Australian Government
National Health and Medical Research Council

NHMRC

Evidence evaluation for *Australian Drinking Water Guidelines* chemical factsheet – LEAD (Research Protocol Stage 2 – extended review)

Organisation

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IMPORTANT: This Research Protocol template is designed for reviews commissioned by NHMRC to inform the update or development of the *Australian Drinking Water Guidelines* (the Guidelines) chemical factsheets and/or related advice in the Guidelines. The Research Protocol should be finalised in collaboration with the NHMRC Water Quality Advisory Committee before commencing work to conduct the search or make eligibility decisions.

A separate Research Protocol should be developed for each chemical (or closely related group of chemicals) for which an evidence review is to be conducted, as the current state of knowledge, health outcomes of interest and sources of evidence will vary.

This template was developed to maximise quality and efficiency in the review process, and has been adapted from an existing template developed for rapid reviews by Cochrane.[1] All sections should be completed. Rationales should be provided throughout for all methodological decisions in the final Technical Report, including any decisions to vary the recommended approaches noted in this template.

For further information about this template or the Guidelines, contact water@nhmrc.gov.au.

Contents

Background

Lead is a metal that is found concentrated in lead ore deposits and in the past was commonly used as an antiknock agent in petrol, in lead-based paints, pigments and glazes, electrical shielding, plumbing, storage batteries, solders, welding fluxes and lead-containing pesticides [2,3]. Due to the phasing out of lead in petrol and solder, concentrations in the air and food are relatively low. Exposure to lead by the general public primarily occurs via the diet; however, exposure can also occur via drinking water primarily from corrosive water effects on household plumbing systems containing lead pipes, solder or fittings [2,3,4].

Lead can be absorbed via inhalation, ingestion and placental transfer. Approximately 10% of ingested soluble lead in adults is absorbed, while in children this is about 50% [2,4]. Lead is distributed via blood to soft tissues including liver, kidney, and bone marrow where it has a biological half-life of less than 40 days, and in skeletal bone lead can accumulate and remain for 20 to 30 years [4]. Exposure to lead has been associated with a range of health effects, primarily with neurodevelopmental effects, impaired renal function, hypertension, reduced fertility and adverse pregnancy outcomes [3]. The International Agency for Research on Cancer (IARC) evaluation of inorganic lead compounds concluded they are probably carcinogenic to humans (Group 2A) [5]. There is currently little evidence that lead interacts directly with DNA at typically encountered blood lead concentrations [5].

Blood lead is used as a biomarker of lead exposure. The effects of concern (i.e. population shifts of IQ in children and blood pressure in adults) are due to chronic exposure. The WHO Provisional Tolerable Weekly Intake (PTWI) used in the 1996 derivation of the NHMRC[4] water quality guideline for lead has since been with withdrawn and is no longer considered to be health protective.

NHMRC (2015)[6] previously concluded a blood lead level greater than 5 µg/dL suggests a person has been, or continues to be, exposed to lead at a level that is above what is considered the average 'background' exposure in Australia, and that if a person has a blood lead greater than 5 µg/dL, their exposure to lead should be investigated and reduced. The NHMRC noted that research on the effects of low-level exposure to lead indicates there is not enough high-quality evidence to conclude that a blood lead level <10 µg/dL was the causing factor for any health effects observed. Thus, it was not possible to make a definitive statement on what constitutes a 'safe level' or what should be considered as a 'level of concern' for blood lead concentrations in children. This arises because the tools of psychologists and psychiatrists used to investigate subtle impacts on intellectual performance and development are not precise, and the outcomes are influenced by such things as genetics, socio-economic status and early life experience / environment.

An initial Stage 1 review of published guidelines and guidance documents for lead carried out by SLR Consulting in 2021 found one existing health-based guidance/guideline value that was suitable to adopt/adapt based on an assessment of administrative and technical criteria (OEHHA 2009)[7]. A DWG from WHO (2011) and current blood lead level guidance from NHMRC (2015a,b) were also identified and considered suitable for potential adaption/adoption in the Guidelines. It was found that potential adaptation of the current NHMRC (2015)[6] advice on blood lead levels (with an aim of keeping blood lead levels under 5 µg/dL) would result in the current Australian drinking water guideline for lead being halved from 10 to 5 µg/L. An initial scan of evidence identified since publication of the current NHMRC (2015)[6] advice was also undertaken and the key studies identified appeared to support the potential adoption of a DWG of 5 µg/L in the Guidelines.

Critical assessment of the individual studies identified in the evidence scan was out of scope of the Stage 1 review. As a result, a targeted search and review of relevant primary studies published since the studies included in the NHMRC (2015)[6] publication will be conducted. Details of methods are provided in later sections.

Objectives of the review

To identify relevant information on the impact of exposure to lead in drinking water at levels higher or lower than the current health-based guideline value on human health outcomes. The process will involve searching for relevant information in primary studies and other evidence sources based on findings from the initial Stage 1 review to derive up-to-date options for health-based guideline values for lead in Australian drinking water supplies.

In particular, this will involve assessing evidence published since the most recent and suitable review identified in Stage 1 (NHMRC 2015) to determine whether a change in the NHMRC (2015)[6] blood lead investigation value is warranted. This will provide NHMRC and the Water Quality Advisory Committee with further information to determine whether NHMRC (2015) is suitable to derive a health-based guideline value for lead in the Guidelines or not.

Methods

For the health-based guideline value and health-related advice in the factsheet where a targeted review of existing advice did not provide suitable guidance to adopt/adapt without further review, an expanded search and review of recent evidence will be undertaken. This will include primary studies published after the most recent health-based agency review found in Stage 1 (NHMRC 2015) which was found suitable for adoption/adaptation based on an assessment of administrative and technical criteria and a critical analysis of the underpinning studies.

For supporting information in the factsheet (e.g. monitoring, treatment information) an evidence scan was conducted at Stage 1 (adopt/adapt) to assess the currency of the existing information in the factsheet. This information will be included, where relevant, in updates to the factsheets. The updates to factsheets are outside of the scope of the Stage 2 review.

The overall approach to reviewing health-related advice of the factsheet is summarised in the table below:

Section of factsheet	Key steps
Health-related advice in chemical factsheet including: • Health-based guideline value • Health considerations • Typical Australian exposure levels(1) • Risk summary	• Screen and assess quality of primary studies and other relevant evidence relating to health-based guideline values for drinking water using an appropriate risk of bias tool (see **Appendix C**) • Present summary of findings (including the derivation of any potential options for guideline values for consideration)

• Derivation of guideline value	• Report details of methods used to search and evaluate the evidence and derive any potential options for guideline values.
(1) Australian exposure levels are not anticipated to be critically evaluated but the data are considered when evaluating risk of harm and are often presented as a concentration range in a chemical factsheet. This information will be handled in a similar manner to the supporting information presented in Stage 1 (adopt/adapt).	

The methods outlined below will govern the searching, selecting, assessment and reporting of the evidence used to inform the update to the chemical factsheet.

Any changes to the Research Protocol once finalised on the advice of the Water Quality Advisory Committee will be recorded and documented in the Technical Report.

Health-related advice in factsheet

Research questions

Health-related advice	Research questions to consider
Health-based guideline value	What level of lead in drinking water causes adverse health effects? What is the endpoint that determines this value? Is the proposed option for a health-based guideline value relevant to the Australian context?
Health considerations	What are the key adverse health hazards from exposure to lead in Australian drinking water? Are there studies in Australia quantifying the health burden (reduce or increase) due to lead? What is the critical human health endpoint for lead? What are the justifications for choosing this endpoint?
Typical Australian water levels or exposure profile	What are the typical levels in Australian water supplies? Do they vary around the country or under certain conditions e.g. drought? (note this was already done in Stage 1) Are there any data for lead levels leaching into water from in-premise plumbing?
Risk summary	What are the risks to human health from exposure to lead in Australian drinking water?

	Is there evidence of any emerging risks that are not mentioned in the current factsheet that require review or further research?

Evidence review for health-related advice in factsheets

Criteria for considering evidence

Study designs	Existing guidelines and guidance from national and international agencies have been considered in Stage 1. This review will consider: ☒ Existing systematic reviews or literature reviews not considered in Stage 1 ☒ Human epidemiological studies ☒ Animal studies [1] ☐ In vitro studies ☐ Other relevant studies or data [please specify] Please specify any study types that will *not* be considered (if any).
Population	☒ Humans, including the general population as well as specific populations who may be at higher risk of adverse health outcomes such as: • Infants and children • People who are pregnant • Aboriginal and Torres Strait Islander peoples • People with iron deficiency • People with pre-existing health conditions such as renal, neurological, haematological or cardiovascular disease • People who ingest higher than average amounts of water (e.g. tropical locations, outdoor workers) • People with certain genetic polymorphisms ☒ Animals or cells as surrogates for human exposure (see footnote 1)

[1] Animal studies may only be consulted if there are insufficient human data. For lead, as current health advice is already based on human epidemiological studies, it is unlikely animal studies will require detailed review.

Exposure	Exposure parameters that will be considered for lead include: • Exposure over a lifetime • Short-term exposure (e.g. over days or weeks during a water contamination event) including during critical time periods (e.g. pregnancy, foetal) • Exposure through drinking, cooking, washing • Combination or reaction with other substances
Comparator(s)	Health-based guidance underpinning current NHMRC drinking water guideline value and blood lead investigation value (NHMRC 2015).
Outcome(s)	The human health outcomes of concern from exposure to lead include: • Mortality • Severe human health outcomes, including incidence of life-threatening illness, disability or chronic disease with ongoing impact on quality of life. • Subtle human health outcomes which may only be recognisable at a population level (e.g. increased blood pressure, IQ decrements). Consideration regarding these outcomes will be given to: • The level of lead in drinking water considered to be safe or acceptable to human health over a lifetime • If deemed relevant from the information reviewed, the level of lead in drinking water considered to be safe or acceptable to human health during a short-term event

Search and screening methods

Expertise	The searches will be: ☒ verified by a content expert [TH] ☐ [conducted/informed/verified] by an information specialist [initials] ☐ independently peer reviewed.
Electronic databases (to search for primary studies published in journal articles and reviews)	☒ MEDLINE/PubMed/TOXLINE ☐ EMBASE ☐ Scopus ☒ SciFinder

(select at least two)	☐ Web of Science ☐ Trials registers [please specify] ☐ Other relevant databases [please specify]
Other sources of evidence	☒ References identified in existing key reviews and/or key articles (backward searching) – limited by publication date (May 2013-onwards) ☐ Articles citing existing reviews and/or key articles (forward searching) ☒ Systematic review references ☒ Data from government/ intergovernmental agencies [check for updates since Stage 1 – same agencies as searched in Stage 1] ☒ Data from industry [e.g. published peer-reviewed articles written by industry, industry reports for exposure information which may or may not have been peer-reviewed] ☐ Contact experts for references ☐ Other [please specify]
Limits:	We will include: ☒ Publicly available documents of guidelines or evidence supporting guidelines (near publication drafts will be accepted if available). ☒ Peer reviewed published or in press studies ☒ Unpublished but publicly available studies (e.g., government reports) ☒ Ongoing studies (e.g., published water quality datasets). ☐ Abstracts and conferences proceedings ☐ Studies in languages other than English [please specify]
Dates:	The search will be conducted from May 2013 to the present date. This is to coincide with the cut-off date for the literature included in the NHMRC (2015)[6] publication.
Key search terms to be used:	Lead AND toxicity AND oral Lead AND health AND oral Lead AND toxicity AND drinking water Lead AND health AND drinking water Lead AND plumbing AND leach(ing) (search terms to be refined as project progresses)

Search strategy:	☐ The complete search strategy for [at least one database] is provided in [Appendix X – please attach]. ☒ Complete search strategies for all electronic sources will be documented in sufficient detail to enable reasonable replication and will be provided in the final report. ☐ If available, the search strategies used to underpin an eligible guideline will be replicated.
Screening search results:	☒ Screening of titles will be performed by researcher [MRC] and verified by content expert [TH] based on inclusion/exclusion criteria and other limits/parameters outlined in this Research Protocol in Excel ☐ Other [please specify]
Abstracts of primary studies:	☒ Single reviewer screens all records. ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Full text of primary studies:	☒ Single reviewer screens all records ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Screening other relevant data:	☒ Single reviewer screens all records ☐ Dual; second reviewer checks all excluded records ☐ Dual; second reviewer checks [X%] of excluded records ☐ Dual; independent screen and cross check [X%] of records
Discrepancy resolution:	☐ Consensus and/or third reviewer ☒ Other [note second reviewer, GDN, will independently check consistency in application of risk of bias tool for a couple of studies]
Excluded primary studies:	☐ Retracted studies will be excluded using [specify method - Endnote 20 will automatically check citations against Retraction Watch database, otherwise citation lists may need to be compared to the database using Zotero]. ☐ All decisions taken during screening will be documented and outlined in the final report with a list of excluded studies and justification of exclusion

	(summary justification for title/abstract exclusions, full citations and justifications for full-text exclusions). [OR] ☒ Studies that are found to be relevant at title/abstract but not included in the final list of studies evaluated are to be listed with a brief justification of why they were excluded.

Data collection and analysis

Expertise	☒ Data extraction will be performed by content expert [TH]. ☐ Data extraction will be performed by [initials] based on framework developed and demonstrated by [specify content expert/methodologist etc and initials].
Data to be extracted from primary studies or other relevant evidence	☒ Details on the review/study [including citation information, publication status, type of study, sample size, and summary of methods] ☒ Population, setting, exposure, comparison and outcome characteristics (PECO) of the study ☒ Data relevant to answering the research questions, along with definitions of outcomes measured, measurement instruments/tools used, and the main conclusions of the study. Where multiple numerical results are presented, all will be extracted. ☐ Other relevant information that should be considered by NHMRC and the Committee [please specify]
Data extraction methods	☒ Single, no second reviewer ☐ Dual; second reviewer checks all data ☐ Dual; second reviewer checks [add proportion] ☐ Dual; independent extraction and cross check [add proportion]
Analysis	☒ Results will be tabulated across studies, grouping together studies of relevance to each research question, and by study design. ☒ Synthesis will be conducted [e.g., presenting combined raw data for same health outcome]. The following tables will be presented: ☒ Table to compare PECO characteristics/ study design features ☒ Table of potential guideline options, comparisons and assumptions

	☐ Table of extracted numerical data for compilation of meta-analyses. Where multiple eligible numerical results are reported from a single study, all will be reported. ☒ Other [Comparisons will likely be presented for: • Overall certainty of evidence for different health endpoints. • Threshold doses (internal and/or external) of lead (if possible) associated with no adverse effects and critical adverse health effect. This may be presented (in the form of a heat map, for example) along with study bias/quality.]
Risk of Bias for included primary studies	☐ Included primary studies will be assessed for Risk of Bias and a narrative summary provided ☒ Included primary studies will be assessed with a Risk of Bias tool [e.g., OHAT/modified OHAT[2] (**Appendix C**)], and information provided about the outcomes as a rating
Overall confidence in results	☒ Overall confidence in body of evidence assessed by a content expert and a narrative summary provided ☒ Overall confidence in body of evidence assessed with regard to Risk of Bias, indirectness/applicability, imprecision, inconsistency between studies and publication bias and any additional factors, with information provided about the outcomes as a rating (e,g. GRADE or OHAT)
Reporting	A summary of relevant studies will be tabulated for consideration by the Water Quality Advisory Committee. See Reporting section below.

Supporting information in factsheet

Questions relating to currency and/or need to update the supporting information in factsheets were covered in the Stage 1 review and are not covered here. The information from the Stage 1 review will be integrated into the final factsheet updates.

Reporting

Evidence Evaluation and Technical Reports

The Evidence Evaluation Report will interpret, synthesise and summarise the findings of the evidence review and address the research questions. This Report will contain high-level information only.

[2] See Appendix C

The Technical Report will contain technical information about the review methodology and any other details relating to the Evidence Evaluation Report. The Technical Reports will describe all details of the methodology used that would be too exhaustive for the Evidence Evaluation Report.

Section	Description of content	Evaluation Report	Technical Report
Executive summary	Overarching statement about review and findings	☒	☐
Introduction and Background	Definitions (key terms, outcome measures, abbreviations), rationale for review and objectives.	☒	☐
Research question/s	Questions underpinning the review for health-related advice	☒	☒
Evidence Evaluation Methods	Brief overview of the approach taken for evidence search and evaluation (reference complete details in Technical Report)	☒	☐
	Approach used to identify and retrieve relevant primary studies [see **Appendix A** for the type of information that can be included in a search strategy]	☐	☒
	Process for selecting studies (i.e. application of inclusion/exclusion criteria) and list of included and excluded studies.	☐	☒
	Methods for data extraction and completed table of extracted data for each piece of evidence	☐	☒
	Methods of assessing quality of primary studies (i.e. use of risk of bias tool). Completed copy of risk of bias tool for each included primary study (**Appendix C**).	☐	☒
	Methods used to analyse/synthesise/summarise or compare data from different sources. Summary of findings tables directly comparing data from different sources and uncertainty.	☒	☒
	Methods used for any calculations and explanatory text for any assumptions if used (can have different levels of information about this in each Report)	☒	☒
Results	Summary of findings tables for each research question. Easy to compare different studies in	☒	☒

	Evaluation Report, more detailed information in Technical Report if required.		
Discussion	Strengths and limitations of the included studies, comparison of existing literature, a discussion of gaps in the evidence (if identified during the evaluation of the evidence) and a suggestion of areas for further research (if required)	☒	☐
Conclusion	Summary of recent evidence and options for guideline values (if any). Note: a recommendation is not part of the process. Recommendations will be made by the Water Quality Advisory Committee.	☒	☐
Review team	List members of Review Team	☒	☐
Declared interests	Documentation of the declared interest(s) of reviewers	☒	☐
Acknowledgements	Documentation of any inputs from individuals not on the Team	☒	☐
References	Included references	☒	☒
Appendices	Additional technical detail or examples of templates used in methods to be provided as required	☐	☒

Acknowledgements

Thanks to the members of the NHMRC Water Team and the NHMRC Water Quality Advisory Committee (the Committee) for their advice on this protocol.

Further information about the Committee, including membership can be found at Water Quality Advisory Committee 2022 – 2025 | NHMRC

Declaration of interests

Team member	**Declaration of interest**
Ms Tarah Hagen	As part day-to-day consulting activities at SLR Consulting, Ms Hagen has:

	• Conducted numerous health risk assessments for mining clients where lead was one of the chemicals of potential concern requiring assessment. • Determined appropriate hazard and dangerous goods classifications for lead-containing mineral products (e.g. concentrates) for clients in the mining industry. • Provided the report "Assessment of International and National Agency Processes for Deriving HBGVs and DWGs" to the NHMRC and also conducted the Stage 1 review of the work described herein.
Mr Giorgio De Nola	As part day-to-day consulting activities at SLR Consulting, Mr De Nola has been involved in numerous health risk assessments as part of contaminated land audits as well as for developer clients where lead was one of the chemicals of potential concern requiring assessment. He was also involved in the Stage 1 review of the work described herein.
Ms Maria Consuelo Reyes Campos	No interest to declare.

References

1. Cochrane (2021). COVID Rapid Review Protocol Template. Accessed 19 February 2021. Available from: https://covidreviews.cochrane.org/sites/covidreviews.cochrane.org/files/public/uploads/covid-19_rr_protocol_template_v4.docx

2. ATSDR (2020). Toxicological Profile for Lead, Agency for Toxic Substances and Disease Prevention, U.S. Department of Human health and Services. Atlanta, US https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf.

3. WHO (2017). Guidelines for drinking-water quality. Fourth edition incorporating the first Addendum, World Health Organization. Geneva. https://apps.who.int/iris/bitstream/handle/10665/254637/9789241549950-eng.pdf;jsessionid=8A179F96A66DD2F070E785831CAB3180?sequence=1.

4. NHMRC (2021). Australian Drinking Water Guidelines 6 2011- V 3.6 (March 2021 update) National Health and Medical Research Council . Canberra, Australia.

5. IARC (2006). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 87. Inorganic and Organic Lead Compounds. World Health Organization. International Agency for Research on Cancer Lyon France.

6. NHMRC (2015). NHMRC information paper: evidence on the effects of lead on human health. National Health and Medical Research Council. May 2015.

7. OEHHA (2009). Public Health Goal for Lead in Drinking Water. Pesticide and Environmental Toxicology Branch. Office of Environmental Health Hazard Assessment. April 2009.

Appendix A – Search strategy and selection of evidence

Example template of documenting a search strategy and how evidence is selected (if required).

Outline specific steps that will be taken to search and select the evidence in enough detail that someone else could reasonably replicate the search, including details such as:

Search terms	[List and define keywords and suggested search string combinations that you will use to search for publications based upon the PECO elements and research questions (present in table if possible) – these will have to be used across all databases for consistency with minor adjustments as appropriate to each database. If there are multiple research questions to answer, several different searches may need to be undertaken.]
Databases	[List at least two databases that will be searched using the agreed search terms (e.g. PubMed, Scopus, Scifinder).]
Publication date	[Specify the publication date range that will be searched across all databases including justifications for any specific date ranges (e.g. for a guideline update NHMRC usually searches from the date of the last literature search so there is no duplication of effort, but if some key pieces of evidence were not considered in the last review these may also be included with justification)]
Language	[Specify the language of publications that the search will be limited to (this is important when there are limited resources to translate publications)]
Study Type	[State what types of publications will be accepted to answer the research question, or what hierarchy will be used by the reviewer in the event that limited evidence is available. State what types of publications will not be accepted.]
Inclusion and exclusion criteria	[Define any other criteria that can be applied to the evidence to select studies for appraisal; and importance (priority rating) of outcomes to be considered as part of the review.]
Validation methods used (if any)	[Details on how you will validate the search strategy and check that it works before you undertake a full search, e.g. performing an initial search based upon the chosen search terms and checking against key publications as determined by the reviewer or expert committee. Include a description of how you will refine the process based on these initial results (e.g. adding/modifying criteria or filters)]
Screening methods	[Details on how you will efficiently screen the results of your search (which can sometimes retrieve thousands of publications). For example, will you only screen the titles or

	abstracts for key words? Will publications that you aren't sure about be screened at full text?]
Quality check	[Methods for checking that key publications have been picked up the search – are there any omissions or missed papers from the database searches?]
Grey literature	[Detail how you will search and retrieve any grey literature (e.g. define what kind of grey literature you will be looking for, what search engines or websites you will use, list any agencies/organisations that will be contacted for information and how this will be done).]
Documentation of search	[Explain how this process will be recorded (e.g. using a PRISMA diagram (Moher et al. 2009)). Explain how you will record which publications were found but excluded with justification.]
Retrieval of publications	[Describe how you will obtain publications, collate papers for review into a literature database (e.g. Endnote) and store in secure backup storage]

Appendix B – Data extraction template

General information	Study ID	
	Date template completed	
	Authors Publication date Publication type Peer reviewed Country of origin Source of funding Possible conflicts of interest	
Study characteristics	Aim/objectives of study Study type/design Study duration Type of water source (if applicable)	
Population characteristics	Population/s studied Selection criteria for population (if applicable) Subgroups reported Size of study	
Exposure and setting	Type of water source (if applicable) Exposure pathway Source of chemical/contamination Comparison group(s)	
Study methods	Water quality measurement used Water sampling methods (monitoring, surrogates)	
Results **(for each outcome)**	Definition of outcome How outcome was assessed Method of measurement Number participants (exposed/non-exposed, missing/excluded) (if applicable)	

Statistics **(if any)**	Statistical methods used Details on statistical analysis Relative risk/odds ratio, confidence interval?	
Author's conclusion	Interpretation of results Assessment of uncertainty (if any)	
Reviewer comments	Results included/excluded in review (if applicable) Notes on study quality e.g. gaps, methods	

Appendix C – Risk-of-bias tool – modified OHAT

To be completed for each study. To discuss with the NHMRC project team before applying modified tool to different study types.

Table x: Risk-of-bias assessment tool for individual studies adapted from OHAT RoB tool (Table 5 in OHAT Handbook (OHAT, 2019)).

Questions and domains that are not applicable to Cohort, Case studies and Observational studies greyed out – this can be amended as required. Refer to OHAT Handbook for more information.

Study ID: **Study Type:**		**RoB:** **Yes/No** **Unknown** **N/A**	**Notes**	**Risk of bias rating** **(--/-/+/++)**
Q				
	Selection bias			
1.	**Randomization**	**N/A**	Randomization: not applicable	
2.	**Allocation concealment**	**N/A**	Allocation concealment: not applicable	
3.	Comparison groups appropriate -			
	Confounding bias			
4.	Confounding (design/analysis) -			
	Performance Bias			
5.	**Identical experimental conditions**			

6.	**Blinding of researchers during study?**			
	Attrition/Exclusion Bias			
7.	**Missing outcome data**			
	Detection Bias			
8.	**Sample characterisation**			
9.	**Outcome assessment**			
	Selective Reporting Bias			
10.	**Outcome reporting**			
	Other Sources of Bias			
11.	**Other threats** (e.g. statistical methods appropriate; researchers adhered to the study protocol)			
	Overall risk of bias rating:			

Risk of bias rating:

Definitely low risk of bias (--)	--	Probably low risk of bias (-)	-	Probably high risk of bias (+)	+	Definitely high risk of bias (++)	++