Final Screening Assessment

EDTA and Its Salts Group

Chemical Abstracts Service Registry Numbers
60-00-4
64-02-8
15708-41-5
21265-50-9

Environment and Climate Change Canada
Health Canada

May 2018

Synopsis

Pursuant to sections 68 or 74 of the Canadian Environmental Protection Act, 1999 (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively as the EDTA and its salts group. Although there are other EDTA salts, substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. The Chemical Abstracts Service Registry Numbers (CAS RN[1]), their Domestic Substances List (DSL) names and their common names are listed in the table below.

Substances in the EDTA and its salts group

CAS RN	DSL name	Common names
60-00-4	Glycine, N,N′-1,2-ethanediylbis[N-(carboxymethyl)-	Ethylene diaminetetraacetic acid (EDTA) or edetic acid
64-02-8	Glycine, N,N′-1,2-ethanediylbis[N-(carboxymethyl)-, tetrasodium Salt	Tetrasodium EDTA
15708-41-5[a]	Ferrate(1-), [[N,N′-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N′,O,O′,ON,ON′]-, sodium, (OC-6-21)-	Ferric monosodium EDTA
21265-50-9[a]	Ferrate(1-), [[N,N′-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N′,O,O′,ON,ON′]-, ammonium, (OC-6-21)-	Ferric ammonium EDTA

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.

The four substances in this group do not occur naturally in the environment. Some of them are primarily used as chelating agents or preservatives in cleaning products, cosmetics, prescription and non-prescription drugs, natural health products, and products used by consumers. Other uses include manufacture of products for printing inks, paints and coatings, ion exchange agents, automotive care, water treatment, food

[1] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

packaging, and pest control. In 2011, only EDTA and tetrasodium EDTA were manufactured in Canada in quantities ranging from 100 to 10 000 kg. In the same year, all four substances were imported into Canada in quantities ranging from 1000 to 10 000 000 kg.

The ecological risks of the substances in the EDTA and its salts group were characterized using the ecological risk classification of organic substances (ERC). The ERC is a risk-based approach that employs multiple metrics for both hazard and exposure based on weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are established based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. The ERC identified the four substances in the EDTA and its salts group as having low potential to cause ecological harm.

Considering all available lines of evidence presented in the screening assessment, there is low risk of harm to the environment from EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA. It is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Owing to their structural similarity and ability to chelate metals, EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA were grouped together for characterization of risk to human health. A read-across approach was used in the absence of substance-specific data for the assessment of human health effects. EDTA salts also dissociate in solution and, accordingly, data from other EDTA salts (e.g., Na_2EDTA) were also taken into consideration in characterizing the hazard of the four substances in this group.

The four substances within this group are not considered to be carcinogenic or genotoxic. In laboratory studies, systemic effects were observed only at high doses equal to or exceeding the limit dose of 1000 mg/kg bw/day and were considered secondary to the chelating properties of substances in this group. In conjunction with the low oral and dermal absorption of substances in the group, health effects from exposure to the EDTA and its salts group are not expected. Inhalation risks to the EDTA and its salts group were not considered to be of concern due to their low to negligible volatility, as well as their potential uses. As hazard is low, risk is also considered to be low and quantitative estimates of exposure and risk were not derived.

On the basis of the information presented in the screening assessment, it is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet any of the criteria set out in section 64 of CEPA.

Contents

List of Tables

1. Introduction

Pursuant to sections 68 or 74 of the Canadian Environmental Protection Act, 1999 (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of four substances referred to collectively as the EDTA and its salts group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group include ethylene diaminetetraacetic (EDTA) or edetic acid, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA. They were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

The substances within the EDTA and its salts group were reviewed internationally through the Cooperative Chemicals Assessment Programme of the Organisation for Economic Cooperation and Development (OECD), and Screening Information Dataset (SIDS) Initial Assessment Profiles (SIAPs) were published. SIAPs are available for EDTA, tetrasodium EDTA, as well as for amino carboxylic acid-based chelants (which include ferric monosodium EDTA and ferric ammonium EDTA). European Union Risk Assessment Reports published by the European Chemicals Bureau are also available for EDTA and tetrasodium EDTA (also identified by OECD as their SIDS Initial Assessment Reports [SIARs]). These assessments undergo rigorous review and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in these processes and consider these assessments reliable. EDTA has also been reviewed by the United States Environmental Protection Agency (US EPA), and ferric monosodium EDTA has been assessed by the US EPA and the European Food Safety Authority (EFSA) (US EPA 2004b, 2011; EFSA 2010). In Canada, Health Canada's Pest Management Regulatory Agency (PMRA) has also reviewed ferric monosodium EDTA as an active ingredient in pesticides (PMRA 2008). The EU Risk Assessment Reports (RAR) for EDTA (EU RAR 2004a) and tetrasodium EDTA (EU RAR 2004b), the SIAP for the amino carboxylic acid-based chelants (OECD 2012), and the EFSA review for ferric monosodium EDTA (EFSA 2010) were used to inform the health effects characterization for the EDTA and its salts group. Older studies and reviews were also taken into consideration, but did not form the basis of this screening assessment.

The ecological risks of substances in the EDTA and its salts group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics, including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of factors including potential emission rates, overall persistence and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further

evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

This screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to July 2016. Additional data were submitted by stakeholders up to May 2016. Empirical data from key studies as well as some results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was peer-reviewed and subject to a 60-day public comment period. Additionally, the draft of this screening assessment (published April 29, 2017) was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

This screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight-of-evidence approach and precaution.[2] This screening assessment presents the critical information and considerations on which the conclusion is based.

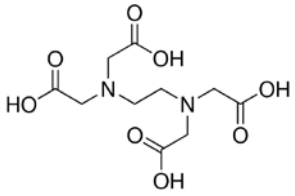
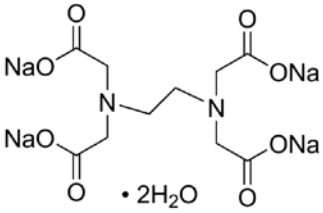
[2] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Hazardous Products Regulations, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for hazardous products intended for workplace use, handling and storage. Similarly, a conclusion on the basis of the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

2. Identity of substances

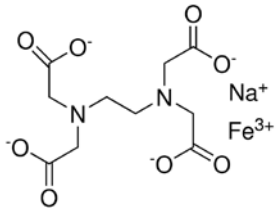
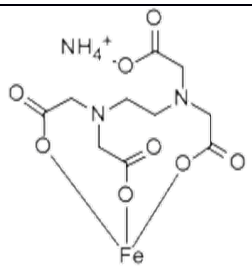
The Chemical Abstracts Service Registry Numbers (CAS RN[3]), Domestic Substances List (DSL) names and common names and/or acronyms for the individual substances in the EDTA and its salts group are presented in Table 2-1.

The four substances within this group all have the same ethylenediamine backbone with carboxylic acid groups on the amine that enable chelation or sequestration of metal ions. CAS RN 60-00-4 is EDTA and has four acetic acid groups, CAS RN 64-02-8 is a sodium salt of EDTA, CAS RN 15708-41-5 is a ferric salt of EDTA, and CAS RN 21265-50-9 is a ferric ammonium salt of EDTA.

Table 2-1. Substance identities

CAS RN (acronym)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight [a] (g/mol)
60-00-4 (EDTA)	Glycine, N,N′-1,2-ethanediylbis[N-(carboxymethyl)- (EDTA or Edetic acid)	 $C_{10}H_{16}N_2O_8$	292.25
64-02-8 (Na_4EDTA)	Glycine, N,N′-1,2-ethanediylbis[N-(carboxymethyl)-, tetrasodium salt (Tetrasodium EDTA)	 $C_{10}H_{12}N_2Na_4O_8$	380.17

[3] The CAS RN is the property of the American Chemical Society, and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

CAS RN (acronym)	DSL name (common name)	Chemical structure and molecular formula	Molecular weight [a] (g/mol)
15708-41-5 [Fe(III)NaEDTA]	Ferrate(1-), [[N,N′-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N′,O,O′,ON,ON′]-, sodium, (OC-6-21)- (Ferric monosodium EDTA)	 $C_{10}H_{12}FeN_2O_8Na$	367.05
21265-50-9 [Fe(III)(NH_4)EDTA]	Ferrate(1-), [[N,N′-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N′,O,O′,ON,ON′]-, ammonium, (OC-6-21)- (Ferric ammonium EDTA)	 $C_{10}H_{16}FeN_3O_8$	362.09

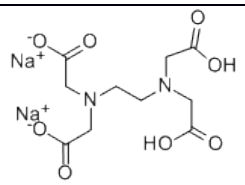
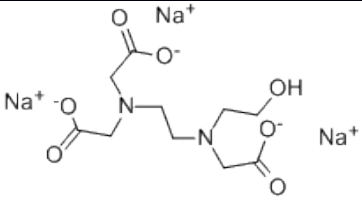
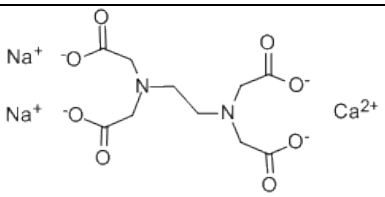
[a] Molecular weights were obtained from the ChemIDplus database.

2.1 Selection of analogues

A read-across approach using data from analogues, where appropriate, has been used to inform the human health assessment. Analogues were selected that were structurally similar and functionally similar to substances within this group (similar physical-chemical properties, toxicokinetics) and that had relevant empirical data that could be used to read across to substances that were data poor. The use of analogues in this screening assessment is consistent with other international assessments (EU RARs 2004a, 2004b; OECD 2012). Details of the read-across data chosen to inform the human health assessment of the EDTA and its salts group are further discussed in the relevant sections of this report.

Information on the identities and chemical structures of the analogues used to inform this assessment is presented in Table 2-2.

Table 2-2. Analogue identities

CAS RN (acronym)	DSL/other name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
139-33-3 (Na_2EDTA)	Disodium EDTA	 C10H14N2Na2O8	336.21
139-89-9 (Na_3HEDTA)	Trisodium HEDTA	 C10H15N2Na3O7	344.20
62-33-9 ($CaNa_2$EDTA)	Calcium disodium EDTA	 C10H12CaN2Na2O8.xH2O	374.27

3. Physical and chemical properties

A summary of physical and chemical properties of the substances in the EDTA and its salts group is presented in Table 3-1, with the range in values indicated for each property. When experimental information was limited or not available for a property, data from analogues were used to generate predicted values for the substance. The four substances in this group are solid at room temperature and do not significantly evaporate to air. They are very soluble in water and have a negative octanol-water partition coefficient. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Experimental physical and chemical property values (at standard temperature) for the EDTA and its salts group

Property	Range	Type of data	Key reference(s)
Physical state	Solid	Experimental	EU RAR 2004a, 2004b
Melting point (°C)	>300 ^{o}C (Na_4EDTA), N/A for others as they decompose > 150 – 200 ^{o}C	Experimental	EU RAR 2004a, 2004b, OECD 2012
Vapour pressure	Estimated to be very low. [a]	Estimated	EU RAR 2004a, 2004b, OECD 2012

Property	Range	Type of data	Key reference(s)
Henry's law constant ($Pa \cdot m^3/mol$)	Undetermined due to lack of vapour pressure data. Fictitious 1×10^{-20}	Estimated	EU RAR 2004a, 2004b
Water solubility (mg/L)	400 (EDTA) or 500 (Na_4EDTA) at 20^oC, >10,000 (Ferric monosodium EDTA and Ferric ammonium EDTA)	Experimental	EU RAR 2004a, 2004b, OECD 2012
Other solubilities (mg/L)	Insoluble in organic solvents (Ferric monosodium EDTA and Ferric ammonium EDTA)	Experimental	OECD 2012
log K_{ow} (dimensionless)	-3.34 to -5.01 [b]	Experimental	EU RAR 2004a, 2004b

Abbreviations: K_{ow}, octanol–water partition coefficient;
[a] For the partially ionic substance (EDTA), as well as ionic substances (tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA).
[b] Partition coefficient cannot be determined for ionic substances; values are for undissociated free acid.

4. Sources and uses

Substances in the EDTA and its salts group do not occur naturally in the environment. The sources of these substances are industrial activities and use of products available to consumers.

All four substances were included in a section 71 survey under CEPA (Canada 2012), which aimed to identify the current sources and uses of these substances in Canada. Information obtained via this survey was considered in this screening assessment.

Annual manufacture and import quantities for these four substances in Canada are summarized in Table 4-1 (Environment Canada 2013).

Table 4-1. Summary of information on Canadian manufacturing and imports of EDTA and its salts group submitted pursuant to a survey under section 71 of CEPA[a]

Common name	Total manufacture (kg)	Total imports (kg)
EDTA	100 – 1000	100 000 – 1 000 000
Tetrasodium EDTA	1000 – 10 000	1 000 000 – 10 000 000
Ferric monosodium EDTA	None	1000 –- 10 000
Ferric ammonium EDTA	None	10 000 – 100 000

[a] Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2013). See survey for specific inclusions and exclusions (schedules 2 and 3).

EDTA and tetrasodium EDTA are used as chelating agents or preservatives in many products, including cleaning products (general purpose cleaners, glass cleaners and tile cleaners) (Household Products Database 1993-), cosmetics, natural health products, prescription and non-prescription drugs, and pesticides. Information submitted in a section 71 survey under CEPA (Environment Canada 2013) indicates that other uses for EDTA include manufacturing of adhesives and sealants, automotive care, building/furnishing materials, detergents, agricultural products, and water treatment. Other uses for tetrasodium EDTA include detergents, paints and coatings, inks and dyes, paper products, rubber and plastic materials, and processing aids used for petroleum products. Ferric monosodium EDTA is used in paper products, whereas ferric ammonium EDTA is not used in products.

According to notifications submitted under the Cosmetic Regulations to Health Canada and information from other sources (Household Product Database 1993-), EDTA and tetrasodium EDTA are used in many diverse cosmetic products, including shampoos and conditioners, cleansers and soaps, hair dyes, hair products, body and face moisturizers, tanning products, massage products, antiperspirants/deodorants, and a permanent eye make-up/tattoo ink (email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced).

EDTA and tetrasodium EDTA are listed in the Natural Health Products Ingredients Database (NHPID) with a non-medicinal role, for use as a chelating agent or preservative antimicrobial for EDTA, and as a chelating agent, preservative antimicrobial, preservative antioxidant, sequestering agent, or stabilizing agent for tetrasodium EDTA (NHPID [modified 2017]; email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced). Both of these substances are listed in the Licensed Natural Health Products Database as being present as a non-medicinal ingredient in natural health products, such as in sunscreens, multivitamin/mineral supplements, first aid gels, anti-itch creams, and anti-acne creams or masks (LNHPD [modified 2016]; email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced). EDTA is also found in tuna oil emulsions, and tetrasodium EDTA is found in headache products

According to information available in Health Canada’s Drug Product Database, EDTA and tetrasodium EDTA are present in certain human and veterinary drugs (where they may be listed under their synonyms ‘edetic acid’ and ‘edetate sodium’, respectively). They are found as active ingredients in certain disinfectants for domestic use, for medical instruments and/or for use in hospitals and health care facilities, food premises and institutional or industrial settings. In addition, EDTA and tetrasodium EDTA are present as non-medicinal ingredients in other non-prescription drugs, such as disinfectants, sunscreens, soaps, and creams (DPD [modified 2015], email from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced). Prescription drugs

containing EDTA as a non-medicinal ingredient include eye drops and a rectal suppository.

In Canada, substances in the EDTA and its salts group may be present in products used in food processing and manufacture, but none of them have been approved to date as food additives. EDTA, tetrasodium EDTA, and ferric monosodium EDTA are used in the manufacture of different types of food packaging materials. Incidental additives, such as boiler water additives, cleaners, and sanitizers, can contain tetrasodium EDTA (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced).

Only ferric monosodium EDTA is currently an active ingredient in pest control products. It is registered as a molluscicide to control slugs and snails (PMRA 2008; US EPA 2011). EDTA and tetrasodium EDTA are listed on the PMRA Formulants List (PMRA 2010).

5. Potential to cause ecological harm

5.1 Characterization of ecological risk

The ecological risks of substances in the EDTA and its salts group were characterized using the ecological risk classification of organic substances (ERC) (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure based on weighted considerations of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., LC_{50}) for characterization. The following is a summary of the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox), and from responses to surveys under section 71 of CEPA or were generated using selected quantitative structure-activity relationship (QSAR) or mass-balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and

biological activity were established. Exposure profiles were also developed using multiple metrics, including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over- and under-classification of hazard and exposure and subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC 2016a. The following describes two of the more substantial areas of uncertainty. Error in empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from QSAR models. However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue (CBR) analysis. Error in underestimation of acute toxicity will be mitigated through the use of other hazard metrics, such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. As the exposure and risk classifications are highly sensitive to emission rate and use quantity, changes or errors in chemical quantity could result in differences in classification of exposure. The ERC classifications thus reflect exposure and risk in Canada on the basis of what is believed to be the current use quantity and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the four substances in the EDTA and its salts group and the hazard, exposure and risk classification results are presented in ECCC (2016b).

The hazard and exposure classifications for the four substances in the EDTA and its salts group are summarized in Table 5-1.

Table 5-1. Ecological risk classification results for the four substances in the EDTA and its salts group

Common name	ERC hazard classification	ERC exposure classification	ERC risk classification
EDTA	low	low	low
Tetrasodium EDTA	low	low	low
Ferric monosodium EDTA	low	low	low
Ferric ammonium EDTA	low	moderate	low

The four substances in this group are classified as having a low potential for ecological risk. Ferric ammonium EDTA is classified as having moderate potential exposure on the basis of the moderate import quantity of the substance. EDTA, tetrasodium EDTA, and ferric monosodium EDTA have low exposure classifications. It is unlikely that these substances result in concerns to the environment in Canada.

6. Potential to cause harm to human health

6.1 Exposure assessment

Environmental media

The substances in the EDTA and its salts group, when in solution, are expected to dissociate into the same anionic species of EDTA in the environment (EU RAR 2004a, 2004b). There were no measured concentrations of these substances in indoor or outdoor air, but exposure is not expected because of their low (EDTA) or estimated to be very low (tetrasodium EDTA, ferric monosodium EDTA, ferric ammonium EDTA) vapour pressure and their moderate (0.4 – 0.5 g/L, EDTA and tetrasodium EDTA) to very high (> 10 g/L, ferric monosodium EDTA, ferric ammonium EDTA) water solubility. The primary environmental compartment for the EDTA and its salts group for industrial release is water (EU RAR 2004a). Adsorption onto the organic fraction in soil or sediment is not expected (EU RAR 2004a, 2004b). Once in soil or water, the substances in the EDTA and its salts group are highly mobile owing to their high water solubility and low vapour pressure (OECD 2012).

Members of the EDTA and its salts group were not measured in Canadian waters, soil or dust. Levels ranging from 26 to 1700 µg/L EDTA have been measured in wastewater treatment plant effluent in the United States and Europe (Barber et al. 2015; WHO 2004; OECD 2004; RIVM 2003; Sillanpää et al. 1997). EDTA in surface waters in Europe was generally below 70 µg/L, but reached up to 900 µg/L EDTA (WHO 2004; OECD 2004; EU RAR 2004a; RIVM 2003).

Substances in the EDTA and its salts group were not measured in Canadian drinking water. EDTA levels up to 30 µg/L were measured in European drinking water (Bergers

and de Groot 1994; WHO 2004), well below the World Health Organization (WHO) guideline value of 600 µg/L for EDTA as a free acid (WHO 2004). Overall, the oral exposure of EDTA from drinking water was expected to be small in comparison to other sources (WHO 2004). Based on the estimated total annual usage reported in response to a survey under section 71 of CEPA (Environment Canada 2013), estimated surface water concentrations using the EAU Drinking Water Spreadsheet (Health Canada 2015) for EDTA and its salts group in Canada are also below the WHO guideline value.

Food

Substances in the EDTA and its salts group are not approved for use as food additives in Canada (personal communications, emails from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced). While it is possible that these substances may be present in products used in food processing and manufacture, dietary exposure from such uses is expected to be negligible. In Canada, with the exception of ferric ammonium EDTA, substances in this group can be present in certain food packaging materials. Tetrasodium EDTA has also been identified as being used in incidental additives for use in food processing establishments. Dietary exposure to EDTA, tetrasodium EDTA, and ferric monosodium EDTA from these uses is expected to be low or negligible.

Considering the above information, exposure of the general population to the EDTA and its salts group through food in Canada is expected to be minimal.

Products available to consumers

Sources of oral and dermal exposure to EDTA and tetrasodium EDTA from products available to consumers included prescription and non-prescription drugs, natural health products, and cosmetics (personal communications, emails from Natural and Non-prescription Health Products Directorate, Therapeutic Products Directorate, or Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, 2016; unreferenced). Oral and dermal exposure to ferric monosodium EDTA was possible from one household product. In contrast, ferric ammonium EDTA is not used in products available to consumers in Canada. Estimates of oral and dermal exposure from use of products available to consumers were not derived given the absence of health effects of concern for this group (see section 6.2).

Inhalation exposures during use of products containing substances in the EDTA and its salts group were not presented for the same reason mentioned above. It was expected that the exposure period to EDTA and tetrasodium EDTA in spray products was short and the majority of their spray particles are too large to be inhaled (RIVM 2006a, 2006b). Inhalation from other products available to consumers was unlikely owing to the low vapour pressure of these substances.

6.2 Health effects assessment

EU Risk Assessment Reports for EDTA (EU RAR 2004a) and tetrasodium EDTA (EU RAR 2004b), the SIAP for the amino carboxylic acid-based chelants (OECD 2012), and the EFSA review on ferric monosodium EDTA (EFSA 2010) were used as the basis for characterizing risk to human health in this screening assessment.

A literature search was conducted from 2003 (the year prior to the 2004 EU RARs) to 2016, and no additional health effects studies were identified, which could result in points of departure lower than those identified by EU RARs (2004a, 2004b).

Under environmental conditions, EDTA and its salts (e.g., Na_2EDTA, Na_3EDTA, $CaNa_2$EDTA) are expected to dissociate into their cationic component (e.g., H^+, Na^+) and their anionic species of EDTA. Thus, on the basis of similar chemical structures and ability to readily associate/dissociate metal ions, as well as exposure patterns (for EDTA and tetrasodium EDTA), systemic toxicity data from EDTA salts were considered for read-across to the four substances in this group. Dermal and oral absorption studies with the analogue $CaNa_2$EDTA were also used in this context because of its similar chemical structures and physiochemical properties. This approach is consistent with reviews by the EU (RAR 2004a, 2004b) and OECD (2012).

Read-across studies with $CaNa_2$EDTA show that substances in the EDTA and its salts group are poorly absorbed after oral and dermal exposure. Following administration of 50 mg radiolabeled $CaNa_2$EDTA to rats via oral gavage, oral absorption after 24 hours is 10 and 6% in males and females, respectively, on the basis of urinary excretion (Foreman et al. 1953). In male humans exposed to 1.5 or 2 mg radiolabelled $CaNa_2$EDTA by the oral or dermal route, recovery in urine was only 5% through the oral route after 24 hours and 0.001% through the dermal route (Foreman and Trujillo 1954). EFSA (2010) also reported less than 5% oral absorption of ferric monosodium EDTA. The US EPA reported that EDTA and 23 of its salts, including ferric [mono]sodium EDTA, did not absorb through the skin (US EPA 2004a). $CaNa_2$EDTA has low distribution to tissues (less than 0.5% of administered dose after 24 hours to gastrointestinal tract, skin, muscle, or kidney), and poor metabolism (only parental compound identified in urine or plasma after 24 hours) and is rapidly eliminated primarily in feces, as well as in urine following oral gavage in rats (Foreman et al 1953).

Acute oral toxicity is low (EDTA, ferric monosodium EDTA) to moderate (tetrasodium EDTA, ferric ammonium EDTA) (EU RAR 2004a, 2004b; OECD 2012; US EPA 2011). Acute dermal toxicity is low (ferric monosodium EDTA) to moderate (ferric ammonium EDTA) and is expected to be similar for EDTA and Na_4EDTA. Acute inhalation toxicity is low (EDTA, ferric monosodium EDTA) or potentially low (tetrasodium EDTA), but is not expected owing to low or estimated very low vapour pressures.

These substances can cause mild skin irritation (EDTA, tetrasodium EDTA, ferric monosodium EDTA), and mild (ferric monosodium EDTA) or strong (EDTA, tetrasodium

EDTA) eye irritation (EU RAR 2004a, 2004b; OECD 2012; US EPA 2011). They are not reported to be skin sensitizers (US EPA 2011; EU RAR 2004a; Sanchez-Pedreno et al. 2009) or respiratory sensitizers (Laborde-Casterot et al. 2012).

A three-month dietary study in male rats established a no observed adverse effect level (NOAEL) of 500 mg Na_2EDTA/kg bw/day (Wynn et al. 1970), equivalent to 435 mg HEDTA/kg bw/day or 565 Na_4EDTA/kg bw/day (EU RAR 2004a, 2004b). There was decreased body weight and food consumption, increased water consumption, diarrhea and increased mortality at the next highest dose (lowest observed adverse effect level [LOAEL] of 2500 mg Na_2EDTA/kg bw/day). Similarly, increased mortality was observed at the LOAEL of 2250 mg Na_2EDTA/kg bw/day in a one-month dietary study in rats, along with decreased white blood cell counts, increased blood urea nitrogen, decreased calcium, decreased organ weights (liver, spleen, thymus), and parakeratosis of the esophagus and forestomach (EU RAR 2004a, 2004b). The NOAEL in this study was 1125 mg Na_2EDTA/kg bw/day. Severe systemic effects observed at high dietary Na_2EDTA concentrations were attributed to mineral sequestration and imbalance. EFSA (2010) also reported that ferric monosodium EDTA was not toxic up to 250 mg /kg bw/day in one- to three-month dietary studies in rats (Appel et al. 2001; Su et al. 1999; Sichuan Provincial Sanitary and Anti-epidemic Station 1993). Given that all indications of toxicity occurred at dose levels exceeding the limit dose of approximately 1000 mg/kg bw/day in test guidelines [e.g., OECD TG 408 (OECD 1998), FDA 2010], these studies were used qualitatively in the risk characterization.

Overall, substances in the EDTA and its salts group were not considered genotoxic (EU RAR 2004a, 2004b) or carcinogenic, in agreement with the EU RAR (2004a, 2004b) and OECD (2012). EDTA is not classified by IARC (2015).

In regard to potential reproductive toxicity of the substances in the EDTA and its salts group, although there was decreased fertility at 3000 mg Na_2EDTA/kg bw/day in a 2-generation dietary reproductive study in rats with limited study details reported, there was no effect reported up to 600 mg/kg bw/day (Yang and Chan 1964). There were also no other reproductive effects in a 2-year 4-generation reproductive study with doses up to 250 mg $CaNa_2$EDTA/kg bw/day in rats (Oser et al. 1963), nor were there male reproductive organ effects or post-implantation effects with 5-day oral exposures to Na_2EDTA in mice (Muralidhara and Narasimhamurthy 1991).

The literature search identified several developmental studies in rats investigating the substances in the EDTA and its salts group or their analogues (including Swenerton and Hurley 1971; Schardein et al. 1981; Kimmel 1977; Sichuan Provincial Sanitary and Anti-epidemic Station 1993). On the basis of similar developmental studies with mineral supplementation or depletion (Hurley and Swenerton 1966; Hurley et al. 1971; Brownie et al. 1986), it was determined that maternal or developmental effects observed at doses approaching or exceeding the limit dose could be attributed to mineral

imbalances. Overall, substances in the EDTA and its salts group are not expected to be developmental toxicants, in agreement with the EU RAR (2004a, 2004b).

6.3 Characterization of risk to human health

On the basis of the available empirical data, substances in the EDTA and its salts group were not considered to be either carcinogenic or genotoxic. Non-cancer effects (including mortality, diarrhea, and decreased food consumption and weight gain) were observed in oral studies (repeated-dose studies, chronic studies and developmental studies) at doses approaching or exceeding 1000 mg/kg bw/day, i.e., the limit dose in test guidelines of short term to chronic duration in rodents [e.g., OECD TG 408 (OECD 1998), FDA 2010]. Consistent with their low oral and dermal absorption, substances in the EDTA and its salts group are expected to be of low toxicity.

Since effects observed in the EDTA and its salts group were compromised by excessively high doses, and these substances are not well absorbed, numerical limits for points of departure (of all durations and routes) were not considered necessary and were not established. No health effects of concern from use of substances in the EDTA and its salts group were identified.

As hazard is low, risk is also considered to be low and quantitative estimates of exposure and risk were not derived.

6.4 Uncertainties in evaluation of risk to human health

Data gaps include lack of both acute dermal studies with EDTA and tetrasodium EDTA and repeated-dose studies by the dermal and inhalation routes of exposure. The weighing of several lines of evidence, including the low acute inhalation toxicity, very low vapour pressure of EDTA and its salts group, low dermal toxicity of ferric monosodium EDTA, and poor dermal absorption of the analogue $CaNa_2EDTA$, supports the determination that dermal and inhalation exposures would not result in effects more serious than those observed in oral studies. The use of oral effects data as a surrogate for dermal and inhalation routes is therefore considered protective.

7. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA. It is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this screening assessment, it is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that EDTA, tetrasodium EDTA, ferric monosodium EDTA, and ferric ammonium EDTA do not meet any of the criteria set out in section 64 of CEPA.

References

Appel MJ, Kuper CF, Woutersen RA. 2001. Disposition, accumulation and toxicity of iron fed as iron (II) sulfate or as sodium iron EDTA in rats. Food Chem Toxicol. 39:261-269.

Barber LB, Loyo-Rosales JE, Rice CP, Minarik TA, Oskouie AK. 2015. Endocrine disrupting alkylphenolic chemicals and other contaminants in wastewater treatment plant effluents, urban streams, and fish in the Great Lakes and Upper Mississippi River Regions. Sci Total Environ. 517:195-206.

Bergers PJM, de Groot AC. 1994. The analysis of EDTA in water by HPLC. Wat Res. 28(3):639-642.

Brownie CF, Brownie C, Noden D, Krook L, Haluska M, Aronson AL. 1986. Teratogenic effect of calcium edetate (CaEDTA) in rats and the protective effect of zinc. Toxicol Appl Pharmacol. 82:426-443. [cited in Swenerton and Hurley 1971].

Canada. 1999. Canadian Environmental Protection Act, 1999. S.C. 1999, c.33. Canada Gazette Part III, vol. 22, no. 3.

Canada, Dept. of the Environment. 2012. Canadian Environmental Protection Act, 1999: Notice with respect to certain substances on the Domestic Substances List [PDF]. Canada Gazette, Part I, vol. 146, no. 48, Supplement.

ChemIDplus [database]. 1993-. [updated 2012 Nov 26; accessed 2016 May 24]. Bethesday (MD): US National Library of Medicine.

[DPD] Drug Product Database [database]. [modified 2015 Jul 17]. Ottawa (ON): Health Canada. [accessed 2016 Jan 12].

[ECCC, HC] Environment and Climate Change Canada, Health Canada. [modified 2017 Mar 12]. Categorization. Ottawa (ON): Government of Canada. [accessed 2016 May 24].

[ECCC] Environment and Climate Change Canada. 2016a. Science approach document: ecological risk classification of organic substances. Ottawa (ON): Government of Canada.

[ECCC] Environment and Climate Change Canada. 2016b. Gatineau (QC): Data used to create substance-specific hazard and exposure profiles and assign risk classifications in the Ecological Risk Classification of organic substances. Available from: eccc.substances.eccc@canada.ca.

[EFSA] European Food Safety Authority. 2010. Scientific Opinion on the use of ferric sodium EDTA as a source of iron added for nutritional purposes to foods for the general population (including food supplements) and to foods for particular nutritional uses. EFSA Journal. 8(1):1414.

Environment Canada. 2013. DSL Inventory Update data collected under the Canadian Environmental Protection Act, 1999, section 71: Notice with respect to certain

substances on the Domestic Substances List. Data prepared by: Environment Canada, Health Canada; Existing Substances Program.

[EU RAR] European Union Risk Assessment Report. 2004a. CAS RN 60-00-4: edetic acid (EDTA). Luxembourg: Office for Official Publications of the European Communities. Report No.: EUR 21314 EN. [accessed 2016 May 24].

[EU RAR] European Union Risk Assessment Report. 2004b. CAS RN 64-02-8: tetrasodium ethylenediaminetetraacetate (Na4EDTA). Luxembourg: Office for Official Publications of the European Communities. Report No.: EUR 21315 EN. [accessed 2016 May 24].

[FDA] Food and Drug Administration. 2010. Guidance for Industry: M3(R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals [PDF]. [accessed 2016 Aug 10].

Foreman H, Trujillo TT. 1954. The metabolism of C^{14} labelled ethylenediaminetetraacetic acid in human beings. J Lab & Clin Med. 43(4):566-571.

Foreman H, Vier M, Magee M. 1953. The metabolism of C^{14} labelled ethylenediaminetetraacetic acid in the rat. J Biol Chem. 203:1045-1053 [cited in EU RAR 2004a].

Health Canada. 2015. Environmental Assessment Unit Drinking Water Spreadsheets [Excel format]. Ottawa (ON): Health Canada. [cited 2016 May 24].

Health Canada. [modified 2015 Dec 14]. Cosmetic ingredient hotlist: list of ingredients that are prohibited for use in cosmetic products. Ottawa (ON): Health Canada, Consumer Product Safety Directorate. [accessed 2016 May 24].

Household Products Database [database]. 1993- . Bethesda (MD): US National Library of Medicine. [updated 2015 Aug; accessed 2016 May 24].

Hurley LS and Swenerton H. 1966. Congenital malformations resulting from zinc deficiency in rats. Proc Soc Exp Biol Med. 123:692-6 [cited in Swenerton and Hurley 1971].

Hurley LS, Gowan J, Swenerton H. 1971. Teratogenic effects of short-term and transitory zinc deficiency in rats. Teratology. 4(2):199-204. [cited in Brown et al. 1986].

IARC 2015 [updated 2016 February 22]. IARC monographs on the evaluation of carcinogenic risks to humans: Volumes 1-115. [accessed 2016 May 24].

Kawamata K, Yoshimoto H, Momma J, Aida Y, Takada K, Kobayashi K and Tobe M. 1980. Comparative toxicity studies of Na2EDTA and CaNa2EDTA in rats. Jpn J Pharmacol. 30(suppl):234 p [cited in EU RAR 2004b].

Kimmel CA. 1977. Effect of route of administration on the toxicity and teratogenicity of EDTA in the rat. Toxicol Appl Pharmacol. 40:299-306.

Laborde-Casterot H, Villa AF, Rosenberg N, Dupont P, Lee HM, Garnier R. 2012. Occupational rhinitis and asthma due to EDTA-containing detergents or disinfectants. Am J Ind Med. 55:677-682.

[LNHPD] Licensed Natural Health Products Database [database]. [modified 2014 Feb 27]. Ottawa (ON): Health Canada. [accessed 2016 Jan 12].

Loretz LG, Api AM, Barraj LM, Burdick J, Dressler WE, Gettings SD, Han Hsu H, Pan YHL, Re TA, Renskers KJ, Rothenstein A, Scrafford CG, Sewall C. 2005. Exposure data for cosmetic products: lipstick, body lotion, and face cream. Food Chem Toxicol 43:279-291.

Muralidhara A, Narasimhamurthy K. 1991. Assessment of in vivo mutagenic potency of ethylenediaminetetraacetic acid in albino mice. Fd Chem Toxicol. 29:845-849 [cited in EU RAR 2004b].

[NHPID] Natural Health Products Ingredients Database [database]. [modified 2017 Oct 10.]. Ottawa (ON): Health Canada. [accessed 2017 Oct 20].

[OECD] Organisation for Economic Co-operation and Development. 2004. SIDS Initial Assessment Profile (SIAP): EDTA: CAS No. 60-00-4. SIAM [SIDS Initial Assessment Meeting] 18;, 2004 April 20-23. March; Paris, France. [accessed 2016 May7 24].

[OECD] Organisation for Economic Co-operation and Development. 1998. Test No. 408: Repeated dose 90-day oral toxicity study in rodents. Paris (FR): OECD. [accessed 2016 May 24].

[OECD] Organisation for Economic Co-operation and Development. 2012. SIDS Initial Assessment Profile (SIAP): Amino carboxylic acid-based chelants category. CoCAM [Cooperative Chemicals Assessment Meeting] 3, 2012 October 16-18. [accessed 2016 May 24].

Oser BL, Oser M, Spencer HC. 1963. Safety evaluation studies of calcium EDTA. Toxicol Appl Pharmacol. 5(2):142-162.

[PMRA] Pest Management Regulatory Agency. 2008. Registration Decision Document RD2008-04, Ferric Sodium, EDTA. Ottawa (ON): Health Canada, PMRA. Cat. No.:H113-25-2008-4E. [accessed 2016 May 24].

[PMRA] Pest Management Regulatory Agency. 2010. PMRA list of formulants [PDF]. Ottawa (ON): Government of Canada. HC Pub. No.: 100460, Cat. No.: H114-22/2010E. [accessed 2018 Feb 19].

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment (NL)]. 2003. Environmental risk limits for ethylenediaminetetraacetic acid (EDTA). Bilthoven (NL):RIVM. Report No.: 601501010/2003. [accessed 2016 May 24].

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment (NL)]. 2006a. Cosmetics fact sheet: to assess the risks for the consumer:

updated version for ConsExpo 4. Bilthoven (NL): RIVM. Report No.: 320104001/2006. [accessed 2016 May 24].

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu [National Institute for Public Health and the Environment]. 2006b. Cleaning products fact sheet: to assess the risks for the consumer. Bilthoven (NL): RIVM. Report No.: 320104003/2006. [accessed 2016 May 24].

Sanchez-Pedreno P, Garcia-Bravo B, Frias-Iniesta J. 2009. Contact allergy to tetrasodium EDTA in a sunscreen. Contact Dermatitis. 61:125-126.

[SCCS] Scientific Committee on Consumer Safety. 2012. The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 8th Revision. [accessed 2015 Oct 2].

Schardein JL, Sakowski R, Petrere J, Humphrey RR. 1981. Teratogenesis studies with EDTA and its salts in rats. Toxicol Appl Pharmacol. 61:423-428.

Sichuan Provincial Sanitary and Anti-epidemic Station. 1993. Acute toxicity, mutagenicity and teratogenicity of NaFeEDTA in rats and mice [unpublished study]. Chengdu (China): Sichuan Provincial Sanitary and Anti-epidemic Station [cited in EFSA 2010].

Sillanpää M, Vičkačkait V, Niinistö L, Sihvonen ML. 1997. Distribution and transportation of ethylenediaminetetraacetic acid and diethylenetriaminepentaacetic acid in lake water and sediment. Chemosphere. 35(12):2797-2805.

Statistics Canada. 2012. Custom tabulation of grooming products data from the Canadian Health Measures Survey Cycle 1 (2007-2009). Prepared for Existing Substances Risk Assessment Bureau, Health Canada by Statistics Canada. Unpublished.

Su YL, Chen ZL, Zhang J, Jiang ZC, 1999. A 90-day rat study on subchronic toxicity of NaFeEDTA [unpublished study]. Beijing; Capital Medical University [cited in EFSA 2010].

Swenerton H, Hurley LS. 1971. Teratogenic effects of a chelating agent and their prevention by zinc. Science. 173:62-64.

[US EPA] US Environmental Protection Agency. 2004a. Focus group decision document for tolerance reassessment of ethylenediaminetetraacetic acid (EDTA) and its salts [PDF]. Washington (DC): US EPA, Office of Prevention, Pesticides, and Toxic Substances. [accessed 2016 May 24].

[US EPA] US Environmental Protection Agency. 2004b. Inert reassessment document for ethylenediaminetetraacetic acid (EDTA). Washington (DC): US EPA, Office of Prevention, Pesticides, and Toxic Substances. [accessed 2016 May 24].

[US EPA] US Environmental Protection Agency. 2011. Sodium ferric ethylenediaminetetraacetate; exemption from the requirement of a tolerance. Federal Register Volume 76, Number 61. Washington (DC): US Government Publishing Office. Doc No.: 2011-7465 [updated 2011 Mar 30; accessed 2015 May 24].

[WHO] World Health Organization. 2004. Guidelines for drinking-water quality, recommendations [PDF]. Vol 1, 3rd ed. Geneva (CH): WHO. [accessed 2016 May 24].

Wynn JE, van't Riet B, Borzelleca JF. 1970. The toxicity and pharmacodyamics of EGTA: oral administration to rats and comparisons with EDTA. Toxicol. Appl. Pharmacol. 16:807-817.

Yang SS, Chan MS. 1964. Summaries of toxicological data: toxicology of EDTA. Food Cosmet Toxicol. 2:763-767 [cited in EU RAR 2004b].