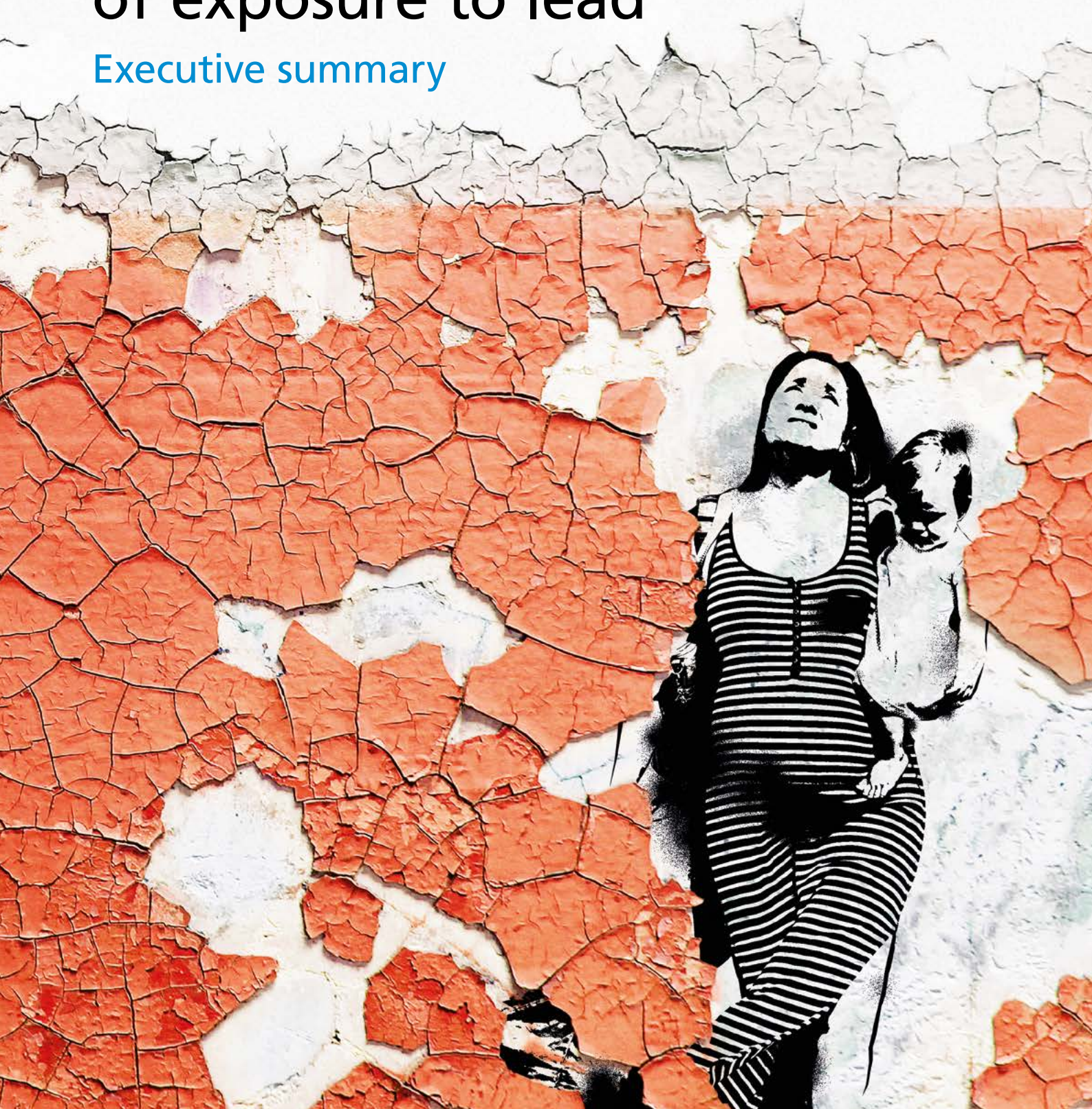
World Health Organization

WHO guideline for clinical management of exposure to lead

Executive summary



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Executive Summary

Purpose and scope

Lead is a widely used metal found in many compounds and products and which can give rise to life-threatening poisoning and long-term negative effects on health. Lead exposure is a significant public health concern; it is estimated to have accounted for 0.90 million deaths from long-term effects and 21.7 million disability-adjusted life years in 2019 *(1)*. Children are particularly vulnerable, and WHO has estimated that lead exposure accounts for 30% of the global burden of idiopathic developmental intellectual disability *(2)*. Individual lead poisoning cases continue to occur; in addition, there have been a number of mass lead-poisoning events around the world, mostly related to contamination of the environment or of food *(3–6)*.

The purpose of this guideline is to assist physicians in making decisions about the diagnosis and treatment of lead exposure for individual patients and in mass poisoning incidents. The guideline can also be used to inform evidence-based treatment protocols. It presents evidence-informed recommendations on interpretation of blood lead concentrations, gastrointestinal (GI) decontamination after ingestion of lead, nutritional supplementation to mitigate the effects of lead exposure and chelation therapy to facilitate elimination of lead. The guideline does not include discussion of methods for preventing lead exposure, such as screening and environmental and household interventions, which will be the subject of a separate guideline.

Methods for guideline development

This guideline was developed according to the procedure laid out in the WHO Handbook for Guideline Development *(7)*. For external contributors, conflict of interest was managed in accordance with WHO policy and procedures.

Work was guided by a steering group that comprised members of staff from WHO departments concerned with public health, environment and food safety at headquarters and in four regions. Development was supported by a guideline development group comprising 15 external experts from the six WHO regions, who provided expertise in public health, clinical toxicology, children's environmental health and lead poisoning prevention and management, including in low-resource settings. A group at the Medical Toxicology and Information Services (later, ESMS Global) in London, United Kingdom, was commissioned to conduct systematic reviews of evidence for the management of lead poisoning. Assessments of the certainty of evidence according to GRADE (grading of recommendations, assessment, development and evaluation) were carried out with the support of a team at the Department for Evidence-based Medicine and Clinical Epidemiology at Danube University, Krems, Austria.

The WHO steering group drafted the initial scope and outline of the guideline, an initial list of possible interventions and a set of research questions to be used for the systematic evidence reviews. The guideline development group extended this work and identified the critical and important outcomes relevant to the clinical management of lead exposure for which evidence would be assessed.

The threshold blood lead concentration for action was agreed by the guideline development group on the basis of extensive evaluations of the toxicity of lead at low levels of exposure carried out by WHO and national agencies. Evidence reviews were conducted for the following interventions: GI decontamination, chelation therapy and nutritional supplements. The review protocols were based on the model used by the Cochrane Collaboration. Systematic searches were carried out in bibliographic databases and clinical trial registers. No date limits were set for the literature searches for chelation therapy and GI decontamination, and the last searches were conducted in March 2020 and July 2020, respectively. For nutritional interventions, a date limit of 1990 was set, and the last searches were conducted in March 2020.

The quality of the body of evidence for chelation therapy in non-pregnant individuals and for nutritional supplements was assessed with the GRADE approach, in which the certainty of evidence for each outcome in the studies found was rated as "high", "moderate", "low" or "very low". This was based on ratings of study design limitations, inconsistency of results, indirectness, imprecision and publication bias. Evidence profiles were constructed for each outcome, which included assessment and judgement of the criteria. The final rating of the certainty of evidence was based on further consideration of these criteria.

At meetings of the guideline development group, the evidence found in each review was presented, with a GRADE evaluation. The guideline development group took note of the evidence, formulated recommendations and proposed the strength of each recommendation. In addition to the certainty of the evidence, the following factors were considered in determining the strength and direction of the final recommendations: values and preferences, the balance of benefits and harms, resource implications, equity, acceptability and feasibility. GRADEPro guideline development tool evidence-to-decision tables

(https://gradepro.org/) were used to note and synthesize these considerations and record the reasons for the strength of the recommendations.

Strong recommendations are those for which the group was confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For a conditional recommendation, the group concluded that the desirable effects of adherence probably outweigh the undesirable effects but was not confident of this interpretation. The interpretations were also considered from the perspectives of patients, physicians and policy-makers.

Each recommendation was adopted by consensus, defined as agreement by at least 80% of the participants. Recommendations were drafted in face-to-face meetings of the guideline development group and finalized in a series of online meetings and email discussions.

In the course of discussing the recommendations, the guideline development group identified three good practice statements. These were not identified through systematic evidence retrieval, synthesis and grading but are considered good clinical practice according to clinical experience in the management of patients with lead exposure.

Informal consultations on the recommendations were held at two WHO technical meetings, in Ahmedabad, India, in June 2017 and in Cairo, Egypt, in December 2018. The external reviewers included clinicians who would potentially be users of the guideline when managing cases of lead exposure.

The draft guideline was reviewed by eight external peer reviewers. The guideline was revised and then finalized in a series of online and email discussions of the guideline development group between July 2020 and July 2021.

Background and sources of lead exposure

There are many sources of lead exposure due to its widespread use and environmental contamination. Most of the lead in the environment is due to human extraction, processing and use of lead. Lead has many uses, in particular in storage batteries, ammunition, pipes and many alloys such as those used for solder. Inorganic lead compounds are found in pigments, paints, glazes and plastics. Lead and lead compounds are also found in some cosmetics, traditional medicines and spices. Organic lead compounds were used extensively as additives in petrol, but this use is now banned in all countries.

There are multiple sources and pathways of exposure. The most important routes of exposure to lead and its compounds are ingestion and inhalation. Most cases of oral lead poisoning result from regular ingestion of small amounts of lead-containing material such as contaminated dust or soil, flakes of lead paint, contaminated food and spices, lead-containing traditional medicines or from ingestion of a lead foreign body. Young children are particularly likely to ingest contaminated soil and dust. Inhalation of lead as fumes or particles is a major occupational route of exposure.

Absorption of lead from the GI tract is affected by dietary factors, age, nutritional status, genetic factors and the form of the lead. Infants and young children absorb a greater proportion of ingested lead than adults. Fasting and dietary deficiencies of iron or calcium are reported to enhance absorption.

Once absorbed, lead is initially bound to erythrocytes in the blood and is distributed to soft tissues and bone. Blood and soft tissues represent the active pool and bone the storage pool. The blood lead concentration reflects recent exposure to lead from exogenous sources and, when there has been previous exposure to lead, also includes lead redistributed from skeletal stores. In individuals who are exposed chronically, bone contains > 90% of the body burden of lead in adults and > 70% in children. Lead can be released from bone during metabolic processes that increase bone turnover, such as occur during pregnancy, lactation and the menopause.

Exposure to lead, even at very low levels, has been associated with a range of negative health effects, and no level without deleterious effects has been identified *(8–10)*. Young children are particularly vulnerable to the neurotoxic effects of lead, which include impaired cognitive and behavioural development that can have life-long impacts *(11)*. The effects of the greatest public health significance, i.e. adverse neurodevelopmental effects in children and cardiovascular disease in adults, are nonspecific and largely subclinical. There is considerable inter-individual variation in the dose-response relation for lead toxicity, and the presenting signs and symptoms are highly variable in both adults and children.

The toxic effects include GI features such as anorexia, abdominal pain, nausea, vomiting, diarrhoea or constipation; neurological features such as headache, lethargy, irritability, ataxia, tonic-clonic convulsions, opisthotonus, cerebral oedema and raised intracranial pressure; haematological features such as anaemia, possibly with basophilic stippling; and signs of renal and hepatic dysfunction. Lead encephalopathy is more common in children than adults, and survivors may have sequalae such as mental retardation and convulsive disorders.

Diagnosis of lead poisoning

Diagnosis of lead poisoning and treatment decisions are based on the history, clinical examination and the results of investigations, including the blood lead concentration, biomarkers of effect such as in a full blood count and, if relevant, medical imaging. The venous blood lead concentration is the definitive biomarker of exposure and risk on which management decisions are routinely based. Information about the collection and analysis of blood samples for lead can be found in WHO guidance *(12)*.

Results of the evidence review

A systematic evidence review was not considered necessary to determine the threshold blood lead concentration at which interventions should be initiated to manage lead exposure and poisoning because reviews by international and national bodies, including WHO, were already available *(8–10, 13)*, which document the adverse health impacts of lead, particularly at low exposure levels of 5 µg/dL and below.

For GI decontamination, evidence was available only from case reports and case series and was therefore rated as of very low certainty *(14)*. The nature of ingestion was diverse. The most commonly reported measures used were removal of the lead-containing material from the GI tract and the blood lead concentration, although the latter was often confounded by administration of chelation therapy.

For nutritional interventions, several randomized controlled trials (RCTs) were found for calcium, iron and zinc supplementation *(15)*. For calcium, four small, RCTs were identified in children, one in pregnant women and one RCT plus a linked non-randomized study in lactating women. In the case of iron, three RCTs were identified in children. These provided very low-certainty evidence that calcium supplementation is associated with a small reduction in the blood lead concentration in children, and moderate-certainty evidence was available of a small reduction in pregnant women. There was also low-certainty evidence of a reduction in blood lead concentration in lactating women and very low-certainty evidence of a faster decline in breastmilk lead concentrations and a reduction in the release of lead from bone as compared with the placebo group. Studies of iron supplementation in iron-deficient children provided very low-certainty evidence of a small reduction in the blood lead concentration. For children who were not iron-deficient, there was moderate-certainty evidence of no effect on blood lead concentration or cognitive or behavioural outcomes. An RCT of zinc supplementation in children provided moderate-certainty evidence of no effect on blood lead concentration or cognitive or behavioural outcomes.

There were a few RCTs on chelation therapy in non-pregnant patients, and the other types of controlled study were subject to a high risk of bias *(16–19)*. Most of the evidence was from case series, which were confounded by the effect of removal from lead exposure. Low-to-moderate-certainty evidence was identified for a lack of benefit on short- and long-term outcomes in children with blood lead concentrations < 45 µg/dL *(19)*.

For patients with higher blood lead concentrations, very low-certainty evidence was found for reduction of the blood lead concentration, increased urinary excretion of lead, improvement in signs and symptoms of lead poisoning in all age groups and reduced mortality in children. For pregnant women, the only evidence identified was from case reports and was, therefore, of very low certainty *(20)*. The main outcomes reported were maternal and newborn blood lead concentrations, and it was not possible to draw conclusions about the impact of chelation on other outcomes, such as reversal of toxic effects in the fetus.

There were insufficient studies for a meta-analysis of the evidence, and the reviews were qualitative. In view of the mainly low- or very low-certainty evidence, recommendations were informed by the clinical experience of guideline development group members. Tables summarizing the findings for each intervention and the evidence-to-decision tables that explain the decisions for reaching each recommendation are available online *(21)*.

The guideline development group agreed that the following guiding principles were applicable to all the recommendations for clinical management of exposure to lead. The agreement was based on consensus and not on systematic evidence retrieval, synthesis or grading.

- Action should be taken as soon as possible to terminate or reduce lead exposure. Lead has no physiological role in the body, and no level of exposure has been identified that does not have a deleterious effect *(8, 9)*. As long as exposure continues, lead will be absorbed, with consequent negative effects on health; further, lead will also be stored in tissues and bone, forming a sink from which it can be remobilized back into blood. All lead exposure is potentially preventable *(22)*.
- Chelation therapy is of limited value during continuing exposure. It may, however, be necessary as a life-saving measure for children with severe poisoning who continue to be exposed, for example when it is not immediately possible to remove lead from the GI tract or until the source of exposure has been identified and terminated.
- As the medical management of people exposed to lead can be complex, it is advisable to seek advice from a clinical toxicologist or other medical practitioner with experience and expertise in the management of lead poisoning. This is particularly important if use of chelation is being considered before exposure has been addressed.

Summary of WHO recommendations for clinical management of lead exposure

The WHO recommendations are summarized in the table below. Note that, in all cases of lead exposure, action should be taken to identify the source of lead and stop ongoing exposure, as this will, in itself, reduce the blood lead concentration and improve clinical features of toxicity.

No.	Recommendation	Strength of recommendation *(certainty of evidence)*
Blood lead concentration that should initiate clinical intervention		
1	In all cases of suspected or confirmed lead exposure the patient or carer should be given information about potential sources of lead exposure, methods for reducing continuing exposure and the importance of good nutrition, in particular adequate dietary intake of iron and calcium.	**Good practice statement**
2	For an individual with a blood lead concentration ≥ 5 µg/dL, the source(s) of lead exposure should be identified and appropriate action taken to reduce and terminate exposure.	**Strong** *(high-certainty evidence of the toxicity of low-level exposure to lead)*
Gastrointestinal decontamination after ingestion of a lead foreign body or other lead-containing material		
1	Take measures to remove solid lead objects, such as bullets, lead pellets, jewellery, fishing or curtain weights, that are *known to be in the stomach.*	**Strong** *(very low-certainty evidence)*
2	Consider whole bowel irrigation (WBI) for removing solid lead objects, such as bullets, lead pellets, jewellery, fishing or curtain weights, that are *known to have passed through the stomach.* Remarks If WBI fails, i.e. the object or objects are not removed, and there is evidence of lead absorption, e.g. an increasing blood lead concentration or features of lead toxicity, consider endoscopic or surgical removal.	**Conditional** *(very low-certainty evidence)*
3	Consider surgical removal of solid lead objects, such as bullets or lead pellets, that are known to be in the appendix *if the patient shows clinical signs of appendicitis or an increasing blood lead concentration.* Remarks If the patient is clinically well, surgical removal is not necessary, but the blood lead concentration should be measured periodically to check for lead absorption. Treatment options should be reviewed if the patient becomes symptomatic or if the blood lead concentration starts rising.	**Conditional** *(very low-certainty evidence)*

No.	Recommendation	Strength of recommendation *(certainty of evidence)*
4	Consider WBI for removing liquid or solid lead-containing substances, such as paint chips, lead-containing complementary or alternative medicines, or ceramic glaze, *when this material is known to be dispersed in the gut.*	**Conditional** *(very low-certainty evidence)*

Nutritional interventions in children and pregnant and lactating women exposed to lead

Children ≤ 10 years of age

1	For a child (≤ 10 years) with a blood lead concentration ≥ 5 µg/dL *who has, or is likely to have, inadequate calcium intake,* administration of calcium supplementation is recommended. Remarks The dose should be sufficient to ensure that the total calcium intake meets the national age-appropriate recommended nutrient intake value.	**Strong** *(very low-certainty evidence)*
2	For a child (≤ 10 years) with a blood lead concentration of ≥ 5 µg/dL *who has, or is likely to have iron-deficiency,* administration of iron supplementation is recommended. Remarks The dose should be in line with WHO guidelines *(23, 24)* or standard clinical practice.	**Strong** *(very low-certainty evidence)*

Pregnant women

1	For a pregnant woman with a blood lead concentration of ≥ 5 µg/dL, *who has, or is likely to have, inadequate calcium intake,* administration of calcium supplementation is recommended	**Strong** *(moderate-certainty evidence)*