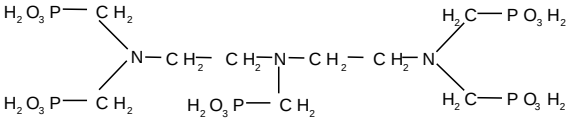
SIDS INITIAL ASSESSMENT PROFILE

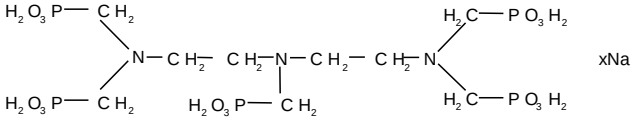
Category Name	DTPMP and salts (Phosphonic Acid Compounds Group 3) Diethylene triamine penta(methylene phosphonic acid) and its sodium salts
Chemical Names and CAS Numbers	

Chemical name	CAS no.	Abbreviation
Diethylene triamine penta(methylene phosphonic acid)	15827-60-8	DTPMP
Diethylene triamine penta(methylene phosphonic acid), xNa Salt	22042-96-2	DTPMP-xNa
Diethylene triamine penta(methylene phosphonic acid), Na Salt	94987-76-5	DTPMP-Na
Diethylene triamine penta(methylene phosphonic acid), 2Na Salt	94987-75-4	DTPMP-2Na
Diethylene triamine penta(methylene phosphonic acid), 3Na Salt	95015-06-8	DTPMP-3Na
Diethylene triamine penta(methylene phosphonic acid), 4Na Salt	94987-77-6	DTPMP-4Na
Diethylene triamine penta(methylene phosphonic acid), 5Na Salt	61792-09-4	DTPMP-5Na
Diethylene triamine penta(methylene phosphonic acid), 6Na Salt	93841-74-8	DTPMP-6Na
Diethylene triamine penta(methylene phosphonic acid), 7Na Salt	68155-78-2	DTPMP-7Na
Diethylene triamine penta(methylene phosphonic acid), 8Na Salt	95183-54-3	DTPMP-8Na
Diethylene triamine penta(methylene phosphonic acid), 9Na Salt	93841-75-9	DTPMP-9Na
Diethylene triamine penta(methylene phosphonic acid), 10Na Salt	93841-76-0	DTPMP-10Na

Structural Formula



Diethylene triamine penta(methylenephosphonic acid)
CAS # 15827-60-8



Diethylene triamine penta(methylenephosphonic acid), xNa Salt
CAS # 22042-96-2

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) will not be significant. The properties of the members of the category are consistent across all end points.

The category is expressed as Phosphonic Acid Compounds Group 3 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 2 is 1-Hydroxy-1,1-ethane-diphosphonic acid (CAS 2809-21-4) and its sodium and potassium salts.

Human Health

Toxicokinetic data on DTPMP and its salts are limited. The available information, together with data for phosphonic acid compounds comprising Group 1 and Group2, suggest that only minor amounts of DTPMP and its salts would enter the body after ingestion or skin contact.

The DTPMP acid and salts are of low oral and dermal toxicity. The oral rat LD_{50} is 4164 mg/kg bw and the rabbit LD_{50} is higher (>4605 mg/kg bw). The acute rat oral LD50 of the heptasodium salt lies between 5838 and 8757 mg/kg bw. The dermal LD_{50} values for the salts are >5838 mg/kg bw for the rat. For the octasodium salt, the oral LD_{50} is >3870 mg/kg bw and the dermal LD_{50} >860mg/kg bw for the rabbit. There is sufficient information from studies performed to an adequate standard, plus additional information from non-key studies, to support these values.

There is evidence that DTPMP acid is an eye irritant, although different severities were reported in the two available assays (mild and severe). While both the formulations tested contained 10% HCl, which could contribute to the irritant response, it would however appear prudent to conclude that the anhydrous acid is a severe eye irritant. Evidence from three studies on DTPMP salts indicates these are only slightly irritating to the eye.

Several studies on DTPMP acid and its salts indicate they have a low skin irritation potential. Although these studies tested formulations and therefore the limit dose for the active acid or salts was not achieved, the presence of hydrochloric acid in the formulations would be expected to exacerbate the response obtained. Therefore, in view of the very limited responses obtained, it is considered likely that the pure acid or salt, if tested to a limit dose, would be, at most, mild skin irritants.

The salt of DTPMP has been studied in a good quality 90 day feeding study conforming to OECD guidelines. Repeated exposure to 842 mg/kg bw/d (males) and 903 mg/kg bw/d (females) resulted in perturbations of iron and calcium homeostasis (in the absence of any concurrent alteration of calcium plasma levels). Changes in some blood parameters and an increase in total bone density were seen at this dose. The NOAEL for this study was therefore 83 mg/kg bw/day based on the mid dose male group. There are a number of further studies available on the salt, covering durations from 90 days, one year or two years. In addition to effects on iron homeostasis and haematological effects, two of these studies have reported effects on liver pathology and NOAELs down to 4 mg/kg bw/d have been assigned. As these are secondary literature, where there is insufficient information for full evaluation, the findings are not considered to outweigh the recent GLP and OECD compliant 90 day study.

Neither the acid nor the salt induces mutations in well-conducted studies in bacteria. The evidence for mutagenic potential in mammalian cells is conflicting. The acid, even when neutralized, can induce mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells in the presence of S9 mix. A negative response was seen when the salt (neutralized with NaOH) was tested. The difference in outcome between the tests on the acid when neutralized with NaOH and on the salt is difficult to rationalize since the species tested should be similar for both test substances and similar dose ranges were tested. It is probable the positive response for the acid does not reflect an ability to interact with DNA due to (1) lack of structural alerts for mutagenicity, (2) lack of evidence for gene mutation potential in sub-mammalian systems and (3) lack of potential to induce gene mutations in another well-conducted assay investigating mutations at the hprt locus in CHO cells. Perturbations of pH and osmolarity are considered to be unlikely causes of the positive response due to the low concentration at which a positive response on the acid was seen (0.73 mM) and because positive responses are only seen consistently in the presence of S9. A plausible alternative explanation is the test substance interacts with S9 resulting in the formation of oxidative species. Evidence for a lack of mutagenic potential of DTPMP in vitro is supported by a negative hprt locus test and in vivo is provided by a well-conducted chromosome aberration study in rat bone marrow following gavage with doses up to 1970 mg/kg bw. Consequently DTPMP and its salt are not considered to pose a genotoxic hazard.

The reproductive NOAEL for DTPMP in the rat is 294 mg/kg bw/day for parental males and 312 mg/kg bw/day for parental females. No histopathological changes were apparent in reproductive tissue from male or female rats following gavage administration of 850-900 mg/kg bw /day of the sodium DTPMP for up to 90 days. Results from a rat reproduction study provided evidence of equivocal fetotoxicity with a NOAEL of 100 mg/kg bw/day and a NOAEL of 312 mg/kg bw/day for teratogenicity of DTPMP in the rat, however these observations were not replicated in a developmental toxicity study on sodium DTPMP which provided a NOAEL of 1000 mg/kg bw/day for fetotoxicity and 2000 mg/kg bw/day for teratogenicity.

Conclusion for Human Health

The chemicals in this category possess properties indicating a hazard for human health (eye irritation, potential perturbations of iron and calcium 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

DTPMP is a polyphosphonic acid of molecular weight 573. 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 ($\geq$ 500 g/l) and low octanol-water partition coefficient (Log Kow = -3.4). Its vapour pressure is very low (1.67×10^{-10} Pa (estimated)). At pH 7, DTPMP in water will be almost fully ionised five times, with a majority of the molecules ionised six times, and some seven or eight 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.

DTPMP 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 (measured Koc = 9748). 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, metal-catalysed photodegradation can be rapid, which promotes further biodegradation. DTPMP is not expected to be bioaccumulative, based on its low Log K_{ow} and read-across from the two related substances ATMP and HEDP.

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.

DTPMP and its salts are of low acute toxicity to fish and aquatic invertebrates. The lowest reliable acute toxic concentrations determined for DTPMP are a 96-h LC_{50} for the rainbow trout, *Oncorhynchus mykiss*, that is in the range 180-252 mg/l and EC50 values determined in acute tests with aquatic invertebrates are all in excess of 150 mg/l. DTPMP is of low chronic toxicity to fish (*O. mykiss* 60-day NOEC: 25.6 mg/l). There are no chronic data for aquatic invertebrates but an acute sub-lethal test with the oyster, *Crassostrea virginica*, yielded a 96-hour EC_{50} for effects on shell growth of 155.8 mg/l and a NOEC of 55.5 mg/l.

The 2Na and 7Na salts of DTPMP are of low acute toxicity to the marine sediment living amphipod *Corophium volutator* (10-day LC_{50}: >2500 mg/kg dw). There are no reliable data describing the acute toxicity of DTPMP to sewage sludge micro-organisms.

The effects of DTPMP observed in tests with algae are likely to be a consequence of nutrient limitation caused by complexation and not true toxicity. Thus, a 95-hour E_rC_{50} for *Selenastrum capricornutum*[1] of 0.45 mg/l is likely to over-estimate the true toxicity. The true toxicity of DTPMP and its salts to algae is best represented by the 95 hour ErC_{50} value of >10 mg/l. This value was obtained in the only test where steps were taken to counter the effects of nutrient complexation and is therefore most likely to be indicative of true toxicity.

No data are available that describe the toxicity of DTPMP to terrestrial plants and invertebrates. DTPMP is of low acute toxicity to birds when administered via the dietary exposure route (*Anas platyrhynchos* and *Colinus virginianus* 14-day LC_{50}: >454 mg/kg bw).

[1]Now known as *Pseudokirchneriella subcapitata*

Conclusion for the Environment

DTPMP and its salts possess properties indicating a hazard for the environment (EC_{50} 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 bioaccumulation potential.

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 DTPMP 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 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 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/).