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Subject: **Risk Assessment - Human health risk of elevated lanthanum in drinking water resources**

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Signed for and on behalf of UniQuest Pty Limited

Professor Michael Moore

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1. EXECUTIVE SUMMARY

We consider that at the proposed rates of application of Phoslock (a bentonite -- lanthanum proprietary product) to water bodies there is no identifiable risk to human health. The worst-case scenario used in the risk assessment, represents an extreme situation that would not occur in practice. On the basis of the pharmacological safety profile of lanthanum carbonate we consider that at the proposed rates of application of lanthanum in Phoslock there will not be any measurable risk to human health.

2. BACKGROUND

This report should be read in conjunction with our previous report of October 2006 (UniQuest project 14447) in which references are included. This risk assessment provides some understanding of the potential for human toxicity associated with the use of Phoslock. Critical to this understanding is the possibility that lanthanum could be released into solution from particulate material in which the lanthanum as La^{3+} (La(III)) is bound to bentonite or counter-ions such as phosphate. All of the bound forms of lanthanum are extremely insoluble and only modest quantities of La^{3+} will be found in solution . In this report there has been no consideration of ingestion of insoluble Lanthanum - either as hydrated oxide, colloids or adsorbed onto clay particles. Lanthanum ion in solution is inferred to be the primary source of exposure. Ingestion of suspended matter could provide available ionic Lanthanum in the gastric environment. However it is assumed that water treatment processes would remove all such suspended insoluble solids discounting these as a significant vector of exposure.

As there is a paucity of evidence of lanthanum toxicity, this risk assessment is based on the available evidence on the pharmacological use of lanthanum carbonate The use of this drug-based data is appropriate since the critical factor in terms of toxicity of lanthanum is the presence of the soluble ion, La^{3+}. In a similar fashion, toxicity in water bodies will be predicated on the release of the lanthanum ion which will then exist in an identical form to the lanthanum ion used in the pharmaceutical preparation.

New data provided by Phoslock (Lanthanum Leaching: Exploration and Remediation, Phoslock, January 2007) demonstrates that under certain conditions, high concentrations of La^{3+} (lanthanum ion) can be achieved when Phoslock is used in soft waters with low alkalinity. This is not wholly relevant to the risk assessment since the risk assessment as initially presented is predicated on release into solution of all of the applied lanthanum into the hypolimnium at a specific dosing rate which is substantially less than the experimental dose

rate, This is a highly conservative risk assessment since it is clear that not all La^{3+} will be released from Phoslock / bentonite or indeed from any La^{3+} bound phosphates. Indeed it is most likely that because of the solubility product only a small proportion is likely to go into solution around ph7. The concentration of dissolved lanthanum in any water body subsequent to Phoslock use is predicated on the quantity of Phoslock used, the volume of the water body and the water quality. The dose administered will drive the load of bound insoluble lanthanum in the water body sediments. In the experiments described in this new data, the concentration of Phoslock used is greatly in excess of that in normal use. The experiments carried out in 2006/7 used Phoslock additions of; 1,000,000, 28,000 and 12,000 μg/litre. Our assessment has been for a maximum addition of 500 μg/litre. Proportionally it is obvious that these higher concentrations of Phoslock are likely to result in greater releases of dissolved Lanthanum (La^{3+}).

Waters destined for human consumption will undergo standard treatment techniques which would impact upon available Lanthanum should Phoslock have been used on that water.

Most water treatment would be expected to remove residual La^{3+} as it removes aluminium (Al^{3+}) at the time of treatment. The quantities of Phoslock used should be predicated on the measured concentration of phosphate in the receiving water. Attempts should be made to use Phoslock stoichiometrically in relationship to the phosphate concentration. If this is not attempted, there is every possibility that concentrations of dissolved La^{3+} ion will be higher. However, in the final analysis, the concentration of dissolved lanthanum cannot be greater than the total amount added to the system unless the system already has residual La^{3+} in it.

Critically, in terms of health risk assessment it clear that the assumption that the total La load will pass into solution at the recommended dosage levels is a very conservative position taking into account the certainty that only a small proportion of the lanthanum load is ever likely to dissolve.

In carrying out the risk assessment we only dealt with the consequences of a single use of Phoslock. Continuing treatment of a water body with Phoslock especially where phosphate is not present will establish a background presence of lanthanum in sediments. Release back into solution will be influenced by the presence of other dissolved metals such as iron and manganese and also by water and sediment parameters such as temperature, hardness and pH. These factors should be taken into consideration where repeated use of Phoslock is likely. We have no information on sedimentary transfers of Phoslock-bound phosphate and of

the time scale of La^{3+} diagenetic release (remobilisation). It would be naive however to assume that some remobilization from sediments could not occur.

3. FIRST REPORT

In our earlier report we considered a maximum La(III) concentration under a "worst case scenario" with total La(III) release from Phoslock of 1.3-2.6 mg/L (the latter figure assumes all the La released is in the hypolimnium; the former that it is equally distributed throughout the water column. This was based on an application rate of 0.25kg/m^2 for Phoslock.

4. THE TASK

Phoslock have requested "direct risks (both chronic and acute) to human health at the following concentrations of La:

500 µg/L
300 µg/L
200 µg/L
100 µg/L
50 µg/L 25 µg/L"

Pennick et al. (2006) calculated the bioavailability of La as $La_2(CO_3)_3$ as 0.001275+/- 0.0008%. Using the mean value, we get the following values for bioavailability:

La concentration	500 µg/L	6.075pg/L of water consumed
	300 µg/L	3.825pg/L
	200 µg/L	2.550pg/L
	100 µg/L	1.275pg/L
	50 µg/L	0.608pg/L
	25 µg/L	0.304pg/L

We have checked that these results agree with our calculations which show that 2.6mg/L of La has a bioavailability of 33.15pg/L of water consumed.

Section 3.4 of our earlier report deals with Toxicology of La(III).

5. CLINICAL PHARMACOLOGY

Lanthanum carbonate, Fosrenol, ($La(CO_3)_3$ 4.5 H_2O) has a molecular weight of 457.8, and is practically insoluble in water. Tablets of 250 and 500 mg are available as a pharmaceutical for use in end stage renal disease patients (ESRD) with a mean C_{max} of lanthanum 1000 ng/litre plasma (Behets et al 2004).

Patients with ESRD can develop hyperphosphatemia that may be associated with secondary hyperparathyroidism and elevated calcium phosphate product, which increases the risk of ectopic calcification. Treatment of hyperphosphatemia usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis, and inhibition of intestinal phosphate absorption with phosphate binders. In such patients there has been no evidence of changes in cognitive function (Altmann et al 2007) or genotoxicity (Damment et al 2005)

5.1 Pharmacodynamics

Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release lanthanum ions that bind dietary phosphate released from food during digestion. It inhibits absorption of phosphate by forming highly insoluble lanthanum phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product (Joy et al 2006).

In vitro studies have shown that in the physiologically relevant pH range of 3 to 5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a two-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal (Joy & Finn 2003; Joy et al 2006).

5.2 Pharmacokinetics

5.2.1 Absorption/Distribution

Following single or multiple dose oral administration of La to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in ESRD patients, the mean lanthanum C_{max} was 1000 ng/L. During long-term administration (52 weeks) in ESRD patients, the mean lanthanum concentration in plasma was approximately 600 ng/L. There was minimal increase in plasma lanthanum concentrations with increasing doses within the therapeutic dose range. The effect of food on the bioavailability of

Fosrenol® has not been evaluated, but the timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) has a negligible effect on the systemic level of lanthanum (Pennick et al 2006).

In vitro, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin,α1-acid glycoprotein, and transferrin. Binding to erythrocytes in vivo is negligible in rats.

In 105 bone biopsies from patients treated with La for up to 4.5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone ranged from 2.0 to 3.6 years. Steady state bone concentrations were not reached during the period studied (D'Haese et al 2003).

In studies in mice, rats and dogs, lanthanum concentrations in many tissues increased over time and were several orders of magnitude higher than plasma concentrations (particularly in the GI tract, bone and liver). Steady state tissue concentrations in bone and liver were achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in these tissues for longer than 6 months after cessation of dosing in dogs. There is no evidence from animal studies that lanthanum crosses the blood-brain barrier (Behets et al 2005; Damment & Shen 2005).

5.2.2 Metabolism/Elimination

Lanthanum is not metabolized and is not a substrate of CYP450. *In vitro* metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40µg/ml does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and 3A4/5). Lanthanum was cleared from plasma following discontinuation of therapy with an elimination half-life of 53 hours.

No information is available regarding the mass balance of lanthanum in humans after oral administration. In rats and dogs, the mean recovery of lanthanum after an oral dose was about 99% and 94% respectively and was essentially all from feces. Biliary excretion is the predominant route of elimination for circulating lanthanum in rats. In healthy volunteers administered intravenous lanthanum as the soluble chloride salt (120 µg), renal clearance was less than 2% of total plasma clearance. Quantifiable amounts of lanthanum were not measured in the dialysate of treated ESRD patients (Behets et al 2004).

6. CLINICAL TRIALS

The effectiveness of La in reducing serum phosphorus in ESRD patients was demonstrated in short-term, placebo-controlled, double-blind dose-ranging study, placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies in both haemodialysis and peritoneal dialysis patients (D'Haese et al 2003; Finn & Joy 2005; Joy & Finn 2003).

6.1 Risk Assessment

In assessment of the toxicology of pharmaceuticals in reused water it has been determined that water concentrations of pharmaceuticals should not exceed 100th of the lowest therapeutic dose. (Excepting the genotoxic carcinogens which are required to be 1/10,000th of the dose.) (NEPC 2007)

Lanthanum is considered to be a relatively safe drug for which the lowest available dose is 250 mg. This means that in terms of safety in water supplies the concentration of lanthanum should be no more than 250 times 10^{-} mg or 2.5 mg/L.

Because of the relative safety of lanthanum no data are available on either reference doses or maximal residue limits. It is it is thus difficult to establish any form of hazard quotient for lanthanum. In terms of risk assessment, the maximum concentration of dissolved La in water is 0.5 mg per litre (500 µg per litre) which is 1/5 of this safety limit as determined by the National Environmental Protection Council, we do not consider that there is an identifiable health risk associated with the highest level of lanthanum described in this risk assessment. Questions still remain regarding retention of lanthanum in the body following chronic administration. Nevertheless, it is clear that there are no likely acute effects of this level of lanthanum ingestion. The matter of chronic consequences is less clear but again unlikely.

To further assess the consequences of chronic exposure and retention of lanthanum in the body, a further calculation can be made in respect of comparison of the amounts of lanthanum likely to be absorbed and the concentrations in plasma achieved therapeutically.

If one assumes that a person could consume up to 2 L of water daily at the highest concentration of lanthanum, 500 µg per litre, then the maximum daily loading of retained lanthanum which would be distributed into the total blood volume of the person would be 12

pg. Human blood volume is around 5 L with a haematocrit of 45%. This would result in a concentration of lanthanum of around 1.3 pg per litre plasma. This is 500,000-fold less than the plasma concentrations found in persons with ESRD taking lanthanum carbonate therapeutically for one year. In these circumstances there appears to be a substantial margin of safety in the use of the highest lanthanum concentration of 500µg/per litre. Much greater margins of safety are associated with the lower concentrations for which consideration was requested that is. 25 to 300 µg per litre.

7. CONCLUSION

In conclusion we consider that at the proposed rates of application of Phoslock there is no identifiable risk to human health. The worst-case scenario used in this risk assessment, represents an extreme situation that is very unlikely to occur in practice. In reality the margin of safety at the highest level of application is substantial and sufficient to ensure that exposures from drinking water would always be very much less than the therapeutic dose used in patients with hyperphosphataemia.

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