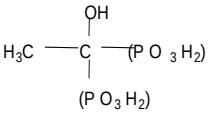
SIDS INITIAL ASSESSMENT PROFILE

Category Name	HEDP and salts (Phosphonic Acid Compounds Group 2) 1-Hydroxy-1,1-ethane-diphosphonic acid and its sodium and potassium salts

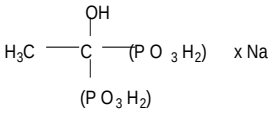
Chemical Names and CAS Numbers

Chemical name	CAS no	Abbreviation
1-Hydroxy-1,1-ethane-diphosphonic acid	2809-21-4	HEDP
1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt	29329-71-3	HEDP-xNa
1-Hydroxy-1,1-ethane-diphosphonic acid, Na Salt	17721-68-5	HEDP-1Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 2Na Salt	7414-83-7	HEDP-2Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 3Na Salt	2666-14-0	HEDP-3Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 4Na Salt	3794-83-0	HEDP-4Na
1-Hydroxy-1,1-ethane-diphosphonic acid, 5Na Salt	13710-39-9	HEDP-5Na
1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt	67953-76-8	HEDP-xK
1-Hydroxy-1,1-ethane-diphosphonic acid, K Salt	17721-72-1	HEDP-1K
1-Hydroxy-1,1-ethane-diphosphonic acid, 2K Salt	21089-06-5	HEDP-2K
1-Hydroxy-1,1-ethane-diphosphonic acid, 3K Salt	60376-08-1	HEDP-3K
1-Hydroxy-1,1-ethane-diphosphonic acid, 4K Salt	14860-53-8	HEDP-4K
1-Hydroxy-1,1-ethane-diphosphonic acid, 5K Salt	87977-58-0	HEDP-5K

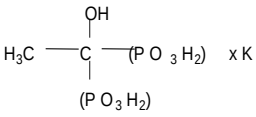
Structural Formula



1-Hydroxy-1,1-ethane-diphosphonic acid
CAS # 2809-21-4



1-Hydroxy-1,1-ethane-diphosphonic acid, xNa Salt
CAS # 29329-71-3



1-Hydroxy-1,1-ethane-diphosphonic acid, xK Salt
CAS # 67953-76-8

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

This category covers a phosphonic acid and sodium salts of that acid. The different salts are prepared by neutralising the acid to a specific pH. Data are available for the acid and some salts. The substances are commercially available as aqueous solutions only and in an environmental context the speciation will be the same. In the present context the effect of the counter-ion (sodium/potassium) will not be significant. The properties of the members of the category are consistent across all end points. The supporting substance (1-hydroxyethylidene)bisphosphonic acid, calcium salt (the calcium salt of HEDP) is used to support the chronic daphnia endpoint.

The category is expressed as Phosphonic Acid Compounds Group 2 because two other groups have been identified, with close structural analogy to the present one. Group 1 is Amino tris(methylenephosphonic acid) (6419-19-8) and

its sodium salts; Group 3 is Diethylene triamine penta(methylene phosphonic acid) (CAS 15827-60-8) and its sodium salts.

Human Health

Animal studies demonstrate that gastrointestinal absorption of 1-hydroxy-1,1-ethane-diphosphonic acid and its salts is low, with the majority of the dose excreted in the faeces. Of the material that enters the systemic circulation, a substantial amount is excreted via urine while bone is the only tissue to exhibit deposition of radioactivity (although it is noted that no adverse skeletal changes were present in sub-chronic and chronic studies suggesting this is of limited toxicological relevance). Internal body burdens are increased after injection, presumably reflecting greater systemic availability.

HEDP and its salts are of moderate acute toxicity to mammals. The rat acute oral LD_{50} of the acid is 1536-2003 mg/kg while the dermal LD_{50} is>6000 mg/kg. The mouse oral LD_{50} is 1100mg/kg. Tests on two salts indicate lower LD_{50} values. The oral LD_{50} for the disodium salt (CAS 7414-83-7) was 1340 mg/kg (rat), 3300mg/kg (mouse) and 581 mg/kg (rabbit). For the tetrasodium salt (CAS 3794-83-0) the values were 940 and 1219 mg/kg in separate studies, with dermal LD_{50} values of >2300 mg/kg. Based on these findings it could be assumed that all sodium and potassium salts will be of moderate acute toxicity, since the effect of these counter-ions will not be significant.

HEDP is considered to be a severe eye irritant/corrosive. Three salts have been tested and these have been found to be mild (CAS 3794-83-0) or moderate irritants (CAS 7414-83-7 and 29329-71-3). Since these results have been obtained on formulations, and higher doses of the pure salts could have been tested, the results obtained may underestimate the irritancy of the pure salts.

The acid and one of the salts (CAS 3794-83-0) are not skin irritants. There is evidence that CAS 29329-73-3 is an irritant when tested under occlusion for 24 hours, but is only slightly irritating when tested under semi-occlusive conditions for 4 hours. CAS 7414-83-7 has been reported to be slightly irritating, but this is a secondary reference, not available for review. HEDP is not a skin sensitiser.

Sub-chronic dietary administration of HEDP in the dog (10000 ppm, equivalent to 1746 or 1620 mg/kg bw/day for males and females respectively) resulted in minor effects associated with perturbations of iron and calcium homeostasis (possibly linked to impaired absorption of these minerals from the diet and/or complexation with the phosphonic acid). The systemic NOAEL from this study is therefore considered to be ≥1746 mg/kg bw/day. A 90 day rat study indicates an NOAEL of >1724 mg bw/kg/day since, again, the only treatment related changes appeared due to perturbations of iron and calcium uptake and homeostasis and were therefore considered to be of doubtful toxicological significance. There is a robust chronic toxicity study on a sodium salt, where indications of anaemia were induced, although these had resolved by the end of the study. A NOAEL of 24 mg bw/kg/day is assigned based on the observation of anaemia at the higher doses.

Sub-chronic toxicity studies demonstrate no adverse microscopic changes in the reproductive organs of male and female rats or dogs given HEDP and its salts at exposures equivalent to approx. 1500-1800 mg/kg bw/day. Results from a study of unknown reliability are consistent with no effect on pregnancy rate in male and female albino rats following continuous administration of up to 0.5% disodium salt in the diet, giving an approximate NOAEL of >447 mg/kg bw/day (the highest dose tested). These observations are consistent with data for phosphonic acid compounds from Group 1 and Group 3, which were not selectively toxic to the male or female reproductive system and which returned NOAELs for reproductive toxicity in the range 275-312 mg/kg bw/day. Additionally, no abnormalities in the reproductive organs were seen in a 2-year study with the sodium salt of HEDP. Using a weight of evidence approach, it is concluded that HEDP is also not likely to be selectively toxic to the reproductive system.

Similar limitations also apply to pregnancy data available for HEDP, with a developmental NOAEL of >250 mg/kg bw/day (the highest dose tested) obtained from a gavage study of unknown reliability in the rabbit. This is broadly comparable with an oral NOAEL of around >1000 mg/kg bw/day obtained in rats given structurally-related analogues from Group 1 and Group 3 during pregnancy. Since physiochemical and physiological considerations indicate that the parent acid and other Group 2 salts will exhibit broadly similar effects on fetal development, a weight of evidence approach leads to a developmental NOAEL of >250 mg/kg bw/day for HEDP and its salts.

Although the mutagenicity data available on HEDP are of limited reliability they provide some evidence for a lack of mutagenic potential. Negative responses were seen in a bacterial mutagenicity assay and a mammalian cell gene mutation assay. A salt has previously been reported to be negative in a bacterial assay and a micronucleus test, although this is secondary literature and therefore of unknown validity. Related acids (ATMP, DTPMP) have been shown to be negative in well-conducted bacterial mutagenicity assays. Conflicting results have been obtained for mammalian gene mutation assays. Positive responses in this assay in the presence of S9 are believed to be artefactual (see SIARs for ATMP and DTPMP). Therefore, despite the absence of a robust genetic toxicology test package performed to current standards, HEDP or its salts are not likely to pose a genotoxic hazard.

Overall, the subchronic toxic effects of HEDP are primarily related to its ability to chelate metal ions and affect calcium and iron homeostasis. The lowest NOAEL is >1724 mg/kg based on a 90 day rat study. There is evidence that some of the salts may have a higher toxicity, as indicated by lower oral LD_{50} values for a sodium salt and lower effect levels for haematological parameters for a sodium salt in a 2 year chronic toxicity study (NOAEL of 24 mg/kg bw/d).

Conclusion for Human Health

The chemicals in this category possess properties indicating a hazard for human health (severe eye irritant/corrosive for the pure acid and its salts, reversible anaemia caused by the substances' ability to chelate metal ions and affect calcium and iron homeostasis). Although these hazards do not warrant further work as they are related to pH effects and chelation properties, they should nevertheless be noted by chemical safety professionals and users.

Environment

HEDP is a diphosphonic acid of molecular weight 206. The phosphonic acid function is a strong acid, and it is frequently produced as a salt for reasons of ease of use. It can form stable complexes with polyvalent metal ions. As a consequence of the ionisation over typical pH ranges, it is of high water solubility (>690 g/l) and low octanol-water partition coefficient (log K_{ow} = -3.52). Its vapour pressure is very low (estimated as $1.24E^{-09}$ Pa). At pH 7, HEDP in water will be fully ionised twice and half of the molecules will be ionised three times.

There is a possibility that the emission of a phosphonic acid could locally decrease the pH in the aquatic environment. In the normal use of these substances, their pH, concentration and water quality have to be monitored very carefully. Therefore, a significant decrease of the pH of the receiving water is not expected. Furthermore, the substances are usually used as salts with near-neutral pH, and their effects on pH are further buffered by the presence of metal ions. Generally the changes in pH of the receiving water should stay within the natural range of the pH, and for this reason, adverse effects on the aquatic environment are not expected due to release of the phosphonic acids.

HEDP and its salts may enter the environment via normal use in water treatment applications. It is predicted and has been shown to be adsorbed by inorganic matrices, and therefore adsorption to sewage sludge and soil is strong. They are not readily biodegradable in laboratory studies carried out under standard conditions. Although these data suggest the potential for persistence, there is, however, evidence of partial degradation by abiotic processes in natural waters, and biodegradation following acclimation, or under conditions of low inorganic phosphate. . In the presence of commonly found metal ions possessing redox properties, such as iron and copper, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. HEDP is not bioaccumulative (measured BCF in fish <2).

As complexing agents, these substances could remobilise metals in the environment; however, their high degree of adsorption to sediments suggests that this is unlikely to occur.

HEDP and its salts are of low acute toxicity to fish. Acute LC_{50}/TL_{50} values determined in short-term and prolonged-term exposure tests are equal to or greater than 180 mg/l. HEDP and its salts are of low acute toxicity to aquatic invertebrates, as supported by 9 results from 5 test species. The lowest reliable acute toxic concentration was determined for HEDP for the invertebrate *Daphnia magna*, with a 48-h EC_{50} of 167 mg/l. A sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 81 mg/l and a NOEC of <52 mg/l. A NOEC of 6.75 mg/l was obtained in a reliable 28-day reproduction test on HEDP with *Daphnia magna*. A reproduction study, of unassignable reliability, was conducted with the sodium salt and with the supporting substance

(1-hydroxyethylidene)bisphosphonic acid, calcium salt (the calcium salt of HEDP), which gave NOECs of 0.1 mg/l ad 3.0 mg/l, respectively. Deficiencies with the 2Na test (non-monotonic dose-response curve) and its inconsistency with the general pattern of toxicity to aquatic invertebrates mean that the result can be discounted.

There are no data for the effects of HEDP on sediment-dwelling organisms. However, given the low order of acute toxicity of ATMP acid and DTPMP salts to the marine sediment living amphipod *Corophium volutator*, it is not expected that HEDP and its salts would show significant toxicity to sediment-dwelling organisms. HEDP is of low acute toxicity to sewage sludge micro-organisms (*Pseudomonas putida* 30-min EC_0: ≥580 mg/l).

The effects of HEDP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 96-hour E_rC_{50} for HEDP to *Selenastrum capricornutum*[1] of 3 mg/l is likely to over-estimate the true toxicity. A 14-day NOEC for HEDP to *S. capricornutum* of 13 mg/l, which might also be subject to the potential effects of complexation, indicates that HEDP is likely to be of low chronic toxicity to algae, atlhough there is evidence that the cultures did not remain in exponential growth during the phase of the test extending from 96 hours to 14 days.

HEDP and/or its di-sodium salt are of low acute toxicity to earthworms (*Eisenia foetida* 14-day LC_{50}: >960 mg/kg dw) and terrestrial plants (*Avena sativa* 14-day EC_{50}: >960 mg/l). HEDP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >284 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Conclusion for the Environment

HEDP and its salts possess properties indicating a hazard for the environment (EC50 in the range 1 – 10 mg/l for algae). However these hazards do not warrant further work as they are related to acute toxicity, pH effects and metal chelation, which may become evident only at very high exposure levels. The substances are not readily biodegradable but have a low potential for bioaccumulation.

Exposure

Current worldwide production of ATMP, HEDP and DTPMP (and their salts) is estimated to be in the range of 50,000 to 100,000 metric tonnes annually. The major uses of HEDP and its salts are as an additive in water treatment, where its ability to both complex with metal ions, and to prevent crystalline scale deposition in solution and onto surfaces through adsorption, are utilised. The substances are also used in detergent and cleaning applications and cosmetics (HEDP only), and in the paper, textiles and photographic industries, and also in off-shore oil well applications.

The major route of environmental exposure is expected to be release, often via wastewater treatment plants, to rivers. Agricultural land could be exposed via spreading of sewage sludge. Oil well use would lead to direct exposure of the marine environment. In rivers, they are expected to partition predominantly to sediment.

Human exposure to HEDP or its salts in manufacturing and formulating is possible, but due to the use of personal protective equipment, limited to accidental situation. Where exposure can occur, dermal exposure is the most likely route of exposure. In these cases PPE is recommended. The concentration of the substance in the product, together with PPE/engineering controls are important factors in the assessment of risk associated with the hazardous properties (mainly corrosivity/irritancy). Where concentrated solutions are handled, engineering controls and PPE are used to control exposure and reduce the risk from the corrosive/irritant properties. In downstream uses, where consumer exposure is possible, much more dilute concentrations are used, which significantly reduces or removes the likelihood of corrosivity/irritancy effects.

Consumer exposure is being assessed in more detail as part of the HERA project (HERA, in progress www.heraproject.com/).