Etidronic acids: Human health tier II assessment

12 September 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phosphonic acid, (1-hydroxyethylidene)bis-	2809-21-4
Phosphonic acid, (1-hydroxyethylidene)bis-, tetrasodium salt	3794-83-0
Phosphonic acid, (1-hydroxyethylidene)bis-, disodium salt	7414-83-7
Phosphonic acid, (1-hydroxyethylidene)bis-, tetrapotassium salt	14860-53-8
Phosphonic acid, (1-hydroxyethylidene)bis-, sodium salt	29329-71-3

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The group contains etidronic acid and four of its salts (etidronates). All five chemicals in this group are based on a common chemical known as etidronic acid (CAS No. 2809-21-4; (1-hydroxyethylidene)bisphosphonic acid). As the parent acid and salts of etidronic acid are highly soluble and available as aqueous solutions (OECD, 2004), these will dissociate into the etidronate anion [(1-hydroxyethylidene)bisphosphonate anion] and their corresponding cations.

Toxic effects of these compounds are expected to derive from the presence of the etidronate anion, or in the case of the parent acid, the low pH of the solution. The presence of different cations in these salts is not expected to significantly affect chemical behaviour or toxicity. The cations Na^+ and K^+ are generally considered safe, with a number of salts containing these cations identified as 'Stage One chemicals identified as low concern to human health' (NICNAS, 2012).

The Organisation for Economic Co-operation and Development's (OECD) Screening information dataset Initial Assessment Profile (SIAP) (2004) on 'HEDP and salts (Phosphonic Acid Compounds Group 2)' considered 13 different sodium and potassium salts of diphosphonic acids, supporting the grouping of these five chemicals together for the purposes of this assessment. The other eight chemicals considered together with these five chemicals in the OECD assessment (2004), are not in the Australian Inventory of Chemical Substances (AICS).

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported for etidronic acid (CAS No. 2809-21-4) under previous mandatory and/or voluntary calls for information:

The chemicals have reported site-limited use including as:

- complexing agents;
- corrosion inhibitors; and
- flame retardants and fire-preventing agents.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Profile (OECD SIAP); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals have reported cosmetic use as:

- chelating agents (controlling viscosity, stabilising emulsions and preventing the formation of radicals).

The maximum authorised concentration of etidronic acid and its salts (expressed as etidronic acid) in finished cosmetic products are 1.5 % in hair-care products, and 0.2 % in soap (CosIng).

The chemicals have reported domestic use as an additive in:

- inks and toners;
- cleaning agents; and
- coatings and paint products.

The chemicals have reported commercial use including in:

- detergents and cleaning products as a water softener and to stablise hydrogen peroxide (bleach);
- the photographic industry;
- water treatment (as chelating agents to prevent scale deposition and buildup in water treatment plants);
- cooling water treatments (deflocculant);
- producing cements/ceramics (as a pH regulator or deflocculating agent);
- a number of applications as a corrosion inhibitor;
- flame retardants and fire-preventing agents;
- coatings and paint products; and
- the textiles industry (detergent, peroxide stabiliser, dye-fixing agent).

The chemicals have reported site-limited use including in:

- manufacturing other chemicals (the acid is used to make the salts);
- offshore mining;
- mineral separation processes particularly for actinides; and
- the paper industry.

The following non-industrial uses have been identified internationally:

- in the pharmaceutical industry; and
- in agrochemicals.

Restrictions

Australian

No known restrictions have been identified with respect to industrial uses.

Etidronic acid (includes disodium etidronate) is listed in Schedule 4 (Prescription only medicine, or Prescription animal remedy) of the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP):

(a) for internal use; or

(b) in topical preparations except in preparations containing 1 % or less of etidronic acid.

International

The chemicals in this group are listed on the following (Galleria Chemica):

EU Cosmetic Directive 89/174/EEC Annex III Part 1—List of substances which cosmetic ingredients must not contain except subject to the restrictions and conditions laid down.

New Zealand Cosmetic Products Group Standard Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

In the above, the maximum authorised concentration of etidronic acid and its salts (expressed as etidronic acid) in the finished cosmetic products are:

- 1.5 % in hair-care products; and
- 0.2 % in soap.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

These chemicals are expected to readily dissociate to form the etidronic anion and rapidly form complexes with metal ions such as iron and calcium. The precise identity of the original salt will have minimal influence on the toxicity, apart from where the pH of the acid form is relevant.

Toxicokinetics

When radiolabelled etidronic acids or its salts were administered orally to animals, absorption by the gastrointestinal tract was very low (generally <1 %). Most of the unabsorbed dose was eliminated in the faeces. The absorbed amount was excreted in the urine (OECD 2004; REACH a,b).

Any amount of the chemical remaining in the body following absorption, partitions or distributes to the bones. No adverse skeletal effects were reported in repeated dose studies from partitioning of the chemical to bones, probably because the amount of chemical reaching the bones is very low (OECD 2004).

Acute Toxicity

Oral

Based on the available data, all five chemicals in this group are considered to have moderate acute oral toxicity (LD50 <2000 mg/kg bw). Therefore, a hazard classification is warranted.

In a number of acute oral gavage studies with etidronic acid (CAS No. 2809-21-4), a median lethal dose (LD50) of 1440–3550 mg/kg bw was established for rats, and 1100 mg/kg bw for mice. The sublethal effects in rats included lethargy, weakness, shortness of breath, tremors and eventual collapse (OECD, 2004; REACH a).

In acute oral gavage studies with disodium etidronate (CAS No. 7414-83-7), the LD50 was 1340 mg/kg bw in rats, 3300 mg/kg bw in mice and 581 mg/kg bw in male rabbits (OECD, 2004). The sublethal effects included irritation of the gastointestinal tract and kidney damage.

In two acute oral gavage studies in rats with tetrasodium etidronate (CAS No. 3794-83-0), the LD50 was 940 or 1219 mg/kg bw. Observed sublethal effects included weakness, diarrhoea, tremors and eventual collapse. In one study at necropsy, rats that died during the study showed discoloured lungs and gastrointestinal tract (OECD, 2004; REACH b).

Dermal

Based on the limited information available, the chemicals in this group are considered to have low acute dermal toxicity (LD50 >2000 mg/kg bw).

In acute dermal toxicity studies with etidronic acid (CAS No. 2809-21-4), the LD50 was established as >6000 mg/kg bw in rabbits (OECD, 2004). Observed sublethal effects included weakness, pain and discomfort (REACH a).

In a study (which used similar methodology to the OECD Test Guideline (TG) 402) that used a formulation containing tetrasodium etidronate (CAS No. 3794-83-0), a dermal LD50 of >5000 mg/kg bw was established in rabbits. An LD50 of >1650 mg/kg bw in rabbits was calculated for the chemical (REACH b). Observed sublethal effects included discharge from the nose and mouth. In addition, severe irritation at the application site was observed, followed by development and shedding of scabs (eschar) (REACH b, c). The extent to which these observations are attributable to tetrasodium etidronate is unclear due to lack of consistency with the dermal toxicity results detailed above, and the skin irritation observations detailed below.

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

The available information is not sufficient to warrant a hazard classification.

No acute exposure studies in animals have been identified. The short-term repeated dose inhalation toxicity studies indicated inflammatory effects in the larynx of exposed rats from doses of 1 mg/m^3 and above of sodium etidronate (CAS No. 29329-71-3) (REACH b). Two of the studies indicated reversibility of inflammatory effects. However, the severity of the effects is not reported to make a classification decision.

Skin Irritation

Based on the available information, the chemicals in this group are not considered to cause skin irritation. Although some chemicals (at ~30 % concentration) are reported to slightly irritate the skin under certain conditions (i.e. occlusive exposure for 24 hours), these effects are not sufficient to warrant a hazard classification.

Etidronic acid (CAS No. 2809-21-4) and tetrasodium etidronate (CAS No. 3794-83-0) are not skin irritants (OECD, 2004).

In skin irritation studies (methodology similar to OECD TG 404), etidronic acid (CAS No. 2809-21-4) was applied to the skin of rabbits for 24 hours. In two tests, no erythema or oedema was observed (scores = 0) in any animal (REACH a). In another test in rabbits, a primary dermal irritation index (PDII) score of 3.6/8 was calculated, and the effects were not reversible within seven days. No individual erythema or oedema scores are available, but necrosis of skin tissue was reported when the chemical was applied to abraded skin (REACH a).

No skin irritation was observed when tetrasodium etidronate (CAS No. 3794-83-0) was applied as a 30 % solution to the skin of rabbits for four hours under semi-occlusive conditions (OECD TG 404). Similarly, only very mild skin irritation (PDII = 0.3) was observed in rabbits in another test with a 31 % formulation (using semi-occlusive or occlusive conditions for four hours). However, with 24-hour exposure under occlusion, irritation effects have been reported (PDII scores of 2.3/8 or 5/8), although the effects were generally reversible within 14 days (REACH b).

In a study (OECD TG 404) with 35 % sodium etidronate (CAS No. 29329-71-3), no skin irritation (PDII score = 0) was observed when the salt was applied to intact skin of rabbits (REACH c). When the salt was applied to abraded skin, some irritation (PDII score = 1.67) was observed after 24 hours. These effects were reversible within 10 days (REACH c).

Eye Irritation

The available data for etidronic acid warrant a hazard classification for serious eye effects. The available data for the salts are from tests conducted at various concentrations. Considering acidity as the key contributor for serious eye effects, the salts in this group should be classified as eye irritants.

In a number of studies, etidronic acid (CAS No. 2809-21-4) was found to be severely irritating to the eyes of rabbits (OECD, 2004; REACH a). Often the effects worsened over the observation period. In one test (non-guideline), observations included bright red erythema, chemosis, and the lower half of the cornea totally opaque by 72 hours post administration, effectively blinding the rabbits (maximum irritation score 90/110). These severe ocular lesions did not improve and were not reversible within the seven-day observation period. The chemical is reported to be corrosive (REACH a).

Another study (non-guideline) also found severe irritation of eyes when the acid was applied to the eyes of rabbits (mean irritation score of 39/110; no individual scores available). After 24 hours, some areas of the cornea were opaque, severe erythema with discharge of blood was observed and the iris was not responding to light. Even after 21 days, 4/6 rabbits had some erythema, continued discharge and ulceration of the cornea (REACH a).

Three salts are considered to be mild to moderate eye irritants, based on tests conducted using formulations of the chemicals (OECD, 2004). A formulation containing 31 % tetrasodium etidronate was reported to slightly irritate the eyes of New Zealand White rabbits (n = 6; study comparable to OECD TG 405). The mild eye effects reported were slight conjunctival irritation (redness, chemosis, discharge) and minor iridial changes. There were no corneal opacities. One rabbit had a corneal ulceration after 48 hours. All eye effects were reversed within three to seven days (REACH b). Another formulation containing tetrasodium etidronate (concentration of the chemical not available) was not irritating to the eyes of three New Zealand White rabbits (OECD TG 405). All eye irritation scores were 0 or 1 at 1, 24, 48 and 72 hours, except for one animal that had a score of two for conjunctival redness after 24 hours (REACH b).

When a 1 % solution of disodium etidronate (CAS No. 7414-83-7) was applied five times to the eyes of rabbits, it was not irritating (details not available) (REACH c). In another non-guideline test with disodium etidronate at 1 % (in mouthwash), 3 % (in toothpaste) or 10 % (in solution), it was found to be slightly irritating to the eyes, but any effects were reversible within four days (REACH c).

Sensitisation

Skin Sensitisation

Based on the data available, the chemicals in this group are not considered to be skin sensitisers.

In a guinea pig maximisation test, etidronic acid was not a skin sensitiser (REACH b). Sodium etidronate (CAS No: 29329-71-3) was also not a skin sensitiser in a guinea pig maximisation test that used a 5 % concentration in the induction phase and 25 % concentration in the challenge phase (REACH c).

Repeated Dose Toxicity

Oral

Based on the data available, the chemicals in this group are not considered to cause serious damage to health from repeated oral exposure.

The toxic effects from subchronic exposure to etidronic acid and its salts are related to its ability to chelate metal ions and affect calcium and iron homeostasis.

Several repeated dose toxicity studies are available in REACH dossiers. In a 28-day oral gavage study (non-guideline) in CD rats, etidronic acid (CAS No. 2809-21-4) was administered at doses of 0, 0.3, 3, 30 or 100 mg/kg bw/day (alone or after administration of milky food). There were no clinical signs of toxicity up to the highest dose tested. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day was established based on minimal enlargement of the tibia in the metaphyseal area at 100 mg/kg bw/day. No treatment-related effects were observed during histological examination of the tibia and sternum at the highest dose (REACH a).

In a 90-day study (methodology similar to OECD TG 408) etidronic acid (CAS No. 2809-21-4) was administered with the diet of Charles River albino rats (n=15/sex/dose) at doses of 154, 524 or 1583 mg/kg bw/day for males and 166, 545 or 1724 mg/kg

bw/day for females. Some of the haematology results suggested changes in iron regulation at the highest dose, but these were not considered significant. Reduction in body weight gain (8 % in females and 16 % in males) was noted. The NOAELs were established as >1583 and >1724 mg/kg bw/day for males and females, respectively (REACH a).

A 90-day study with etidronic acid (CAS No. 2809-21-4) in beagle dogs found no treatment-related effects at any dose level tested. The NOAELs were established as >1746 mg/kg bw/day in males and >1620 mg/kg bw/day in females, based on the highest doses tested (REACH a).

In a two-year study with disodium etidronate (CAS No. 7414-83-7) (similar to OECD TG 453, except for the number of animals/dose group) in Sprague Dawley (SD) rats (n = 40/sex/dose), a NOAEL of 24 mg/kg bw/day was established based on indications of anaemia at doses of 78 and 96 mg/kg bw/day and above in male and female rats, respectively (OECD, 2004, REACH b, c).

In a two-year study, male Wistar rats were administered ^{14}C-radiolabelled sodium etidronate (CAS No. 29329-71-3) at 0.184 mg/kg bw/day in their drinking water. There were no treatment-related effects on bones. Only minimal accumulation of the chemical in the bone was reported (the only parameter examined) (REACH b).

Dermal

No data are available.

Inhalation

Based on the limited data available from short-term exposure studies, the chemicals in this group are not considered to cause serious damage to health from repeated inhalation exposure. Available data indicated only local effects in animals following repeated exposure.

In an inhalation toxicity study, Wistar rats were exposed (nose only) to sodium etidronate (CAS No. 29329-71-3) at a concentration of 0.5 mg/m^3 for 14 days. Treatment-related inflammatory effects in the respiratory tract were observed (REACH b). In a similar study with a 14-day recovery period following 14 days of exposure, there were no histopathological alterations in the nose, larynx and trachea of Wistar rats (REACH b).

Wistar rats were exposed (nose only) to sodium etidronate (CAS No. 29329-71-3) at 94 mg/m^3, five hours a day for six days over 14 days. All exposed animals showed moderate inflammation of some parts of larynx immediately after exposure, which was not completely reversed during the four-week recovery period. Moderate to severe laryngitis was also reported immediately after exposure, reducing to mild laryngitis during the recovery period (REACH b).

SD rats were exposed to sodium etidronate (CAS No. 29329-71-3) at 1 mg/m^3, six hours a day for 2, 4, 6 or 8 weeks. Inflammatory effects in the larynx were observed in all treated animals. The dose was reported as the lowest observed adverse effect concentration (LOAEC) (REACH b).

Genotoxicity

Based on the available data, the chemicals in this group are not considered to be genotoxic.

In a bacterial reverse mutation assay using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 (similar to OECD TG 471), disodium etidronate (CAS No. 7414-83-7) gave negative results, with or without metabolic activation (REACH a, b).

In an in vitro mammalian cell mutagenicity assay using mouse lymphoma L5178Y cells (methodology similar to OECD TG 476), sodium etidronate (CAS No. 29329-71-3) caused no increase in the number of mutations up to 21 mg/L concentration, with or without metabolic activation (REACH b, c).

In an in vivo mouse micronucleus assay (similar to OECD TG 474 but with some deviations), disodium etidronate (CAS No. 7414-83-7) administered intraperitoneally caused no increase in the number of micronucleated polychromatic erythrocytes. The

chemical did not induce micronuclei under the conditions of the test (REACH b).

A dominant lethal assay with sodium etidronate (CAS No. 29329-71-3) in male mice (oral gavage doses of 20, 200 or 1000 mg/kg bw/day, once daily for five days) produced negative results. There were no treatment-related effects on conception rates, implantations, resorptions, foetal deaths or mutagenic indices (REACH a).

Carcinogenicity

The available data are not sufficient to make a conclusion on carcinogenicity about this group of chemicals. The single study available indicated that occurrence of neoplastic lesions in treated rats was considered normal for the strain of rats used in the study (details not available).

Only one relevant study is identified (Combined Chronic Toxicity/Carcinogenicity Study in 1979—similar to OECD TG 453; conducted prior to the adoption of OECD guidelines and the number of animals per dose group was the only deviation reported from the test guideline). In this study, disodium etidronate (CAS No. 7414-83-7) was administered in the diet of SD rats (n = 40/sex/dose) at doses of 0, 500, 2000 or 10000 ppm (0, 19, 78 or 384 mg/kg bw/day in males and 0, 24, 96 or 493 mg/kg bw/day in females) for 104 weeks. There were haematological effects (such as decreased haemoglobin concentrations and increased red cell counts) in rats at the two high dose groups; the animals in the highest dose group were anaemic. Increased microcytosis (abnormally small red blood cells) and presence of giant platelets were observed in some rats in the highest dose group. While tumour incidences in some tissues (e.g. the pancreas, adrenal glands and uterus) were elevated compared with controls, all tumour incidences were reported to be within the expected range for rats of this strain (details not available). The NOAEL for carcinogenicity was reported as 384 and 493 mg/kg bw/day for males and females, respectively (REACH a, c).

No carcinogenicity data are available in the OECD report (2004) for any of the chemicals in this group.

Reproductive and Developmental Toxicity

Based on the limited data available, the chemicals in this group are not considered to cause reproductive or developmental toxicity.

In a non-guideline study, albino rats were administered disodium etidronate (CAS No. 7414-83-7) (continuous administration in both sexes or administration to pregnant rats only on gestation days (GD) 5–15) in the diet at doses of 0.1 % or 0.5 %. The pregnancy rate was unaffected at both doses (about 112 mg/kg bw/d or 447 mg/kg bw/day). The live litter size was decreased in dams receiving the high dose during gestation, suggesting foetotoxicity (REACH a, b).

In a non-guideline study, disodium etidronate (CAS No. 7414-83-7) was administered in the diet of New Zealand White rabbits at doses of 0, 25, 50 or 100 mg/kg bw/day on GD 2–19. There were no maternal toxicity or foetotoxicity effects at any dose level; the NOAEL for maternal toxicity and foetotoxicity was reported as 100 mg/kg bw/day (REACH a, b, c).

Other information

There are some animal studies conducted using administration methods irrelevant for human exposure. These studies have been conducted to investigate the effects of these chemicals in bone mineralisation or calcium accumulation.

Disodium etidronate (CAS No. 7414-83-7) injected intraperitoneally at 1 mg/kg bw/day for three weeks to rats that were fed a calcium deficient diet resulted in low plasma calcium levels, decreased accumulation of calcium in bones, thinner bone trabeculae and decreased thickness of the cortex of the diaphyseal bone. Altered bone resorption and mobilisation of skeletal calcium due to treatment was indicated. The effects were minimal or absent in rats that received a normal diet, or parathyroidectomised rats which were fed a calcium deficient diet (REACH c).

Irregular mineralisation of the long bones was observed in female beagle dogs that received disodium etidronate (CAS No. 7414-83-7) by subcutaneous injection for four weeks up to 60 mg/kg bw/day. The changes were fully reversed during the 20-week recovery period (NOAEL = 2 mg/kg bw/day) (REACH c).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include serious eye damage (from the acid) or eye irritation (from the salts), and acute oral toxicity. Chronic exposure to high doses may also affect calcium and iron homeostasis.

Public Risk Characterisation

No cosmetic or domestic uses have been identified in Australia. These chemicals are reported to be used as additives in some domestic products and as chelating agents in cosmetics used overseas. New Zealand and the European Union (EU) have restricted the use of these chemicals in cosmetics (1.5% in hair-care products and 0.2% in soap). Currently, there are no restrictions on using these chemicals in cosmetics or domestic products in Australia, but the function in cosmetics as a chelating agent would not indicate use of high concentrations. Domestic cleaning products may include higher concentrations.

If these chemicals are used in cosmetics and domestic products in Australia, the main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and potential oral exposure from lip and oral hygiene products. Considering the potentially low health hazards (eye irritation and acute oral toxicity), risks are not expected to be unreasonable if the chemicals are only used at low concentrations in cosmetics and domestic products.

Occupational Risk Characterisation

Given the critical health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise ocular exposure to the chemicals are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

Assessment and risk management of these chemicals is considered to be sufficient providing the recommendation for classification and labelling is implemented and all requirements are met under workplace health and safety.

Regulatory Control

Public Health

Considering the potentially low health hazards anticipated from the concentrations expected in cosmetics, no regulatory controls are recommended for using these chemicals as chelating agents in cosmetics.

Considering the low health hazards and potentially low exposure, no regulatory controls are recommended for potential domestic uses such as use in cleaning products.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Although the etidronic acid is classified for serious eye damage (Xi; R41 or H318), the salts of etidronic acid should be classified with the risk phrase 'Irritating to eyes' (Xi; R36) according to the Approved Criteria or 'Causes serious eye irritation' (H319) according to the GHS classification.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing these chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral and ocular exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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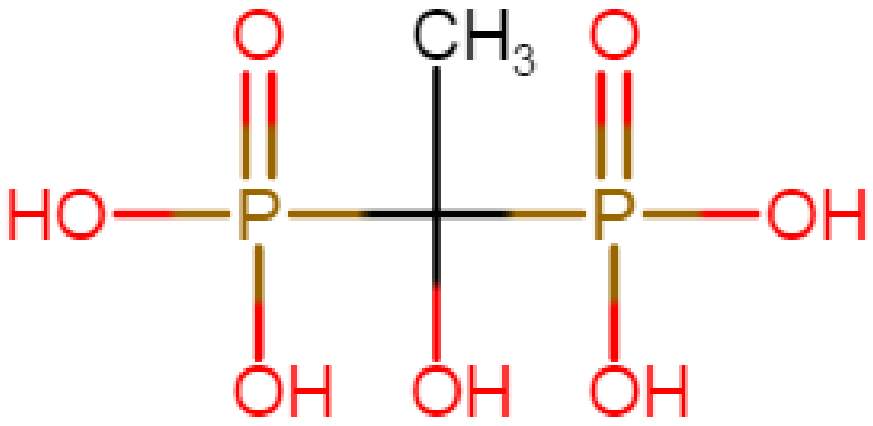
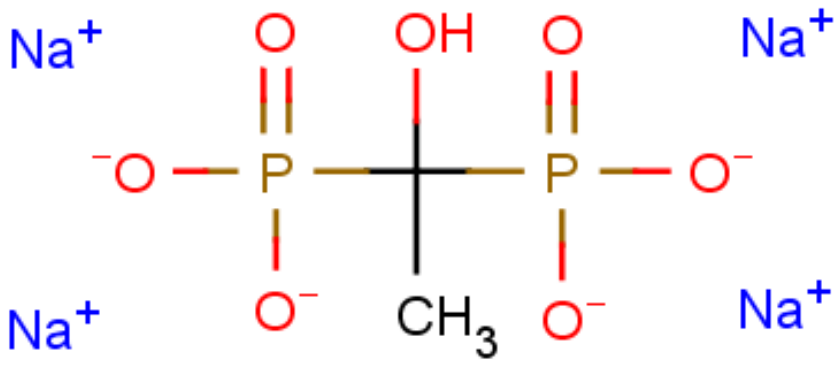
Last Update 12 September 2013

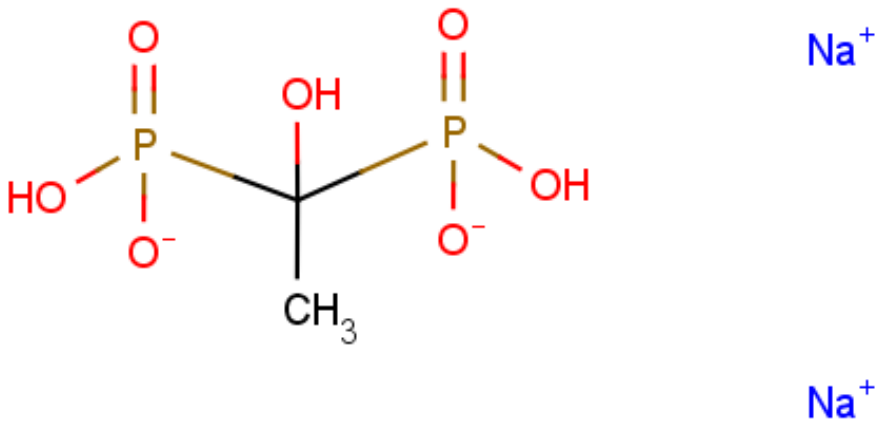
Chemical Identities

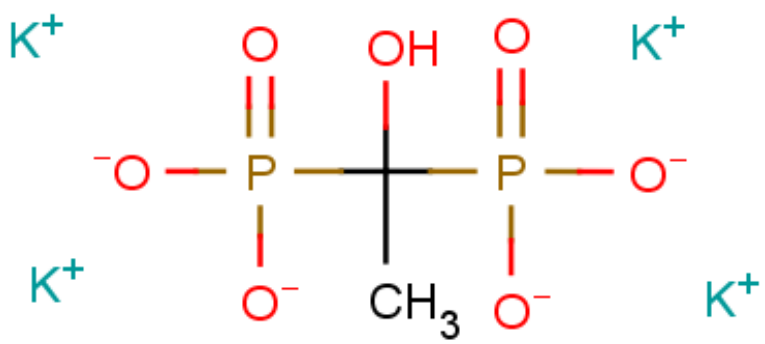
Chemical Name in the Inventory and Synonyms	**Phosphonic acid, (1-hydroxyethylidene)bis-** etidronic acid 1-hydroxyethylidene-1,1-diphosphonic acid 1-hydroxy-1,1-diphosphonoethane 1-hydroxy-1,1-ethane-diphosphonic acid HEDP
CAS Number	2809-21-4
Structural Formula	

	
Molecular Formula	C2H8O7P2
Molecular Weight	206.03

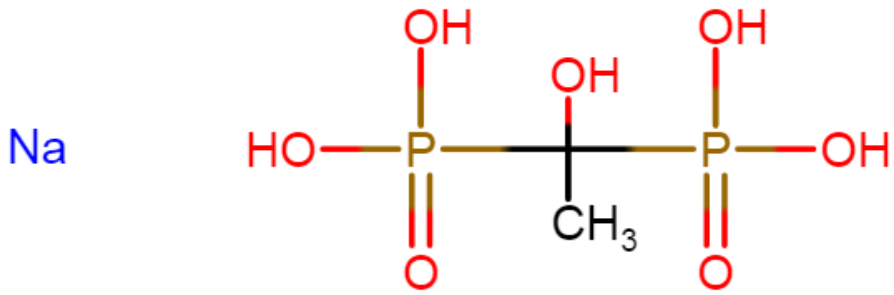
Chemical Name in the Inventory and Synonyms	**Phosphonic acid, (1-hydroxyethylidene)bis-, tetrasodium salt** tetrasodium etidronate tetrasodium 1-hydroxyethylidene-1,1-diphosphonate tetrasodium 1-hydroxyethane-1, 1-diphosphonate (1-hydroxyethylidene)diphosphonic acid, tetrasodium salt phosphonic acid, P,P'-(1-hydroxyethylidene)bis-, sodium salt (1:4)
CAS Number	3794-83-0
Structural Formula	
Molecular Formula	C2H8O7P2.4Na
Molecular Weight	293.96

Chemical Name in the Inventory and Synonyms	**Phosphonic acid, (1-hydroxyethylidene)bis-, disodium salt** disodium etidronate

	etidronate disodium (1-hydroxyethane-1,1-diyl)diphosphonic acid disodium salt disodium dihydrogen (1-hydroxyethylidene)bisphosphonate ethane-1-hydroxy-1,1-diphosphonic acid, disodium salt
CAS Number	7414-83-7
Structural Formula	
Molecular Formula	C2H8O7P2.2Na
Molecular Weight	249.99

Chemical Name in the Inventory and Synonyms	**Phosphonic acid, (1-hydroxyethylidene)bis-, tetrapotassium salt** tetrapotassium etidronate diphosphonic acid, (1-hydroxyethylidene)-, tetrapotassium salt phosphonic acid, P,P'-(1-hydroxyethylidene)bis-, potassium salt (1:4) ethane-1-hydroxy-1,1-diphosphonic acid, tetrapotassium salt tetrapotassium (1-hydroxyethylidene)bisphosphonate
CAS Number	14860-53-8
Structural Formula	

Molecular Formula	C2H8O7P2.4K
Molecular Weight	358.39

Chemical Name in the Inventory and Synonyms	**Phosphonic acid, (1-hydroxyethylidene)bis-, sodium salt** sodium etidronate 1-hydroxyethanediphosphonic acid, sodium salt phosphonic acid, p,p'-(1-hydroxyethylidene)bis-, sodium salt (1:?) hydroxyethylidene diphosphonic acid, sodium salt
CAS Number	29329-71-3
Structural Formula	
Molecular Formula	C2H8O7P2.xNa
Molecular Weight	230.02

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