PHOSLOCK®

Phoslock Water Solutions Ltd.
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Toxicity Assessment of Phoslock® & Lanthanum to Human Health

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Executive Summary

Phoslock® is a new but fast emerging effective P-inactivation and blue-green algae management tool which was developed by the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia. Phoslock® consists of bentonite clay (~95%) and lanthanum (~5%). In order to minimise any toxic impacts of Phoslock® to human health, this toxicity assessment report has been constructed to analyse and interpret relevant scientific literature and assessment studies using Phoslock® and/or lanthanum carbonate or lanthanum chloride.

Bentonite is not considered toxic to humans. Bentonite has been approved as a food additive in Australia. In contrast to the toxicity of other similar products or metals such as alum or aluminium used in the water industry, lanthanum is used as a beneficial agent to human health. Lanthanum carbonate (Fosrenol®) has been used as a phosphate binder for treatment of hyperphosphatemia in patients with chronic kidney disease who are undergoing dialysis. The bioavailability of lanthanum is extremely low, ≤0.0007% in animals and 0.00127% (± 0.00080%) in humans. The majority of the oral dose of lanthanum carbonate is excreted in the faeces. The kidneys are not significantly involved in the clearance of lanthanum from the human body; the main excretion route for absorbed lanthanum being via the liver into bile. No effects of lanthanum accumulation in bones have been observed. Studies have shown that lanthanum is not genotoxic and the evidence that lanthanum does not cross the blood-brain barrier is substantive.

We suggest that there is no risk to human health by a Phoslock® application to a water body (including drinking water reservoirs) at the Phoslock Water Solutions Ltd proposed dose rate of 100 g Phoslock®:1 g Filterable Reactive Phosphorus (FRP). The safety margin is substantial and sufficient to ensure that the only exposure of lanthanum (in Phoslock®) would always be much less than the therapeutic dose used in patients with hyperphosphataemia.

1. Introduction

Phoslock® is a modified clay product that was developed by the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Australia to remove phosphorus from water bodies and eliminate the chance of blue-green algal blooms. Phoslock Water Solutions Limited (PWS) manufactures and applies Phoslock® to water bodies ranging from; recreational lakes; drinking water reservoirs; and, intensive aquaculture ponds in order remove excess FRP (in the form of PO_4) and control algal blooms.

Phoslock® consists of bentonite clay (~95%) and lanthanum (~5%). During the manufacturing process of Phoslock®, modified bentonite clay and lanthanum chloride ($LaCl_3$) are mixed in an aqueous solution. The lanthanum (La) is adsorbed onto sites within the bentonite and becomes the active compound that removes phosphate. Bentonite (CAS No. 1302-78-9) consists of a group of clays formed by the crystallisation of vitreous volcanic ash that's deposited in water. Bentonite has been used in food, agriculture, pharmaceutical, cosmetics, medical, detergent, paint, dyes, polishes, paper and drilling industries. Bentonite has been approved as a food additive in Australia (NICNAS, 2001).

Lanthanum was discovered in 1839 by a Swedish scientist, Carl Gustav Mosander. Lanthanum is one of 15 elements that are commonly known as the rare earth elements. Natural lanthanum is a mixture of two stable isotopes, ^{138}La and ^{139}La. Lanthanum belongs to a group of elements known as the 'lanthanides'. It is the most electropositive (cationic) element of the rare earth group, is uniformly trivalent, and its binding is almost exclusively ionic. It is a hard 'acceptor' with an overwhelming preference for oxygen-containing anions. Therefore, the most common biological ligands are the carboxyl and phosphate groups with which it can form very tight complexes (reviewed by Persy *et al.*, 2006).

There are several lanthanum compounds that are available commercially. These include oxide, carbonate, chloride and fluoride. Among these compounds, lanthanum carbonate has been used in the medical industry for preparing a pharmaceutical drug. Fosrenol® ($La_2(CO_3)_3$), the FDA (US Food and Drug Administration) approved drug, is used as a phosphate binding agent for patients with hyperphosphataemia. Another application of lanthanum is found to be in water treatment, for removing oxyanions, such as phosphate and arsenate. It is this feature of lanthanum that is utilised in Phoslock®.

Lanthanum (La^{3+}) is not influenced by redox reactions (as in the case of Al^{3+}), and when bound with PO_4 forms the insoluble compound, $LaPO_4$ (Rhabdophane). Lanthanum and lanthanum salts are not on the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999a) and they are unlikely to be classified as hazardous substances in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999b). However, it has also been found that the free/unbound lanthanum (from the dissolution of $LaCl_3$) can be toxic to aquatic organisms depending on the concentration (Peterson *et al.*, 1974). This issue limited its use significantly, until an appropriate carrier that could lock the lanthanum ions into its structure was discovered in

the mid 1990s by the CSIRO. Lanthanum toxicity and the availability of its free form was dramatically reduced by incorporating the lanthanum ions into the structure of a high exchange capacity mineral, such as bentonite, hence the development of the innovative product, Phoslock®.

Several independent organisations and researchers have conducted extensive laboratory and field studies on the ecotoxicity of Phoslock® and lanthanum using a range of aquatic organisms and the United States Environmental Protection Agency toxicity testing criteria (summarised by Afsar & Groves, 2009). However, very little information is available on the toxicity of Phoslock® and/or lanthanum to human health. In order to ensure that the innovative nutrient inactivation product 'Phoslock®' is safe in relation to human health, this report, therefore, summarises the properties of Phoslock® and the scientific information available on the toxicity of Phoslock® and lanthanum to human health.

2. Properties of Phoslock®

Phoslock® was originally manufactured and applied in the form of a slurry, containing 20% (w/w) of the active Phoslock®. A dry, free flowing granular form was developed in 2004, resulting in ease of transportation and reduced application cost. Another advantage of granular Phoslock® is that during the manufacturing (granulation) process significant dewatering of the slurry occurs that significantly reduces the amount of residual lanthanum associated with the product. With the introduction of the free flowing granular form, the active Phoslock® concentration was increased to more than 90% (w/w). The major properties of granular Phoslock® are listed in Table 1. By adhering to strict quality control measures, Phoslock Water Solutions Limited maintains a high concentration of the active Phoslock® consistently in the supplied product. Moreover, the low dust level and the acceptable degree of packaging stability of Phoslock® make the transportation and the application of the product convenient as well as minimising any possible health risk associated with dust levels to the personnel involved in these processes.

Physical & Chemical Properties	Description
Phoslock® content	>90% (Bentonite content is ~95% and Lanthanum is ~5% on a dry matter basis)
Water content	8% - 10%
Appearance	Light brown free flowing granules
Packaging stability	No deterioration of the packaging or physical appearance of the product
Size of the granules	0.5 − 3 mm
Bulk density	850 − 1200 kg m^{-3}
Dust content	<1% weight 50 µm
pH	7.0 − 7.5

Table 1: Summary of properties of Phoslock® granules.

3. Toxicity of bentonite to human health

Bentonite is not considered toxic to humans or the environment. In Australia, bentonite has been approved as a food additive (NICNAS, 2001). Bentonite is utilised in the removal of impurities in oils where its adsorptive properties are crucial. In drinks such as beer, wine and mineral water, and in products like sugar or honey, bentonite is used as a clarification agent. Bentonite is used as an animal feed supplement, as a pelletizing aid in the production of animal feed pellets, as well as a flowability aid for unconsolidated feed ingredients such as soy meal. Bentonite is used as a filler in pharmaceuticals, and due to its absorption/adsorption functions, it allows paste formation. Such applications include industrial protective creams, calamine lotion, wet compresses, and antiirritants for eczema. In medicine, bentonite is used as an antidote in heavy metal poisoning. Personal care products such as mud packs, sunburn cream, baby and face powders, and face creams all contain bentonite.

The expected acute oral toxicity of bentonite in humans is very low (LD_{50}>15 g/kg) (HSDB, 2000). In a 33 day dietary (2 and 6%) and a 90 day dietary (1, 3, and 5%) study in chickens, no changes in behaviour, overall state, clinical and biochemical parameters and electrolytic composition of the blood occurred (NICNAS, 2001). Repeat dietary administration of bentonite did not affect calcium or phosphorus metabolism (NICNAS, 2001). Bentonite did not cause fibrosis after one year of exposure of 60 mg dust (<5 µm) in a rat study (Tatrai, 1985).

Bentonite is not on the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999a), and based on the available information, it is unlikely to be classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999b) as it doesn't meet the criteria of a hazardous substance.

4. Toxicity of Phoslock® and/or lanthanum to human health

Although no scientific study is available on the toxicity of Phoslock® to human health, a large amount of scientific literature is available on lanthanum toxicity to human health due to lanthanum carbonate (Fosrenol®) being used as an oral drug in the medical industry. Phosphate accumulation in the human body and hyperphosphatemia are associated with an increased mortality risk. Lanthanum carbonate (Fosrenol®) is an effective non-aluminium, non-calcium oral phosphate binder for treatment of hyperphosphatemia in patients with chronic kidney disease who are undergoing dialysis. Tablets of 500, 750 and 1,000 mg are available for use in end stage renal disease patients (ESRD) with a mean C_{max} of lanthanum 1,000 ng/L plasma (Behets *et al.*, 2004). The FDA approved human dose rate for Fosrenol® (as appears on the Fosrenol® website - http://www.fosrenol.com/) is 750 – 3,000 mg per day. Moreover, Fosrenol® has also just been approved for inclusion on the Australian Public Benefits Scheme (Pharmaceutical Benefits Advisory Committee (PBAC) meeting notes, 2008; http://www.health.gov.au/pbs). Upon ingestion of Fosrenol® tablets, lanthanum carbonate dissociates in the acid environment of the upper gastrointestinal tract to

release lanthanum ions that allow the formation of lanthanum phosphate in the body. This insoluble lanthanum phosphate is eliminated in the faeces without significant absorption of lanthanum. Efficacy and safety have been demonstrated in several Phase III clinical trials in both Europe and North America.

The accumulation of lanthanum in the body of dialysis patients is negligible, mainly because of its ultra-low gastrointestinal absorption and route of elimination. The kidney is not significantly involved in the clearance of lanthanum; the main excretion route for absorbed lanthanum being via the liver into bile (Damment & Pennick, 2007). Biliary elimination (80%) and direct transport across the gut wall into the lumen (13%) represent the main routes of elimination. This implies that the removal of lanthanum is not dependent on renal function; of a lanthanum dose of 1 g/day in healthy volunteers, only 0.00003% was excreted in the urine (Damment & Gill, 2003). The presence of lanthanum in the liver (Das *et al.*, 1988) is consistent with excretion of lanthanum by the liver. However, clinical studies of up to four years have not disclosed any hepatotoxic effect of the drug in patients treated with this phosphate binder (reviewed by Persy *et al.*, 2006).

The bioavailability of lanthanum is extremely low, ≤0.0007% in animals (Damment & Gill, 2003), with the majority of an oral dose being excreted in the faeces. In the human body, the absolute bioavailability of lanthanum (administered as lanthanum carbonate) was also extremely low (0.00127% ± 0.00080%), with individual values in the range of 0.00015% to 0.00224% (Pennick *et al.*, 2006). Studies have shown that oral doses of lanthanum carbonate are only minimally absorbed by the gut – in dogs, the rate of absorption is 0.00005% (Pennick *et al.*, 2003) – with the majority of an oral dose being excreted in the faeces. This is in contrast to other water treatment products such as aluminium; when administered, 0.06 – 0.10% was absorbed from the gastrointestinal tract (Johanneau *et al.*, 1997; Coburn *et al.*, 1991). Moreover, in contrast to lanthanum, absorbed aluminium eliminated mainly via kidney and biliary excretion is negligible (Coburn *et al.*, 1991).

No effects of lanthanum on bones have been observed in animals with normal renal function loaded with lanthanum at doses up to 2000 mg/kg/day for two years (Damment *et al.*, 2003). Patients treated with lanthanum carbonate for one year did not experience any of the aluminium-like toxic effects on bones expressed as either osteomalacia or adynamic bone desease (De Bror & D'Haese, 2004). On the other hand, rats with chronic renal failure loaded with very high doses (1,000 – 2,000 mg/kg/day) of lanthanum carbonate for 12 weeks showed an impairment of bone mineralisation (Behets *et al.*, 2004). However, several further studies produced evidence that the observed lesions were pharmacologically mediated and resulted from phosphate depletion induced by the administration of high doses of lanthanum carbonate rather than being the consequence of a direct toxic effect of the compound (reviewed by Persy *et al.*, 2006). Further evidence of the absence of any direct toxicity of lanthanum on bones includes the fact that the bone lanthanum concentration does not correlate with the various histomorphometric bone parameters, and the effects of lanthanum on bone mimic those induced by feeding a low phosphate diet, are normalized with phosphate repletion (Damment & Shen, 2005), and are similar to those observed in rats treated with sevelamer (Behets *et al.*, 2005).

Studies have shown that lanthanum is not genotoxic and that lanthanum carbonate is unlikely to present a latent hazard in therapeutic use (Damment *et al.*, 2005). There is no evidence from studies that lanthanum crosses the blood-brain barrier (Evans, 1990; Behets et al. 2005; Damment & Shen, 2005). In fact, lanthanum is routinely used as tracer to investigate the integrity of this barrier, as lanthanum ions cannot cross the plasma membrane and are excluded from passing between vascular endothelial cells in the central nervous system (CNS) by tight junctions (Kato *et al.*, 1989; Xu & Ling, 1994). Furthermore, lanthanum is almost completely bound in plasma to a variety of proteins (>99.9%), effectively limiting access to some tissue compartments, especially the brain (Pennick *et al.*, 2006).

The acute oral toxicity of lanthanum chloride in rats is very low (LD_{50} = 2370 – 4184 mg/kg) (Cochran, 1995; Sax, 1984; RTECS, 2000). In a study by giving lanthanum chloride subcutaneous injections to frogs, mice and rats determined LD_{50} to be >1,000, 3,500 and >500 mg/kg for frogs, mice and rats respectively (Sax, 1984).

5. Risk assessment of Phoslock® to human health

The possibility of direct exposure of Phoslock® and/or lanthanum to the human body is very limited during or after an application of Phoslock® to a water body. PWS has identified the following potential hazards associated with the application of Phoslock®, potential pathways of these hazards to human body, risks associated with these hazards, and control or mitigation strategies.

5.1. Hazard 1: Phoslock® dust

5.1.1. Pathway - Inhalation of Phoslock® dust or contact to skin

One possibility of Phoslock® exposure to human body is via inhaling Phoslock® dust or contact to skin during manufacture and/or application.

5.1.2. Risk associated with Phoslock® dust inhalation or contact to skin

The MSDS of Phoslock® states that the 'rare earth modified clay', or Phoslock® is a non-hazardous and non-dangerous good. No risk has been associated with contact of Phoslock®. However, through inhalation or contact to skin, a person may feel discomfort or some irritation may occur.

5.1.3. Mitigation/control strategies for dust inhalation or contact to skin

Although Phoslock® is a non-hazardous substance; PWS has taken several protective measures to prevent inhalation and/or contact to skin or eyes. During manufacturing and application to a water body, all workers must wear personal protective equipment (PPE) including eyewear, gloves, work clothing, boots, face masks etc. During application, public access should be restricted to the application area until the Phoslock® has dispersed. The MSDS of Phoslock® states that if inhaled, a person should be removed

from the contaminated area. In case of contact, skin should be flushed with running water.

5.2. Hazard 2: Phoslock® and/or lanthanum in water

5.2.1. Pathway - Drinking Phoslock® treated water

Another possibility of Phoslock® exposure is via drinking Phoslock® treated water soon after application. Through drinking Phoslock® treated water, a person can uptake lanthanum.

5.2.2. Risk associated with drinking Phoslock® treated water

Lanthanum uptake via drinking Phoslock® treated water may cause some negative effects on human health if the concentration exceeds the recommended daily uptake limit prescribed by e.g. Fosrenol®.

5.2.3. Mitigation/control strategies for drinking Phoslock® treated water

The possibility of lanthanum uptake via drinking Phoslock® treated water is very limited. However, this is further reduced by ensuring the water body is kept off line after the application for few days (~7 days) until the Phoslock® clay particles associated with lanthanum have settled on the bottom (with dissolved La concentrations being continuously monitored after the Phoslock® application). On the other hand, once dissolved/free lanthanum binds with anions, they also sink and settle on the sediment as an insoluble complex which reduces the chance of lanthanum exposure to the human body when drinking Phoslock® treated water. Moreover, most water treatment would be expected to remove residual lanthanum as it removes aluminium at the time of treatment. The quantities of Phoslock® applied in the water body are determined by the concentration of phosphate available in the water body and the portion of total phosphorus that has the potential to be released as FRP. Therefore, the availability of free lanthanum in the water column for a prolonged period of time is highly unlikely.

Once lanthanum binds with phosphate, it is no longer free or bioavailable. The lanthanum-phosphate ($LaPO_4$) complex is known to have extremely low solubility and able to form even when there are low concentrations of phosphate present in the water body and at low pH. The extent of the insolubility of lanthanum-phosphate complexes were studied by Firsching & Brune (1991) and Firsching & Kell (1993). The authors reported its solubility product, K_{sp}, in freshwater to be -26.15 (Firsching & Brune, 1991) and in seawater -27.92 (Firsching & Kell, 1993), making it the least soluble among the rare-earth-phosphate complexes and far less soluble than aluminium and ferric phosphate complexes.

In case of lanthanum ingestion via drinking even a large volume of Phoslock® treated water, there is no risk to human health. The FDA approved the human dose rate for Fosrenol® or $La_2(CO_3)_3$ (as appears on the Fosrenol® website) at 750 – 3,000 mg per day. This being the case, applying Phoslock® on a reservoir at the dose rate of 50 ppm

(a typical dose rate of Phoslock® in a water body with an average concentration of phosphorus and alkalinity) and accepting that 100% of La (5% La in the product) will be leached out of the product (which will not happen because alkalinity and PO_4 will "soak up" the "free" La), then: the person would need to drink 300 L of reservoir water per day to ingest the minimum dose of La that corresponds to the lowest Fosrenol® daily intake. The maximum daily dose of Fosrenol® is 3,000 mg and therefore the average person would need to drink 1,200 L of reservoir water per day to get the maximum dose of La that is the Fosrenol® daily intake. These large volumes of water could not be drunk by a person per day and therefore an application of Phoslock® would never deliver as much as La that a Fosrenol® tablet delivers. Therefore, even ingestion of Phoslock® directly after an application would not pose a risk to human health risk.

5.3. Hazard 3: Lanthanum accumulation in fish

5.3.1. Pathway - consuming Phoslock®/lanthanum accumulated fish

A third possibility of Phoslock® exposure is via consuming Phoslock®/lanthanum that has accumulated in aquatic organisms such as fish.

5.3.2. Risk associated with consuming Phoslock®/lanthanum accumulated fish

Lanthanum uptake via consuming Phoslock® accumulated in fish may cause some negative effects on human health if the concentration exceeds the recommended daily uptake limit prescribed by e.g. Fosrenol®.

5.3.3. Mitigation/control strategies for not consuming Phoslock®/lanthanum accumulated fish

The risk via consuming Phoslock®/lanthanum accumulated fish harvested from Phoslock® treated water after application is reduced as shown in a fish health investigation, after three successive applications of Phoslock® in Lake Okareka (New Zealand). Lake Okareka fish health monitoring report (Landman *et al.*, 2007) demonstrated that trout and koura accumulated La only in the liver and hepatopancreas tissues, not in the flesh/muscle following the application of Phoslock®. It was also demonstrated that the accumulated La was removed from the fish liver and hepatopancreas tissues within few months and the concentrations of La returned to baseline before another Phoslock® application one year later, suggesting a biological capacity to depurate lanthanum by the Lake Okareka biota (Landman *et al.*, 2007). This is also consistent with the findings that the main excretion route for absorbed La in humans or animals is via the liver into bile (Damment & Pennick, 2007).

The highest concentration of La measured in the liver of male and female trout in Lake Okareka after one and two months of Phoslock® application was 1.2 and 0.8 mg/kg respectively (Landman *et al.*, 2007). Similarly, the highest concentration of La in the hepatopancreas tissues of male and female trout was 0.8 and 1.0 mg/kg respectively (Landman *et al.*, 2007). Therefore, in total the highest concentration of La in one trout was 2.0 mg/kg. This being the case, applying Phoslock® on a reservoir at the dose rate similar to Lake Okareka, a person would need to consume 375 kg of fish per day to

ingest the minimum dose of La that corresponds to the lowest Fosrenol® daily intake. The maximum daily dose of Fosrenol® is 3,000 mg and therefore the average person would need to consume 1,500 kg of fish per day to get the maximum dose of La that is the Fosrenol® daily intake. These large quantities of fish would not be consumed by a person per day and therefore an application of Phoslock® would never deliver as much as La to fish body that a Fosrenol® tablet delivers. Moreover, fish liver and hepatopancreas tissues are not generally consumed by humans. However, even consumption of large quantities of lanthanum accumulated fish liver and hepatopancreas tissues harvested from Phoslock® treated water body will not pose any risk to human health.

6. Conclusion

In conclusion we consider that a Phoslock® application to a water body including drinking water reservoirs at applicable dose rates shows that there is no identifiable risk to human health. The margin of safety in the case that all lanthanum is leached out of the product after application to a water body such as a drinking water reservoir is substantial and sufficient to ensure that exposures from ingestion of lanthanum would always be significantly much less than the therapeutic dose used in patients with hyperphosphataemia.

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