt	150-38-9
Ethylenediaminetetraacetic acid (EDTA) tetrapotassium salt	5964-35-2
Ethylenediaminetetraacetic acid (EDTA) disodium salt, dihydrate	6381-92-6
Ethylenediaminetetraacetic acid (EDTA) potassium salt	7379-27-3
Ethylenediaminetetraacetic acid (EDTA) sodium salt	7379-28-4
Ethylenediaminetetraacetic acid (EDTA) copper (II) salt	12276-01-6
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt	14025-15-1

Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt	14025-21-9
Ethylenediaminetetraacetic acid (EDTA) disodium iron (II) salt	14729-89-6
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt	15375-84-5
Ethylenediaminetetraacetic acid (EDTA) sodium iron (III) salt	15708-41-5
Ethylenediaminetetraacetic acid (EDTA) iron (III) salt	17099-81-9
Ethylenediaminetetraacetic acid (EDTA) monosodium salt	17421-79-3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt	17572-97-3
Ethylenediaminetetraacetic acid (EDTA) diammonium salt	20824-56-0
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, dihydrate	61916-40-3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt, dihydrate	65501-24-8
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt, trihydrate	67401-50-7
Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt, dihydrate	73513-47-0
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, trihydrate	73637-19-1
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt, dihydrate	73637-20-4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

January 26, 2004

Memorandum

Subject: Ethylenediaminetetraacetic acid (EDTA) and the salts of EDTA: Science Assessment Document for Tolerance Reassessment.

From: Elissa Reaves, Toxicologist
Reregistration Branch 2
Health Effects Division (7509C)

Through: Pauline Wagner, Branch Chief
Reregistration Branch 2
Health Effects Division (7509C)

To: Lower Risk Pesticide Chemical Focus Group
Kathryn Boyle, Chair
Registration Division (7505C)

Background:

Attached is the Lower Risk Pesticide Chemicals Focus Group's science assessment for EDTA and the salts of EDTA. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, and exposure profile of these EDTA salts. In performing this assessment, EPA has utilized reviews previously performed by the Federal Drug Administration (FDA) and relied on peer-reviewed evaluations performed by the Food and Agriculture Organization of the World Health Organization (FAO/WHO), and the Cosmetic Ingredient Review (CIR).

I. Executive Summary:

The EDTA salts evaluated in this report include ammonium, calcium, copper, iron, potassium, manganese, sodium, and zinc. EDTA is a man-made amino acid chelating (binding)

agent with an affinity for metals such as lead, mercury, cadmium, and aluminum. EDTA's ability to complex is used commercially to either promote or inhibit chemical reactions, depending on application. EDTA has been used extensively as a food additive to sequester trace metals that catalyze the oxidation of oils, vitamins, and unsaturated fats that cause rancidity, flavor changes, and discoloration. Permissible levels of EDTA calcium disodium salt in food range from 25 to 800 ppm, and an acceptable daily intake of 2.5 mg/kg was established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1973. EDTA has also been used in food contact surface sanitizing solutions, to control the interactions of trace metals in formulations of liquid soaps, cosmetics, and pharmaceuticals, in metal working, in pulp and paper processing, in rubber and polymer chemistry, and in textile processing and dyeing.

EDTA and its salts are eliminated from the body, 95% via the kidneys and 5% by the bile, along with the metals and free ionic calcium which was bound in transit through the circulatory system. The binding of divalent and trivalent cations by EDTA can cause mineral deficiencies, which seem to be responsible for all of the known pharmacological effects. Sensitivity to the toxic effects of EDTA is, at least in part, related to the deficiency of zinc.

The available ecotoxicity data for EDTA indicate that these compounds are slow to degrade under typical environmental conditions but are not expected to bioconcentrate. EDTA compounds range from practically non-toxic to moderately toxic on an acute basis depending on the salt. Algae and invertebrates are among the most sensitive species based on predictive modeling for acute and chronic endpoints for EDTA, depending on the compound. EDTA and its salts also do not appear to be very toxic for terrestrial wild mammals and adverse effects from reasonably expected agricultural uses are not expected.

Based on available information on EDTA and its salts, their expected use patterns, their safe history of use as food additives, extensive use in commercially-available pharmaceuticals, and their low risk, the Agency has determined that a quantitative risk assessment is not required for these compounds.

II. Use Information:

There are several variations of nomenclature for EDTA and its salts. Therefore, this document will refer to ethylenediaminetetraacetic acid as EDTA. The salts of EDTA will be presented as ethylenediaminetetraacetic acid (EDTA) sodium salt, etc.

The tolerance exemptions being reassessed in this document, the 40 CFR location of the established tolerance exemption, and the use pattern as an inert or active ingredient are listed in Table 1.

Table 1. Tolerance Exemptions Being Reassessed in this Document			
Tolerances Exemption Expression	**40 CFR ◊**	**Limits**	**Uses**
Ethylenediaminetetraacetic acid (EDTA)	180.1001 (c)	3%	pesticide formulations, sequestrant
Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt, dihydrate	180.1001 (c)	--	sequestrant
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt, trihydrate	180.1001 (c)	5%	pesticide formulations, sequestrant
◊Residues listed in section (c) of 40 CFR 180.1001 are exempted from a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops or to raw agricultural commodities after harvest.			

Most of the pesticide products in which EDTA chemicals are incorporated as an inert ingredient are non-food products. Residential products that contain EDTA chemicals typically are less than 1% of the formulation. However, the tolerance exemptions are needed for a small number of pesticide products applied to food crops containing EDTA chemicals.

The following Table lists identifying information for EDTA and its salts which are currently regulated by the Agency.

Table 2. EDTA and the salts of EDTA		
Chemical Substance (Common Name)	**CAS Reg. No.**	**List Classification***
Ethylenediaminetetraacetic acid (EDTA)	60-00-4	3
Ethylenediaminetetraacetic acid (EDTA) calcium disodium salt	62-33-9	3
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt	64-02-8	3
Ethylenediaminetetraacetic acid (EDTA) disodium salt	139-33-3	3
Ethylenediaminetetraacetic acid (EDTA) trisodium salt	150-38-9	3
Ethylenediaminetetraacetic acid (EDTA) tetrapotassium salt	5964-35-2	3
Ethylenediaminetetraacetic acid (EDTA) disodium salt, dihydrate	6381-92-6	3
Ethylenediaminetetraacetic acid (EDTA) potassium salt	7379-27-3	3

Ethylenediaminetetraacetic acid (EDTA) sodium salt	7379-28-4	--
Ethylenediaminetetraacetic acid (EDTA) copper (II) salt	12276-01-6	--
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt	14025-15-1	3
Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt	14025-21-9	3
Ethylenediaminetetraacetic acid (EDTA) disodium iron (II) salt	14729-89-6	3
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt	15375-84-5	3
Ethylenediaminetetraacetic acid (EDTA) sodium iron (III) salt	15708-41-5	3
Ethylenediaminetetraacetic acid (EDTA) iron (III) salt	17099-81-9	3
Ethylenediaminetetraacetic acid (EDTA) monosodium salt	17421-79-3	3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt	17572-97-3	3
Ethylenediaminetetraacetic acid (EDTA) diammonium salt	20824-56-0	3
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, dihydrate	61916-40-3	3
Ethylenediaminetetraacetic acid (EDTA) tripotassium salt, dihydrate	65501-24-8	--
Ethylenediaminetetraacetic acid (EDTA) tetrasodium salt, trihydrate	67401-50-7	3
Ethylenediaminetetraacetic acid (EDTA) disodium zinc salt, dihydrate	73513-47-0	3
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, trihydrate	73637-19-1	3
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt, dihydrate	73637-20-4	3

*****Inert ingredients are categorized into four lists as described in the 52 FR 13305, Inert Ingredients in Pesticide Products Policy Statement. List 3 includes inert ingredients of unknown toxicity, inert ingredients that have not yet been evaluated for list reclassification.
-- Not available in OPPIN
Source: OPPIN database 10/2003

According to the OPPIN database, EDTA, EDTA sodium salt, EDTA disodium salt, EDTA trisodium salt, EDTA tetrasodium salt, EDTA potassium salt, EDTA tripotassium salt,

EDTA tetrapotassium salt, EDTA sodium iron (III) salt, and EDTA copper (II) salt have active ingredient PC codes. However, only tetrasodium EDTA and EDTA copper (II) salt have current registrations and sodium iron (III) EDTA is currently pending registration. All other active ingredient uses of EDTA salts have been canceled.

Use in Food Contact Surface Sanitizing Solutions:

Tetrasodium EDTA is currently used in food contact surface sanitizing solutions as specified under 21 CFR 178.1010 (b) (19). Disodium EDTA is also used in food contact surface sanitizing solutions (21 CFR 178.1010 (b) (44)).

Use in Cosmetics:

EDTA and several of its salts function as chelating agents in cosmetics. A safety assessment of EDTA and several salts by the Cosmetic Ingredient Review (CIR 2002) indicated EDTA was used in over 4,000 cosmetic formulations. This report also indicated that cosmetic formulations generally contain less than 2% of EDTA salts. However, historical data submitted to the FDA in 1984 revealed one formulation for each EDTA and tetrasodium EDTA contained concentrations of 25%. The product containing a 25% concentration of EDTA was not identified. Examples of products containing EDTA chemicals include: bubble baths, bath soaps and detergents, deodorants, facial makeups and lotions, colognes and toilet waters, hair products (shampoos, rinses, conditioners, dyes and colors), nail basecoats and undercoats, and nail creams and lotions.

FDA Uses:

EDTA: EDTA has been used under medical supervision to treat heavy metal poisoning. Large doses of EDTA (or one of its salts) function to scavenge the heavy metals from the body. EDTA preferentially binds with the heavy metal present with the resultant complex then being excreted.

Calcium disodium EDTA: Calcium disodium EDTA can be used as a food additive and is permitted for direct addition to food for human consumption, as long as 1) the quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food, and 2) any substance intended for use in or on food is of appropriate food grade and is prepared and handled as a food ingredient (21 CFR 172.120). Certification of calcium disodium EDTA when used as a diluent in color additive mixtures for food use is not necessary for the protection of the public heath, and therefore is exempt from the certification under section 721 (c) of 21 CFR 73.1. Calcium disodium EDTA may also be used to promote stability of color, flavor, texture retention, and to retard struvite (mineral) formation. It is also used as a sequestering agent in the production of pharmaceuticals. An acceptable daily intake (ADI) of 2.5 mg/kg calcium disodium EDTA was established by the FAO/WHO (1974).

Disodium EDTA: Disodium EDTA can also be used as a food additive for direct addition to food for human consumption in specified foods and is not to exceed prescribed levels under 21 CFR 172.135. It is also approved by FDA as a component of sanitizing solutions for use on food processing equipment and on dairy-processing equipment (21 CFR 178.1010 (b) (44)). Disodium EDTA may also be safely used in designated foods as a stabilizer for vitamin B_{12}, promoter for color retention, and as a cure accelerator with sodium ascorbate or ascorbic acid.

Tetrasodium EDTA: Tetrasodium EDTA can be used in sanitizing solutions for use on food processing equipment and utensils and on food-contact surfaces in public eating places (21 CFR 178.1010(b) (19)).

Sodium iron EDTA: A provisional maximum tolerance daily intake of 0.8 mg/kg/bw was established by the Joint FAO/WHO Committee (FAO/WHO 2000) at the end of the twenty-seventh meeting.

High Production Volume (HPV) Challenge Program:

HPV chemicals are those that are manufactured or imported into the United States in volumes greater than one million pounds per year. There are approximately 3,000 HPV chemicals that are produced or imported into the United States. The HPV Challenge Program is a voluntary partnership between industry, environmental groups, and the EPA which invites chemical manufacturers and importers to provide basic hazard data on the HPV chemicals they produce/import. The goal of this program is to facilitate the public's right-to-know about the potential hazards of chemicals found in their environment, their homes, their workplace, and in consumer products.

The Agency notes that EDTA, disodium EDTA, and tetrasodium EDTA are included on the Agency's list of chemicals included in the High Production Volume (HPV) Challenge Program. These chemicals are being handled by SIDS (Screening Information Data Set) Program and have been confirmed by the ICAA (International Council of Chemical Associations) for incorporation in the HPV initiative of the ICAA. However, these EDTA chemicals are currently not sponsored by any company or consortium.

Other Uses:

EDTA: EDTA has been used under medical supervision to treat heavy metal poisoning. Large doses of EDTA (or one of its salts) function to scavenge the heavy metals from the body. EDTA preferentially binds with the heavy metal present with the resultant complex then being excreted.

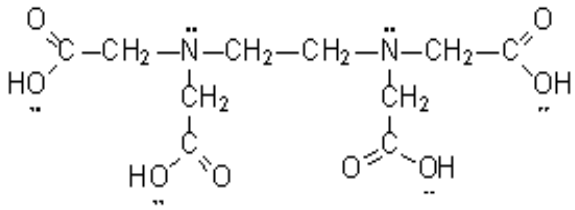
EDTA is also used as a chelating agent in boiler and cooling water, in nickel plating, and in wood pulping processes. EDTA is also in detergents for household and textile use, industrial germicides, metal cutting fluids, pharmaceuticals, and is used as a bleaching agent in color film processing, etching agent in metal finishing and semiconductor production, activator in

butadiene-styrene co-polymerization, in gas scrubbing, and as a component of blood anticoagulants (TOXNET 2003).

Trisodium EDTA: Trisodium EDTA salts are used in detergents, liquid soaps, shampoos, agricultural chemical sprays, pharmaceutical products, oil emulsions, and in textiles to improve dyeing, scouring and detergent operations. Trisodium EDTA is also used as a metal chelating agent, in metal cleaning and plating, in the treatment of chlorosis, to decontaminate radioactive surfaces, as a metal deactivator in vegetable oils, as an anticoagulant of blood, as an eluting agent in ion exchange, to remove insoluble deposits of calcium and magnesium soaps, as an antioxidant, in the clarification of liquids, in analytical chemistry spectrophotometric titration, to aid in reducing blood cholesterol, and to treat lead poisoning and calcinosis (NTP 2003).

III. Physical/Chemical Properties:

As a group, EDTA and the EDTA salts are white crystalline or powder in structure. The effectiveness of EDTA as a chelator for a particular metal ion is given by its stability constant with the metal ion. The stability constants for different metal-EDTA complexes vary considerably, and any metal which is capable of forming a strong complex with EDTA will at least partially displace another metal with a weaker stability constant (FAO/WHO 2000). The EDTA salts are soluble in water, have low sorption to soil and sediments, have no significant vapor pressure, and have a biodegredation half-life of weeks to months (EPA 2003).



Ethylenediaminetetraacetic acid (EDTA)

(Figure of EDTA obtained from: http://scifun.chem.wisc.edu/chemweek/chel&chlor/chel&chlor.html)

IV. Hazard Assessment

The key toxicological data in the following sections were obtained from published reports by peer reviewed committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE), Cosmetic Ingredient Review (CIR), published studies in peer reviewed journals, as well as from NIOSH (www.cdc.gov/niosh/rtechs), and other databases available on websites such as TOXNET (www.toxnet.nlm.nih.gov), and SIRI (http://www.hazard.com/msds/index.php).

In general, EDTA and the salts of EDTA are a group known as sequestrants which have the ability to chelate metals. EDTA is not totally absorbed when ingested. Various sources rate

the absorption as poor to good with the upper limit on absorption being defined numerically as 20%. Elimination occurs mainly by the kidneys (95%) with some (5%) via the bile (FAO/WHO 1974, CSTEE 2003, CIR 2002).

In the sections below, the available toxicological data for EDTA and specific EDTA salts are summarized first in the following table, followed by a discussion of the toxicity of EDTA, salts of EDTA, and cations.

A. Toxicological data available for EDTA and the salts of EDTA:

Table 3. Toxicity data for EDTA and the salts of EDTA[1]

	Oral LD_{50} mg/kg			
Chemical	**CAS No.**	**mouse**	**rat**	**Reference**
Ethylenediaminetetraacetic acid (EDTA) calcium disodium salt	62-33-9	10,000	10,000	Oser et al., 1963 as cited in FAO/WHO 1967; SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) disodium salt	139-33-3	2050	2000	FAO/WHO 1967 and 1974, SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) trisodium salt	150-38-9	2150	2150	NTP 2003; SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) sodium iron (III) salt	15708-41-5	5,000	5,000	SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) disodium zinc dihydrate salt	73513-47-0	–	5,000	SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) disodium copper (II) salt, trihydrate	73637-19-1	–	1750	SIRI 2003
Ethylenediaminetetraacetic acid (EDTA) disodium manganese (I) salt, dihydrate	73637-20-4	–	5,000	SIRI 2003

In general, EDTA and its salts are mild skin irritants but considered severe eye irritants. A report by the Scientific Committee on Toxicity, Ecotoxicity, and the Environment (CSTEE 2003) concluded “both EDTA and tetrasodium EDTA are mild skin irritants, but comparatively potent eye irritants”. Similarly, tetrasodium EDTA should not be applied to the eye unless first neutralized, because it forms a solution sufficiently alkaline to be injurious to the eye (Grant, 1986 as cited in TOXNET).

The greatest risk in the human body will occur when the EDTA attempts to scavenge the trace metals used and required by the body. The various toxicity studies, particularly the Kimmel (1977) and Schardein et al. (1981) studies, indicate that developmental effects will

occur if the body is not properly supplemented with necessary trace metals.

Several short term studies, reviewed by FAO/WHO in 1974, reported no adverse effects from administering doses up to 5% of EDTA and its salts to lab rodents daily and for several weeks. Only diarrhea and lowered food consumption were reported in animals given 5% disodium EDTA. However, abnormal effects were seen in animals that were fed mineral deficient diets. Abnormal symptoms were observed in male and female rats fed a low mineral diet (0.54% Ca and 0.013%Fe) with the addition of 0%, 0.5%, or 1% disodium EDTA for 205 days. Rats fed a low percent of disodium EDTA in the diet for short term studies with adequate minerals showed no signs of toxicity. Rats fed 0.5% disodium EDTA for 44-52 weeks were without deleterious effects on weight gain, appetite, activity and appearance. Rats fed 1% disodium EDTA with adequate mineral diet for 220 days showed no evidence of dental erosion.

Disodium EDTA administered by different routes; 3% in diet, gastric intubation, or subcutaneously, produced different teratogenic rates in rats (Kimmel 1977). Disodium EDTA administered to pregnant rats on Days 7 to 14 of gestation by dietary admixture (954 mg/kg/day) produced maternal toxicity and fetal death and malformations in 71% of the offspring. Rats given 1250 mg/kg or 1500 mg/kg by gavage exhibited more maternal toxicity than the diet group, but produced only 21% malformations in the offspring at the lower dose. The subcutaneously administration of 375 mg/kg was also maternally toxic, but did not result in malformations in the offspring. Differences in toxicity and teratogenicity are probably related to absorption differences and interaction with metals. Animals in the study by Kimmel (1977) were maintained on deionized water and possibly became zinc deficient, thus causing teratogenicity in the offspring. Similarly, EDTA and four of its salts (disodium, trisodium, calcium disodium, and tetrasodium) were administered to pregnant rats during Days 7 and 14 of gestation (Schardein et al., 1981). Equimolar doses based on 1,000 mg/kg (58.4 to 83.2 mg/ml) given by gastric intubation produced no teratogenic effects on the offspring, even at maternally toxic doses. Unlike the study by Kimmel (1977), the rats were given tap water ad libitum and probably did not suffer from zinc deficiency.

The Agency reviewed data from an early teratogenicity study submitted for disodium EDTA (EPA 1979). Female Sprague-Dawley rats were administered disodium EDTA in the diet ranging from 2% to 3%, or 3% EDTA plus 1,000 ppm zinc, during pregnancy. The conclusions in the memo reported that “disodium EDTA ingested during pregnancy is teratogenic in rats at 2% in the diet and greater.” However, it was also concluded that the diet “supplemented with 1000 ppm zinc prevented the detrimental effects of EDTA during pregnancy in the rat.” Effects from disodium EDTA in the young were likely due to “an induced deficiency of zinc...” and that “cells undergoing rapid growth and development are particularly sensitive to deficiency of zinc.” Likewise, evaluation of EDTA and tetrasodium EDTA by the CSTEE (2003) concluded that “teratogenicity is most likely due to zinc depletion by the very high doses applied...”.

The FAO/WHO Expert Committee on food additives (1974) reviewed acute toxicity data for calcium disodium EDTA and disodium EDTA. The Expert Panel commented that “the use of calcium disodium EDTA is preferable to that of disodium EDTA.” In fact, the Expert Panel

concluded that "because of disodium EDTA's effect on calcium, the use of disodium EDTA as a food additive was not recommended." However, the Committee also concluded that "under certain circumstances, necessitating an accurate complexing of calcium, disodium EDTA may be used provided no excess of disodium EDTA remains and the only compound finally present is calcium disodium EDTA."

A 2002 safety assessment of EDTA, calcium disodium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA was performed by an expert panel of the Cosmetic Ingredient Review (CIR). This assessment considered numerous toxicological studies, including various acute, subchronic, and chronic/carcinogenicity toxicity studies, and mutagenicity studies. This report also details extensive use of these EDTA salts in numerous cosmetic products with EDTA salt formulations most commonly used at $\leq$2%, although a few formulations were reported using up to 10% and 25%. Based on the available information, the panel concluded that "EDTA, calcium disodium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA, are safe as used in cosmetic formulations."

Trisodium EDTA was tested in a bioassay for carcinogenicity by the National Cancer Institute. Trisodium EDTA administered to male and female rats at low (3,750 ppm) or high (7,500 ppm) concentrations for 103 weeks produced no compound-related signs of chemical toxicity, and tumor incidence was not related to treatment (NCI, 1977). The CSTEE (2003) also evaluated this study by the National Cancer Institute and concluded that "there is no concern for EDTA with regard to carcinogenicity."

EDTA has been demonstrated to affect inhibition of DNA synthesis in primary cultures of mammalian cells, which may be due to impairment of enzymes involved in DNA replication (Heindorff et al., 1983). EDTA has also been demonstrated to enhance mutagen-induced aberration frequencies in *Drosophila melanogaster*, *Chlamydomonas reinhardi*, *Neurospora crassa* and *Zea mays* by interfering with the DNA repair process that takes place after exposure to mutagens (Heindorff et al., 1983).

Mutagenicity studies such as mouse lymphoma were negative for EDTA and its salts except for a few positive tests when administered with sterile distilled water. Genotoxicity studies for EDTA and its salts were mixed positive and negative results, depending on assay type and cell type (CCRIS 2003 and Genetox 2003). The RTECS (2003) database for EDTA reported the following mutation data: DNA damage in mouse lymphocyte at 40,500 µmol/L; DNA inhibition in hamster fibroblast at 500 µg/L and in rat other cell types at 600 µmol/L; unscheduled DNA synthesis in hamster embryo at 100 µmol/L; mutation in mammalian somatic cells in mouse lymphocyte at 25, 200 µmol/L; and sister chromatid exchange in hamster embryo at 30 µmol/L.

B. Cations: Calcium, Copper, Iron, Manganese, Potassium, Sodium, and Zinc:

Cations such as calcium, copper, iron, manganese, potassium, sodium, and zinc are required for proper functioning of human biological systems. For risk assessment purposes, an important feature of these cations is that overall the body does have an effective means of processing them. The primary means of exposure to these cations is ingestion. Therefore, the following section focuses on the dietary exposure of these cations and the body's requirements for these cations. The importance of each cation is briefly discussed in the following section.

Calcium: The human body burden of calcium is approximately 1 kg for a 70 kg adult; thus, 1/70th of our weight is calcium. The calcium cation is necessary for bone and teeth formation. It is also important to the proper functioning of nerves, enzymes, and muscles, and plays a role in blood clotting and the maintenance of cell membranes. The recommended daily allowances (RDAs) for calcium are 1000 mg/day for adults aged 19 to 50 years, and 1200 mg/day for individuals older than 50 years.

Copper: Copper is an essential element for all biota and is naturally found in a wide variety of mineral salts and organic compounds, and in the metallic form. At least 12 major proteins require copper as an integral part of their structure. Copper is essential for the utilization of iron in the formation of hemoglobin. Adverse health effects are related to both deficiency and excess. Except for occasional acute incidents of copper poisoning, few effects are noted in normal populations. The mean daily dietary intake in adults ranges between 0.9 and 2.2 mg. The acceptable range of oral intake (AROI) is 20 µg/kg body weight per day for adults and 50 µg/kg body weight per day for infants (WHO 1998).

Iron: The human body burden of iron is approximately 4 g for males, 2.5 g for females or approximately 38 mg/kg body weight. Iron is essential for the synthesis of heme proteins which function in the process of oxygen transport and oxidative metabolism that includes haemoglobin, myoglobin, the cytochromes as well as catalases and peroxidases. The allowable daily intake (ADI) is 0.5 mg/kg (WHO 2003a).

Manganese: Manganese is an essential trace element for both animals and man. It is necessary for the formation of connective tissue and bone, growth, carbohydrate and lipid metabolism, embryonic development of the inner ear, and reproductive functions. Daily intake on manganese is estimated at 2-3 mg/day in adults and at least 1.25 mg/day in pre-adolescent children (WHO 1981).

Potassium: The human body burden of potassium is approximately 140 g for a 70 kg adult. The potassium cation is important in regulating blood pressure, regulating cellular water content, maintaining proper pH balance, and transmission of nerve impulses. It helps to regulate the electrical activity of the heart and muscles. The potassium RDA is 900 mg/day.

Sodium: The human body burden of sodium is approximately 20 g for a 70 kg adult. The sodium cation is necessary for the nerves and muscles to function properly. It is the principal cation of extracellular fluid, and helps to maintain the body's water balance. These electrolytes, the electrically charged ions in the body fluids, consist to a great extent of sodium and

potassium. There is no Recommended Daily Allowance (RDA) for sodium.

Zinc: Zinc is an essential element in the nutrition of man. It functions as an integral part of numerous enzymes. The daily intake for an adult ranges from 14 to 20 mg/day. The recommended dietary allowance (RDA) for adult mean and women is 15 mg/day; however, the requirement for zinc changes throughout life. The Food and Nutrition Board of the United States (1980 as cited in WHO 2003b) evaluated zinc dietary allowances and recommended zinc as follows: 2 mg for infants 0.5 years, 5 mg for 0.5-1.0 years, 10 mg for children 1-10 years, 15 mg for mean and women 11-51+ years, 20 mg for pregnant women, and 25 mg for lactating women. Similar figures were recommended by WHO (2003b).

C. Ammonium Salt

Ammonium phosphates dissociate to the negatively charged anion and the positively charged ammonium cation (NH_4^+). Humans cannot convert atmospheric nitrogen to any form that can be used as part of any of the various metabolic cycles. Therefore, reduced nitrogen (NH_4^+) has to enter the body from an outside source. These sources are the nitrogen-containing amino acids in protein which are consumed daily as part of the diet. Although the human body can produce some amino acids, ten amino acids are considered "essential" amino acids, i.e., they must be consumed in the diet.

Generally the body works to maintain a balance of nitrogen intake and nitrogen excretion. The estimated daily ammonia intake through food and drinking water is 18 mg. In contrast, 4000 mg of ammonia per day are produced endogenously in the human intestine.

Ammonia and the ammonium ion are integral components of normal human metabolic processes. Ammonia is released following deamination that occurs when protein is used by the body for energy production. The liver converts ammonia via the urea cycle into urea. According to FDA in the "Evaluation of the Health Aspects of Certain Ammonium Salts as Food Ingredients" (1974), "the normal liver so readily detoxifies ammonium ion from alimentary sources that blood concentrations of ammonium salts do not rise to the levels necessary to evoke toxic response." Approximately 80% of the body's excess nitrogen is eliminated through the kidneys as urea, approximately 25 to 30 grams per day.

D. Structure Activity Team Report (SAR) Assessments performed by OPPT

There are SAR assessments for 15 of the EDTA salts. The evaluations for EDTA, tetrasodium EDTA trihydrate, disodium EDTA, sodium EDTA, trisodium EDTA, and potassium EDTA indicate no absorption through the skin. A low to moderate concern for human health effects was expected due to good absorption through the lungs and GI tract. With the exception of EDTA, which is expected to be absorbed through all routes, concerns for human health effect included cardiotoxicity, effects on blood clotting, developmental toxicity, and neurotoxicity as

CNS effects from the chelation of metals such as calcium, magnesium, and iron *in vivo*.

The SAR assessments for the remaining 9 salts including calcium disodium EDTA, disodium zinc EDTA dihydrate, disodium zinc EDTA, ferric EDTA, sodium ferric EDTA, disodium cupric EDTA, disodium cupric EDTA trihydrate, disodium manganese EDTA, and disodium manganese EDTA dihydrate indicated no absorption through the skin but expected good absorption through the lungs and GI tract. The evaluations indicated low concern for human health effects due to the binding of other metals present (e.g., copper, zinc, iron).

E. Special Considerations for Infants and Children

Based on available Agency information, EDTA and its salts used in formulations for agricultural use sites have certified limits of less than 4% by weight. Likewise, concentrations in formulations for residential use sites have certified limits of less than 1% by weight. Therefore, given the wide spread occurrence of EDTA in the food supply, the amount of EDTA that can be applied to food as a result of its agricultural or residential uses should not significantly increase the existing amounts in the food supply.

EDTA and its salts should not pose a teratogenic concern based on previous studies in lab rodents. Study results indicate no teratogenic effects are likely in lab rodents at doses up to 1000 mg/kg (Schardein et al., 1981). Adequate minerals in the diet and administration of tap water prevented possible teratogenic effects of EDTA during pregnancy. Teratogenic effects observed in lab rodents noted by Kimmel (1977) were likely due to animals maintained on deionized water and a semi-purified diet, and housed in nonmetallic caging. Infants and children will unlikely be exposed to high concentrations as in lab rodents. The maximum human consumption of EDTA and its salts in foods was reported to be on the order of 0.4 mg/kg/day (Schardein et al., 1981). Infants and children also generally drink tap water instead of deionized or distilled water.

EDTA is also used therapeutically in adults and pregnant women. A therapeutic dose of 1.2 to 2.0 grams per day is generally given to adults (Domingo, 1998). Information is also available indicating EDTA treatment of pregnant women is possible without affecting the development of the fetus. Treatments of EDTA to pregnant women include 75 mg/kg/day calcium disodium EDTA for seven days and 1 gram twice a day for three days, under medical supervision. Healthy, normal infants were delivered four weeks and eight days after chelation therapy, respectively (Domingo, 1998).

EPA also believes there would be a very low exposure of infants to EDTA. First, premature or very young infants ingest only formula or breast milk. (It is generally recommended that infants not consume solid food until 4 to 6 months of age). Regulation of infant formulas is under the purview of the FDA (www.fda.gov/fdac/features/596_baby.html). Calcium disodium EDTA, disodium EDTA, and tetrasodium EDTA are used as direct food additives (21 CFR 172.120, 172.135, and 178.1010, respectively). However, all manufacturers of infant formula must begin with safe food ingredients, which are approved either generally as safe or approved as food additives for use in infant formula. Neither EDTA nor the salts of EDTA are

currently approved by the FDA for use in infant formula. Therefore, infants consuming only infant formula or breast milk would be exposed to very low amounts of EDTA. Second, even if young infants were to be fed some solid food, given the characteristics of EDTA and its salts, residues are not likely to be present at concentrations for potential sensitivity.

Once past this several month time-period, there is no longer a concern for potential sensitivity to infants and children. Older infants, like adults, process EDTA through well understood metabolic pathways. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary.

V. Exposure Assessment

Exposure to EDTA and salts of EDTA may be through FDA-approved uses as food additives, in sanitizing solutions, pharmaceutical products, or through their use in soaps, shampoos, or cosmetics. EDTA has also been administered safely under medical supervision as treatment for heavy metal poisoning.

Residues from the formulations in agriculture use sites (certified limits <4% by weight) and residential use sites (<1% of typical formulations) are not likely to exceed levels currently consumed in commonly eaten foods. In addition, the use of EDTA and EDTA salts in pesticide products is expected to result in much lower exposure than the FDA-regulated use of these compounds, as well as lower exposure than the use in pharmaceuticals or cosmetic products. For example, EDTA and its salts were reported to FDA as used in over 4,000 cosmetic formulations for cosmetic products such as baby products, shampoos, and skin care preparations which generally contained <2% of EDTA salts. Historical data submitted to the FDA in 1984 indicated that EDTA and tetrasodium EDTA each were used in one formulation with concentrations as high as 25%. These cosmetic formulations containing EDTA and its salts may remain in contact with body surfaces for a few minutes to as long as a few days (CIR 2002). EDTA and its salts are not absorbed through the skin (dermal contact). The salts of EDTA are of low risk to humans, since absorption through ingestion is of lower toxicity, especially with sufficient trace minerals within the daily diet. There is no reason to expect that reasonable use will constitute any significant hazard. Therefore, a quantitative screening-level exposure assessment has <u>not</u> been conducted.

VI. Risk Characterization

As noted previously, EDTA, disodium EDTA, and tetrasodium EDTA are included on the Agency's list of chemicals included in the High Production Volume (HPV) Challenge Program. EDTA and its salts have traditionally been administered medically as effective treatment to heavy metal poisoning. Some of the EDTA salts are also approved by the FDA as food additives and sanitizing solutions, as previously discussed. Residues from the pesticide use of EDTA or its salts are not likely to exceed levels commonly consumed in the daily diet.

Taking into consideration all available information on EDTA and its salts, including the

relatively low risk via oral and dermal routes, FDA's allowance of specific EDTA salts as direct food additives; their presence in soaps, shampoos, cosmetics, and cleaning products, as well as their historical use in the treatment of heavy metal poisoning, the use of EDTA or its salts as inert and active ingredients in pesticide products are unlikely to pose a significant hazard to the general public or any population subgroup. Exposure from the aforementioned uses are expected to result in human exposure below any dose level that could possibly produce an adverse effect. As a result, HED is conducting a qualitative approach to assessing human health risks from exposure to EDTA and its salts.

VII. Environmental Fate/Ecotoxicity/Drinking Water Considerations:

Environmental Fate Characterization

The environmental fate and occurrence of EDTA and its salts have been well studied. SAR assessments performed by OPPTS for 15 EDTA salts contains summaries of the environmental fate of EDTA. The Hazardous Substance Database (TOXNET) also contains extensive summaries of the environmental fate of EDTA. In addition, the hazardous substance database (HSDB) information has been supplemented with 11 volumes (sequential Volumes 2 through 12 with MRIDs 459249001 through 459249011) that Neudorff North America submitted to the Agency (Neudorff 2003) to provide required environmental fate information. Summary information was also obtained from the Danish Environmental Protection Agency (DEPA 2003) website (http://www.mst.dk/udgiv/publications/2001/87-7944-596-9/html/kap07_eng.htm#7.6) to essentially confirm the assessment from the previously mentioned sources.

EDTA is a strong organic acid (approximately 1000 times stronger than acetic acid), and does not appear to occur naturally. It has a high affinity for alkaline-earth ions (for example, calcium and magnesium) and heavy-metal ions (for example, lead and mercury). This affinity generally results in the formation of highly stable and soluble hexadentate chelate complexes. EDTA's ability to complex is used commercially to either promote or inhibit chemical reactions, depending on application.

The primary sources of EDTA release to the environment are domestic sewage (for example, from use in detergents, soaps, and cleaning products) and industrial effluents (for example, from the bleaching of textiles and paper; processing of photographic material; electroplating; bottle cleaning; and industrial cleaning of pipe and tank systems). EDTA is also used as a food additive, as an "inert" ingredient in pesticides, in pharmaceuticals, and in a variety of consumer products. EDTA is also released through land disposal of products which contain EDTA. Detergent preparations are probably the predominant source of EDTA found in domestic sewage, contributing an estimated 100 parts per billion (ppb) to the total concentration of EDTA in average sewage streams, with smaller amounts probably originating from food and other consumer products. As is also given in the ecotoxicological section of this document, effluent from a sewage treatment plant in England had EDTA concentrations that ranged from 200 to 1200 ppb, while environmental water concentrations in a river in England ranged from zero to 1120 ppb. Workers involved in the manufacture or use of EDTA may be exposed by inhalation

and dermal contact. Based on its uses, the most probable routes of general human exposure to EDTA would be ingestion and dermal contact.

When released to soil, EDTA is mobile and expected to complex trace metals and alkaline earth metals, thereby causing an increase in the total solubility of the metals. EDTA may eventually predominate as the Fe(III) chelate in acidic soils and as the Ca chelate in alkaline soils. EDTA and its chelates are expected to leach readily through soil. When released to water, EDTA is also expected to form soluble complexes with trace metals and alkaline earth metals. It would not be expected to sorb appreciably to sediments or suspended solids in water, and is known not to be retained or altered chemically in typical water treatment facilities. (However, it has been reported recently (MRID 45924907, journal article published in 2001) that, depending in a complex way upon speciation and local conditions, some sorption (approximately 6 to 25%) occurred within a contact time of one month in a sediment removed from a lake in Finland.)

As discussed further below, when released to soil or water EDTA is slow to degrade, with aerobic biodegradation (mineralization) being the dominant mechanism. Recalcitrance to degradation is associated with the high thermodynamic stability of metal complexes and is problematic for treatment facilities. Only in technically specialized bioreactors and/or with specially selected microbial populations can biodegradation be accelerated. Biodegradation in subsoil or under anaerobic conditions is essentially negligible. Abiotic degradation in the environment (except for photolysis, as discussed below) is also negligible. Results in sediments were similar to those for soil. Although EDTA is slow to degrade under typical environmental conditions, based on experimental results with bluegill sunfish and its intrinsic physicochemical properties (ionic nature and water solubility), EDTA is not expected to bioconcentrate.

In a variety of representative United States soils, common values for the degree of aerobic metabolism of EDTA (mineralization as evidenced by carbon dioxide production from radiolabeled positions) at a temperature of 30 ^{0}C and soil concentrations of 2-4 ppm are 13-45% after 15 weeks and 65-70% after 45 weeks. Rates of metabolism followed first-order kinetics. Based on these rates, the OPP reviewer extrapolates the first-order aerobic soil metabolism half-lives at 30 ^{0}C to range roughly from 17 to 75 weeks (4 to 18 months). Results in three sediments after four weeks of incubation were similar, with OPP reviewer-extrapolated first-order aerobic half-lives ranging roughly from 48 to 76 weeks (11 to 18 months). There is good evidence that co-metabolism is the mechanism for EDTA biodegradation. Microbial oxidation occurs at all three carbon centers (carboxyl, acetate-2, and ethylene-1,2 bridge), indicating complete mineralization eventually. The rate of biodegradation of EDTA in soils is reported to vary among soils with rates depending upon environmental factors such as pH, temperature, soil classification, organic matter, and types and population of microbes.

Based on its physicochemical properties and collateral experimental results, EDTA is not expected to volatilize from soil or water. When released to the atmosphere, EDTA should sorb to particulate matter, and appears to have the potential to photolyze.

Compounds identified as possible biodegradation products of the ammonium ferric

chelate of EDTA are as follows: ethylenediamine triacetic acid (ED3A), iminodiacetic acid (IDA), N,N-ethylenediamine diacetic acid (N,N-EDDA), N,N'-EDDA, ethylenediamine monoacetic acid (EDMA), nitrilotriacetic acid (NTA) and glycine. In water, EDTA may react with photochemically generated hydroxyl radicals (half-life of approximately 230 days or 8 months). The following photodegradation products of Fe(III)-EDTA have been identified: carbon monoxide, formaldehyde, ED3A, N,N-EDDA, N,N'-EDDA, IDA, EDMA and glycine.

Ecotoxicity and Ecological Risk Characterization

Predicted toxicity based on structure activity relationships performed by OPPT, indicate EDTA ranges from practically non-toxic to moderately toxic on an acute basis depending on the salt. EDTA *per se*, appears less toxic than many of the salts reviewed. Algae is the most sensitive species on a chronic basis. Table 4 lists the estimated toxicity for several compounds of EDTA. Algae and invertebrates are among the most sensitive species based on predictive modeling for acute and chronic endpoints for EDTA depending on the compound. Based on the environmental fate profile of EDTA and its salts, exposures from labels uses are unlikely to reach concentrations necessary to elicit effects in most aquatic organisms. Using laboratory rat data as a surrogate for terrestrial wild mammals and birds, EDTA and its salts do not appear to be very toxic and adverse effects from labeled uses are not expected.

Table 4. Ecotoxicity of EDTA and Selected Salts

Property	EDTA; Sodium EDTA; Disodium EDTA; Trisodium EDTA; Tetrasodium EDTA; and Potassium EDTA; Sodium Hydrogen Ferric EDTA; Fe (III) EDTA	Disodium Manganese EDTA; Disodium Cupric EDTA; Disodium Zinc EDTA	Disodium Manganese üEDTA; Disodium Cupric üEDTA; Disodium Zinc üEDTA	Calcium Disodium EDTA
Fish (96-h LC_{50}; mg/L)	430	100	20	100
Daphnia (48-h LC_{50}; mg/L)	100	100	14	100
Green Algae (96-h EC_{50}; mg/L)	3.0	30	25	60
Fish (Chronic; mg/L)	10	10	3.0	10
Daphnia (Chronic; mg/L)	23	10	2.0	10
Algae (Chronic; mg/L)	0.88	9	12	6.3

Monitoring for EDTA in surface water has been extensively studied, but only a few reported concentrations were readily available for this review. Concentrations of EDTA have been measured to as high as 1120 ppb (1.1 ppm) in the Lea River, England. In addition, concentrations have been measured in sewage effluent, mainly from detergent products, ranging from 200 to 1200 ppb (0.2 to 1.2 ppm). With the exception of chronic risks to algae, measured concentrations in surface do not exceed the toxicity endpoints for aquatic organisms.

VIII. Cumulative Exposure:

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.”

EPA does not have, at this time, available data to determine whether EDTA and its salts have a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to EDTA and its salts and any other substances and EDTA and its salts do not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that the EDTA and its salts have a common mechanism of toxicity with other substances. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA’s Office of Pesticide Programs concerning common mechanism determinations

and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

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