Australian Government

National Health and Medical Research Council

ADMINISTRATIVE REPORT

REVIEW OF LANTHANUM FACT SHEET FOR INCLUSION IN THE *AUSTRALIAN DRINKING WATER GUIDELINES 2011*

Administrative Report
Review of lanthanum fact sheet for inclusion in the *Australian Drinking Water Guidelines 2011*

Summary

The National Health and Medical Research Council (NHMRC), in collaboration with the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), has developed a lanthanum fact sheet for inclusion in the *Australian Drinking Water Guidelines (2011)* (ADWG). This document summarises the review process.

Background

Lanthanum is a metallic chemical element with the chemical symbol La. For its use in water treatment, lanthanum is prepared on a bentonite base (lanthanum-modified clay). It is applied to bodies of water to reduce the available phosphate, to in turn reduce eutrophication and algal blooms (e.g. cyanobacteria). It is proposed to be used in recreational water and in drinking water supplies.

Reason for Review

In 2009, a draft fact sheet on lanthanum was originally developed for inclusion in the ADWG. Although NHMRC conducted public consultation on the draft lanthanum fact sheet, it was not finalised and was not included in the 2011 version of the ADWG.

This was because in 2010, NICNAS commenced a Secondary Notification Assessment on lanthanum-modified clay (bentonite, lanthanian) and NHMRC deemed that it would be appropriate to await the outcome of this review.

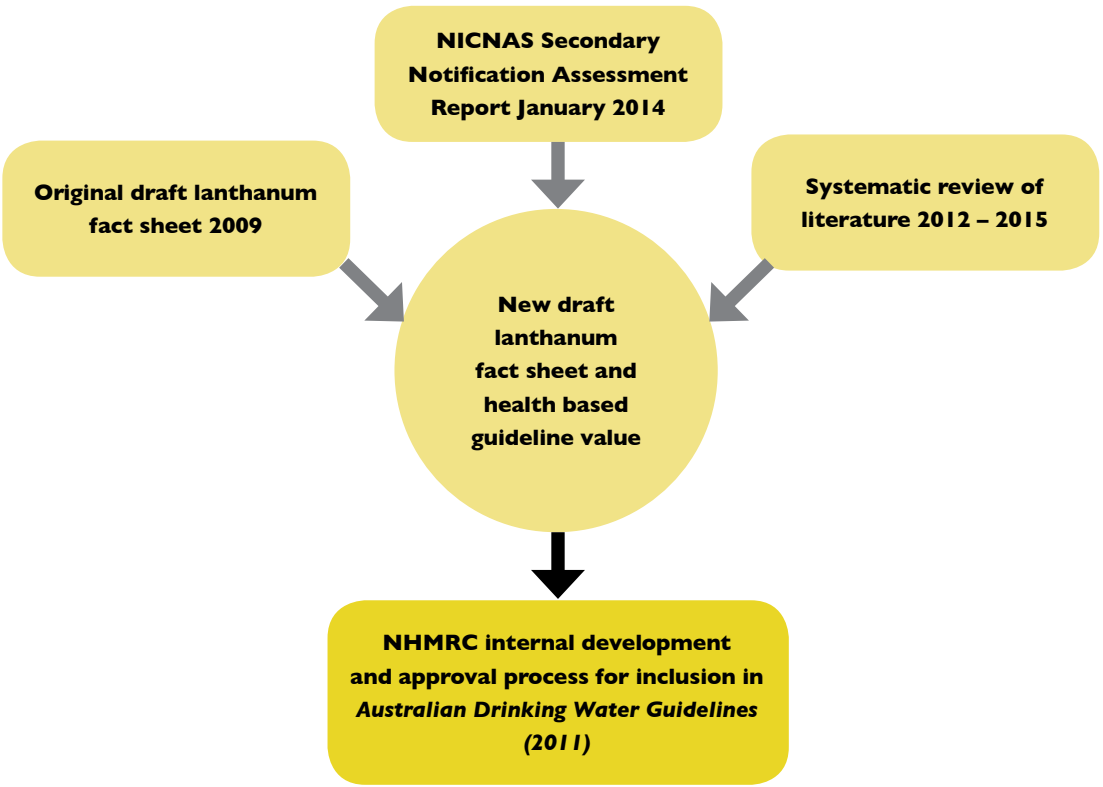
In 2014, NICNAS published its Secondary Notification Assessment Report and requested that NHMRC consider finalising the draft lanthanum fact sheet and health based guideline value for inclusion in the ADWG, as a mechanism to manage concentrations of lanthanum in treated drinking water supplies.

Since 2015, NHMRC and NICNAS have collaborated to review the published literature on lanthanum and to update the draft fact sheet for inclusion in the ADWG.

Purpose of Project

- To consider the 2009 draft ADWG fact sheet on lanthanum.
- To consider the published NICNAS Secondary Notification Assessment Report (2014).
- To consider any recent published literature on the safety or health effects of lanthanum.
- To synthesize the evidence from these three sources, and to produce a draft fact sheet and health based guideline value.

Process



2009 Draft Lanthanum Fact Sheet

A draft background document and draft fact sheet on lanthanum for inclusion in the ADWG (2011) was originally developed following a review of the available scientific evidence by an independent consultant. Since the 2009 draft fact sheet was not published, it was used as a starting point for this project.

Additional Evidence

The NICNAS Secondary Notification Assessment Report (2014) available on the NICNAS website: http://www.nicnas.gov.au, built upon an initial assessment of lanthanum modified clay as a new chemical in 2001.

NICNAS recommended in its 2014 report that, '*risk to humans is considered acceptable if the lanthanum levels are maintained in accordance with a controlled concentration for lanthanum of no greater than 0.002 mg/L when present in drinking water*'.

Review of Literature 2012 - 2015

Rather than review all the relevant literature on the safety of lanthanum, it was decided to focus on the time period 2012-2015 that had not been captured in the NICNAS Secondary Notification Assessment Report. The risk assessment conducted by NICNAS was of sufficient quality to rely upon it as a summary of the published literature and unpublished reports obtained through the Secondary Notification process.

The literature search was conducted by the Therapeutic Goods Administration library service using the following search strategy:

- Lanthanum and synonyms (lanthanum ion, lanthanum carbonate, lanthanum chloride, lanthanum nitrate, lanthanide flurorides, lanthanide hydroxides, lanthanide oxides).
- Toxicology (and synonyms), health effects, epidemiology.
- Humans or animals.
- English language only.
- Date range: November 2012 – October 2015.
- Databases searched: OVID Medline, OVID Embase, AGRIS, AGRICOLA, National Toxicology Program.

Once duplicates were removed, 151 papers were identified.

These references were imported into Covidence (https://www.covidence.org/), an online tool for conducting systematic reviews. Two reviewers screened the references by title and abstract to determine if they met the inclusion criteria (see Box 1). Conflicts were discussed and resolved.

Twenty-five individual references were considered likely to meet the inclusion criteria based on title and abstract screening, and full text articles were obtained. Following full text review, two journal articles were considered relevant (see Appendix B).

BOX 1

INCLUSION CRITERIA

- Studies with lanthanum and a control.
- Studies measuring some kind of toxic or health related endpoint (including pharmacological studies on lanthanum in end-stage renal failure cases).
- Studies in humans or non-human mammals (that is, not aquatic invertebrates or fish, etc).
- Studies in whole animals or humans (not *in vitro*, cell cultures).
- Published between November 2012 and October 2015.

EXCLUSION CRITERIA

- Non-English language studies.
- Studies that do not contain original data, such as reviews, editorials or commentaries.
- Studies that have not been peer reviewed (e.g. conference abstracts, technical reports, theses/dissertations, working papers from research groups or committees, and white papers).

Quality Assessment of Individual Studies

Risk of bias ratings for the two individual animal studies, were collected using a tool developed by the National Toxicology Program's Office of Health Assessment and Translation (a detailed guide to using this tool is available here: http://ntp.niehs.nih.gov/go/38673 (see Appendix C).

NICNAS Review of Draft Fact Sheet

NICNAS reviewed the draft lanthanum fact sheet from 2009, the NICNAS Secondary Notification Assessment Report (2014) and the two studies that were considered relevant (see Appendices B and C), and updated the draft fact sheet accordingly.

NHMRC Water Quality Advisory Committee (WQAC) Consideration

On 2 May 2016, WQAC agreed for the updated draft lanthanum fact sheet to progress to NHMRC Council for approval for public consultation.

NHMRC Council and CEO Consideration

NHMRC Council considered the draft lanthanum fact sheet at its 208th Session on 14 July 2016, and agreed to request NHMRC's CEO to release it for public consultation. The CEO agreed to this on 18 August 2016.

Public Consultation

Public consultation was conducted between 5 September 2016 and 4 November 2016. NHMRC worked with WQAC and NICNAS to ensure due consideration was given to the issues raised during public consultation. A summary of this process, including the issues raised and how these were dealt with to finalise the fact sheet is provided in the Public Consultation Report (see Appendix A).

WQAC Endorsement of Lanthanum Fact Sheet

The lanthanum fact sheet was endorsed by WQAC at its meeting on 11 April 2017.

NHMRC Council and CEO Approval for Publication

NHMRC Council considered the final lanthanum fact sheet at its 211th Session on 13 July 2017 and recommended the CEO to publish it as part of the *Australian Drinking Water Guidelines (2011)*.

The CEO approved the publication of the lanthanum fact sheet and public consultation summary report, on 4 August 2017.

Appendices

Appendix A: Public consultation report lanthanum fact sheet: summary of key issues

Appendix B: Studies considered for full text review

Appendix C: Risk of bias tool

Public Consultation Report
Lanthanum Fact Sheet: Summary of key issues

Background

The Australian Drinking Water Guidelines 2011 (ADWG) have been developed by the National Health and Medical Research Council (NHMRC) and are designed to provide an authoritative reference to the Australian community and the water supply industry on what defines safe, good quality drinking water, how it can be achieved and how it can be assured. The ADWG undergo rolling revision to ensure they represent the latest and best scientific evidence on good quality drinking water.

NHMRC sought public comment on the draft fact sheet for inclusion in the ADWG between Monday 5 September 2016 and Friday 4 November 2016. Stakeholders were invited under paragraph 13(d) of the *NHMRC Act 1992* to make submissions to NHMRC about the draft amendments. The draft amendment is the addition of a fact sheet and guideline value for lanthanum.

Lanthanum is a chemical element, which when bound to bentonite clay may be applied to bodies of water to reduce excessive nutrients (phosphate), with the aim of reducing algal blooms (e.g. cyanobacteria). It may be used in recreational water and in drinking water supplies.

The ADWG contains fact sheets and guideline values for a number of chemicals that might be present in drinking water. The guideline value for each chemical is the concentration that, based on present knowledge, does not result in any significant risk to the health of the consumer over a lifetime of consumption and is consistent with water of good quality.

NHMRC has worked with the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to develop this draft fact sheet.

Consultation Questions

The questions asked at public consultation were as follows:

1. Is the information provided relevant and clear?

2. Are there any issues in relation to the safety of lanthanum in drinking water that you feel have been omitted?

3. Do you have any general comments on the draft fact sheet?

Submissions

NHMRC received three public consultation submissions from the following industry/government agencies:

- Western Australian Department of Health
- Phoslock Water Solutions Pty Ltd
- Environmental Health Standing Committee's (enHealth) Water Quality Working Group

Full submissions are available on the NHMRC Public Consultation website.

Water Quality Advisory Committee Consideration and Final Amendments to the Lanthanum Fact Sheet

The public consultation submissions raised a number of issues. The Water Quality Advisory Committee (WQAC) gave due regard to all submissions and carefully considered issues that were raised. Key issues and WQAC's responses are summarised in the table below. As NICNAS has conducted the hazard assessment of lanthanum, NICNAS also provided input on issues raised in relation to the derivation of the guideline value.

Note that comments on issues unrelated to the public consultation were not considered as part of this process.

#	Comment	Response
1	Request that NHMRC defer the finalisation of the fact sheet until an additional study has been completed by Dr D'Haese on gastrointestinal absorption and tissue distribution of lanthanum after exposure to various doses of Phoslock, lanthanum chloride [$LaCl_3$] and lanthanum carbonate [$La_2(CO_3)_3$].	NICNAS considered this request and noted that the results of this study are unlikely to change the guideline value for lanthanum. The fact sheet relates to lanthanum, not Phoslock. Exposure to lanthanum in drinking water is in relation to suspended lanthanum. Lanthanum phosphate is the most important form of suspended phosphate and does not appear to be considered in the study. Lanthanum in the form of suspended Phoslock may be less bioavailable than other forms of suspended Phoslock and as a result, less toxic. A methodology to distinguish suspended Phoslock from other forms of suspended lanthanum could allow a different guideline to be applied for Phoslock if it were supported by regulators.
2	The sentence 'There is uncertainty on the cumulative effect of lanthanum concentrations from dosing a body of water over a number of years' should be referenced.	This paragraph has been reworded to clarify the intention.
3	Concern that reference to the NICNAS Secondary Notification Report (2014) was not appropriate and that primary studies should be referenced.	WQAC considered that as NICNAS had reviewed the primary studies in determining the NOAEL, that it was appropriate for NHMRC to refer to the NICNAS report.
4.	Requested that the commercial name Phoslock not be used in the fact sheet.	The reference to Phoslock in the fact sheet has been removed, except in relation to the NICNAS Secondary Notification Assessment.
5	There are other sources of lanthanum that could enter drinking water (for example, fertiliser, weathering of rock, leaching from tailings of mining). Do the natural background levels of lanthanum in different Australian water sources exceed the proposed guideline value of 0.002 mg/L?	WQAC considered this, including the limited data available on current levels of lanthanum in drinking water supplies in Australia. Members agreed that based on the limited analytical data it appears that lanthanum level in drinking water supplies are below the guideline value of 0.002 mg/L.
6	Concern that the draft fact sheet assumes that all lanthanum from Phoslock is bioavailable, which is not the case.	The fact sheet and guideline value is on lanthanum. Reference to Phoslock in this context has been removed.

#	Comment	Response
7.	Concern about the appropriateness of the study used to set the NOEL, and concern about the studies that were used in the NICNAS 2014 report.	As described in Chapter 6 of the Australian Drinking Water Guidelines, the health-related guideline values are very conservative, and are calculated using a range of safety factors. They always are on the side of safety, particularly where scientific data are inconclusive or where the only data available are from animal studies. NICNAS reviewed the issues raised and reiterated the conclusions of its 2014 Secondary Notification Report. NICNAS advised that the toxicokinetic data and health effects for lanthanum are based on the pharmacological use of insoluble lanthanum carbonate and studies using soluble lanthanum salts. Regardless of the source of lanthanum, the systemic toxicological effects are mediated by lanthanum ions (i.e. soluble lanthanum). The NOAEL chosen for deriving the guideline value has been adjusted to reflect the ionic lanthanum dose and not the dose of the test substance used (i.e. lanthanum chloride) in the study. The adjusted value did not account for hydration. NICNAS noted that animal and human studies have reported that absorbed lanthanum accumulates in the liver (animals) and bone (animals and humans) after repeated oral administration of lanthanum compounds. However, the extent and potential adverse consequences of lanthanum accumulation in humans is unknown. The derivation of the guideline value involves: • the identification of critical health effects and appropriate NOAEL for the critical effects; • comparison of the estimated or measured human dose from exposure; and • application of uncertainty factors to account for intraspecies variations and interspecies variations. This methodology is conservative in nature and intended to cover the guideline value that does not present a risk over an individual's lifetime. The NOAEL for the identified critical health effects that was used to derive the guideline value was an external dose, not an absorbed dose.
8.	Requests additional information on removal methods to assist water suppliers, particularly in relation to the soluble forms of lanthanum.	WQAC discussed this and has reworded the information in this section. The guideline value has been developed as a result of a perceived need to manage the use of lanthanum as a water treatment chemical. While standard water treatment technologies are likely to reduce the amount of soluble and insoluble lanthanum, it is not the intention that water suppliers apply additional methods to remove lanthanum. Rather consideration should be given prior to application of lanthanum-based products that the finished water will still be suitable for its purpose.
9.	Requests additional information on method to detect and quantify lanthanum, particularly which methods would allow detection and quantification at the levels of the guideline value.	Additional information provided in relation to the analytical methods and limit of reporting.
10.	Requests that the fact sheet use the term 'drinking water' not 'potable water'.	Agreed and change to fact sheet made.

Appendix B: Studies considered relevant for full text review

Study	Conclusions
Brabu, Haribabu et al. 2015	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Lack of control group for acute oral toxicity study in mice. Paper describes initial biocompatibility studies, including acute toxicity, conducted on lanthanum oxide nanoparticles, a potential component for medical devices.
Taketani, Ueda et al. 2014	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Conference abstract. Not peer reviewed.
Isakova, Barchi-Chung et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Toxic or health related end-point not relevant. The end-point examined in the study is the change in fibroblast growth factor (FGF23) affected by different treatments of lanthanum carbonate. This particular endpoint alone is not sufficient to make a determination of the repeat dose toxicity effects of the chemical in humans since study only considered sensitive populations (i.e. increase in FGF23 levels is an indication of disordered mineral metabolism in chronic kidney diseases) is not relevant to the general population.
Seifert, de las Fuentes et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Toxic or health related end-point not relevant. Study may be considered based on non-standardised end-points such as changes in serum and urinary phosphorus levels and cardiovascular effects. However, this is not sufficient to be considered for repeat dose toxicity effects of lanthanum carbonate since study design specifically examined the effects on these parameters.
Zhang, Wen et al. 2013	**EXCLUDE BASED ON THE EXCLUSION CRITERIA** – Study does not contain original data. Paper is a review of randomised control trials which examined the efficacy and safety of lanthanum carbonate.
Zhai, Yang et al. 2015	**EXCLUDE BASED ON THE EXCLUSION CRITERIA** – Study does not contain original data. Paper is a review of published studies on the efficacy and safety of lanthanum carbonate and calcium based phosphate binders. Although, this review can be useful in looking at the studies considered to update the literature on Phoslock SN but not really useful in lanthanum guideline setting.
Uhlig 2014	**EXCLUDE BASED ON THE EXCLUSION CRITERIA** – Study does not contain original data. Commentary.
Hoo Fung, Antoine et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Studies in human or non-human mammals. The study calculated weekly dietary intake rates of several metals detected in fish tissue samples. Although lanthanum levels were below detection limits, the method used for the calculation of the intake rates can be useful when definitive lanthanum concentrations are detected in drinking water reservoirs.
Mayfield and Fairbrother 2015	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Studies with lanthanum and a control, and studies in humans or non-human mammals. Several studies on anthropogenic sources of lanthanum were found in this paper and can be useful to update the literature on environmental exposure in the NICNAS report.
Koontz, Balikian et al. 2012	**EXCLUDE BASED ON THE EXCLUSION CRITERIA** – Abstract only. Unable to determine if it has been peer reviewed. Full study details of the clinical trial not available.
Kalaitzidis and Elisaf 2014	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Study does not contain original data. Not a full experimental study but a comparison (safety, efficacy, cost) of treatments to control hyperphosphatemia in patients.
Cheng, Cheng et al 2014	**INCLUDE BASED ON INCLUSION CRITERIA** – Lanthanum and control, toxic or health related endpoints considered, study in mice (whole animal, mammals). Thirty-day repeat dose toxicity study in CD-1 mice by intragastric administration at doses of 0, 2, 10, or 20 mg/kg bw/day. Study reported adverse effects of lanthanum chloride (vehicle: saline) in the liver (supported by histopathology), kidney, and spleen at a NOAEL of 2 mg/kg bw/day. This NOAEL supports the NOAEL for neurotoxicity (brain alterations and learning decrements) as indicated in the Phoslock SNA.

Study	Conclusions
Valcheva-Traykova 2014	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Study does not contain original data.
Lloret, Ruiz-Garcia et al. 2013	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Study does not contain original data. The paper is a review of several studies that examined the safety and efficacy of lanthanum carbonate (Fosrenol) in tablet formulation and the consideration of Fosrenol in powder form.
Xu, Zhang et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Toxic or health related endpoint not considered relevant. Study specifically looked at the effects of lanthanum carbonate treatment on serum phosphorus levels. Adverse effects of treatment (e.g. gastrointestinal) already reported in previous studies cited in the Phoslock SNA report.
Rombola, Londrino et al. 2012	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – No control group. Study can be considered as a repeat dose toxicity study in humans. However, the study design used only one lanthanum carbonate dose (no control group and no baseline data) and the only significant effects (i.e. reduction in mean serum phosphate levels, calcium × phosphorus product levels, increase in plasma bicarbonate concentration) were not considered adverse.
Willshire, Broe et al. 2014	**EXCLUDE BASED ON EXCLUSION CRITERIA** - Conference abstract. Review of clinical studies that have not been peer reviewed.
Wu, Yang et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Studies *in vitro*, cell cultures. Paper describes *in vitro* study of lanthanum chloride on primary cerebral cortical neurons examining cytotoxicity.
Hong, Pan et al. 2015	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Exposure route (intra nasal) not considered relevant. Six-month repeat dose toxicity study in CD-1 mice administered lanthanum chloride intra-nasally and effects of the chemical in pulmonary toxicity. Although varying lung effects (supported by histopathological changes) were observed, a clear dose-response relationship was not established. Hence, a reliable NOAEL cannot be established for this study.
Frazao and Adragao 2012	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Study does not contain original data. Paper contains a review of the efficacy and safety of several calcium-free phosphate binders in the treatment of chronic kidney disease. Summary of clinical trials were presented based on the different treatments.
Cheng, Li et a. 2012	**INCLUDE BASED ON INCLUSION CRITERIA** – Sixty-day repeat dose toxicity study in CD-1 mice by intragastric administration at 0 or 20 mg/kg bw/day. Study reported adverse effects of lanthanum chloride (vehicle: saline) in liver, kidney, and heart (all supported by histopathology) at a LOAEL of 20 mg/kg bw/day. Note that no dose-response and NOAEL can be established for this study since only one treatment dose was used.
Locatelli , Vecchio et al. 2014	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Does not contain original data. Review and expert opinion of safety profiles of phosphate binders.
Wilson, Keith et al. 2013	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Did not have a control and the toxic or health related endpoint was not considered relevant for the general population. Study specifically examined phosphate binding capacity of lanthanum carbonate monotherapy which showed dose-relativity. No other effects were investigated which limits the study design for the purpose of looking at a threshold of lanthanum effects.
Stevens, Patel et al. 2013	**EXCLUDE BASED ON EXCLUSION CRITERIA** – Conference abstract. Not peer reviewed.
Matsuo, Iida et al. 2014	**EXCLUDE BASED ON NOT MEETING INCLUSION CRITERIA** – Does not measure a relevant toxic or health related end point. The study describes the toxicokinetics (i.e. absorption, distribution, and elimination) and effects of lanthanum carbonate treatment on serum phosphorus levels of Sprague-Dawley rats.

References

Brabu, B., S. Haribabu, et al. (2015). "Biocompatibility studies on lanthanum oxide nanoparticles." Toxicology Research **4**(4): 1037-1044.

Cheng, J., Z. Cheng, et al. (2014). "Immune dysfunction and liver damage of mice following exposure to lanthanoids." Environmental Toxicology **29**(1): 64-73.

Cheng, J., N. Li, et al. (2012). "Organ histopathological changes and its function damage in mice following long-term exposure to lanthanides chloride." Biological Trace Element Research **145**(3): 361-368.

Frazao, J. M. and T. Adragao (2012). "Non-calcium-containing phosphate binders: comparing efficacy, safety, and other clinical effects." Nephron. Clinical Practice **120**(2): c108-119.

Hong, J., X. Pan, et al. (2015). "Molecular mechanism of oxidative damage of lung in mice following exposure to lanthanum chloride." Environmental Toxicology **30**(3): 357-365.

Hoo Fung, L. A., J. M. Antoine, et al. (2013). "Evaluation of dietary exposure to minerals, trace elements and heavy metals from the muscle tissue of the lionfish Pterois volitans (Linnaeus 1758)." Food and Chemical Toxicology **60**: 205-212.

Isakova, T., A. Barchi-Chung, et al. (2013). "Effects of dietary phosphate restriction and phosphate binders on FGF23 levels in CKD." Clinical Journal of the American Society of Nephrology : CJASN **8**(6): 1009-1018.

Kalaitzidis, R. G. and M. S. Elisaf (2014). "Hyperphosphatemia and phosphate binders: effectiveness and safety." Current Medical Research and Opinion **30**(1): 109-112.

Koontz, T., S. Balikian, et al. (2012). "Fosrenol for enhancing dietary protein intake in hypoalbuminemic dialysis patients (FREDI) study." Kidney Research and Clinical Practice **31**(2): A68.

Lloret, M. J., C. Ruiz-Garcia, et al. (2013). "Lanthanum carbonate for the control of hyperphosphatemia in chronic renal failure patients: a new oral powder formulation - safety, efficacy, and patient adherence." Patient Reference and Adherence **7**: 1147-1156.

Locatelli, F., L. D. Vecchio, et al. (2014). "Phosphate binders for the treatment of hyperphosphatemia in chronic kidney disease patients on dialysis: a comparison of safety profiles." Expert Opinion on Drug Safety **13**(5): 551-561.

Valcheva-Traykova et al. (2014). "Involvement of lanthanides in the free radicals homeostasis." Current Topics in Medicinal Chemistry **14**(22): 2508-2519.

Matsuo, A., A. Iida, et al. (2014). "The utility of the phosphate binder, ferric citrate hydrate (JTT-751), about phosphorus absorption-reducing effect in normal rats." Renal Failure **36**(8): 1291-1297.

Mayfield, D. B. and A. Fairbrother (2015). "Examination of rare earth element concentration patterns in freshwater fish tissues." Chemosphere **120**: 68-74.

Rombola, G., F. Londrino, et al. (2012). "Lanthanum carbonate: A postmarketing observational study of efficacy and safety." Journal of Nephrology **25**(4): 490-496.

Seifert, M. E., L. de las Fuentes, et al. (2013). "Effects of phosphate binder therapy on vascular stiffness in early-stage chronic kidney disease." American journal of nephrology **38**(2): 158-167.

Stevens, K. K., R. K. Patel, et al. (2013). "Sustained phosphate loading impairs endothelial function: A single blind cross over trial." Nephrology Dialysis Transplantation **28**(Suppl_1): i331-i351.

Taketani, Y., H. Ueda, et al. (2014). "Correction of hyperphosphosphatemia by dietary phosphorus restriction or phosphorus binder similarly ameliorates vascular complications and mineral disorders in CKD rats." Circulation **130**: A12004.

Uhlig, K. (2014). "Evidence of comparative effectiveness without evidence of effectiveness: The case of phosphate binders in CKD." American Journal of Kidney Diseases **63**(1): 13-15.

Willshire, D. A., M. E. D. Broe, et al. (2014). "Lanthanum carbonate: Safety data after 9 years." "Nephrology. Conference: 50th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology Melbourne, VIC Australia. Conference Start: 20140825 Conference End: 20140827. Conference Publication: (var.pagings). 19 (pp 21), 2014. Date of Publication: August 2014."

Wilson, R. J., M. S. Keith, et al. (2013). "The real-world dose-relativity of sevelamer hydrochloride and lanthanum carbonate monotherapy in patients with end-stage renal disease." Advances in Therapy **30**(12): 1100-1110.

Wu, J., J. Yang, et al. (2013). "Lanthanum induced primary neuronal apoptosis through mitochondrial dysfunction modulated by Ca2+ and Bcl-2 family." Biological Trace Element Research **152**(1): 125-134.

Zu, J., Y.X. Zhang, et al. (2013). "Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China." BMC Nephrology **14**: 29.

Zhai, C. J., X. W. Yang, et al. "Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systematic review and meta-analysis." International Urology and Nephrology **47**(3): 527-535.

Zhang, C., J. Wen, et al. (2013). "Efficacy and safety of lanthanum carbonate on chronic kidney disease-mineral and bone disorder in dialysis patients: a systematic review." BMC Nephrology **14**: 226.

Appendix C: Risk of bias tool

CHENG ET AL. (2014)		
STUDY SUMMARY		
Experimental animal study design	**Health measures**	**Results**
Route: Oral (gavage) **Species, Strain, Sex**: Mice, CD-1, Male **Control**: Yes, distilled water **Chemical**: Lanthanum chloride **Purity**: 99.5% **Doses**: 2, 10, 20 mg/kg bw/day **Vehicle**: Saline **Dosing period**: 30 days **No of animals**: 15 per dose group **OECD Guideline**: No **GLP compliance**: Yes, stated "certificate available"	**Endpoint**: Repeated dose toxicity **Toxicity parameters**: Lanthanum levels in organs, haematology, hepatic biochemistry, liver histopathology **Statistical analysis**: One-way ANOVA with mean levels between control and treatment groups as factor	**Lanthanum levels in organs**: Lanthanum accumulation was highest in the liver, then kidney, spleen, and lung. Statistically significant lanthanum levels were reported at 10 and 20 mg/kg bw/day doses **Haematology**: No treatment-related changes in WBC, RBC, Hb, PLT, Ret, HCT, MCV, MCH and MCHC were reported **Hepatic biochemistry**: No treatment-related changes in ALT, AST, ALP, LDH, CHE, CHOL, TBA, TG AND A/G were reported. Statistically significant change in TBIL were reported at the 10 and 20 mg/kg bw/day dose groups, however, this effect on its own is not considered relevant to humans **Liver histopathology**: Fatty degeneration, mild cloudy swelling, congestion, and disruption of cytoarchitecture were seen in the 10 and 20 mg/kg bw/day dose groups ***No observed adverse effect level (NOAEL) for the study is 2 mg/kg bw/day based on increased lanthanum levels in the organs (highest in the liver) supported by liver histopathology***

RISK OF BIAS ASSESSMENT			
Bias Domain	**Criterion**	**Response**	
Selection	1. Was administered dose or exposure level adequately randomized?	++	Yes, "animals were randomly divided" to control and three treatment groups
	2. Was allocation to study groups adequately concealed?	NR	Not reported
	3. Did selection of study participants result in appropriate comparison groups?	n/a	Not applicable to experimental study in animals
Confounding	4. Did the study design or analysis account for important confounding and modifying variables?	n/a	Not applicable to experimental study in animals
Performance	5. Were experimental conditions identical across study groups?	NR	Not reported
	6. Were the research personnel and human subjects blinded to the study group during the study?	++	Yes, noting that the only description of the blinding was in the histopathological examination (i.e. "the identity and analysis of the pathology slides were blind to the pathologist")
Attrition / Exclusion	7. Were outcome data complete without attrition or exclusion from analysis?	NR	Not reported
Detection	8. Can we be confident in the exposure characterization?	++	Yes, the purity of the test substance is >99% and the method of administration was conducted consistently
	9. Can we be confident in the outcome assessment?	++	Yes, standard criteria for measurement and "standard laboratory practices" were used
Selective reporting	10. Were all measured outcomes reported?	++	Yes, the parameters to be measured described in the methodology were adequately reported in the results and discussion sections
Other sources	11. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

CHENG ET AL. (2012)			
STUDY SUMMARY			
Experimental animal study design	**Health measures**	**Results**	
Route: Oral (gavage) **Species, Strain, Sex**: Mice, CD-1, Male **Control**: Yes, distilled water **Chemical**: Lanthanum chloride **Purity**: Not reported, "analytical grade" **Dose**: 20 mg/kg bw/day **Vehicle**: Saline **Dosing period**: 60 days **No of animals**: 20 per group **OECD Guideline**: No **GLP compliance**: Not indicated	**Endpoint**: Repeated dose toxicity **Toxicity parameters**: Bodyweight, organ weight, lanthanum levels in organs, haematology, hepatic biochemistry, histopathology of liver, kidney and heart **Statistical analysis**: One-way ANOVA with mean levels between control and treatment group as factor	**Bodyweight and organ weight**: Statistically significant decrease in BW and increase in liver, kidney, and heart weights **Lanthanum levels in organs**: Lanthanum accumulation was highest in the liver, then kidney, and heart. No treatment-related change in lanthanum levels in the organs **Haematology**: No treatment-related changes in blood sugar and lipids **Liver biochemistry**: Treatment-related changes in ALT, ALP, CHE, GLB, A/G, and DBIL were reported **Kidney biochemistry**: Treatment-related changes in UA, Cr, and BUN were reported **Heart biochemistry**: Treatment-related changes in AST and LDH were reported **Liver, kidney, and histopathology**: The dosed animals showed light abnormal changes in liver tissue and focal congestion of kidney tissue ***Lowest observed adverse effect level (LOAEL) for the study is 20 mg/kg bw/day based on changes in liver, kidney, and heart biochemistry (supported by histopathology).***	
RISK OF BIAS ASSESSMENT			
Bias Domain	**Criterion**	**Response**	
Selection	1. Was administered dose or exposure level adequately randomized?	+	Yes, "animals were randomly divided" (no randomisation method specified) to control and only one treatment group
	2. Was allocation to study groups adequately concealed?	NR	Not reported
	3. Did selection of study participants result in appropriate comparison groups?	n/a	Not applicable to experimental study in animals
Confounding	4. Did the study design or analysis account for important confounding and modifying variables?	n/a	Not applicable to experimental study in animals
Performance	5. Were experimental conditions identical across study groups?	NR	Not reported
	6. Were the research personnel and human subjects blinded to the study group during the study?	++	Yes, noting that the only description of the blinding was in the histopathological examination (i.e. "the identity and analysis of the pathology slides were blind to the pathologist")
Attrition / Exclusion	7. Were outcome data complete without attrition or exclusion from analysis?	NR	Not reported
Detection	8. Can we be confident in the exposure characterization?	++	Yes (note that the purity (in %) of the test substance was not specified), the method of administration was conducted consistently
	9. Can we be confident in the outcome assessment?	++	Yes, accepted criteria for measurement and "standard laboratory practices" were used
Selective reporting	10. Were all measured outcomes reported?	++	Yes, the parameters to be measured described in the methodology were adequately reported in the results and discussion sections
Other sources	11. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	++	None identified

Risk of bias response options for each criterion	
++	Definitely Low risk of bias: There is evidence of low risk bias practices
+	Probably Low risk of bias: There is indirect evidence of low risk of bias practices OR it is deemed that deviations from low risk of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
- NR	Probably High risk of bias: There is indirect evidence of high risk of bias practices OR there is insufficient information (e.g., not reported or "NR") provided about relevant risk of bias practices
-	Definitely High risk of bias: There is direct evidence of high risk of bias practices (may include specific examples of relevant high risk of bias practices)