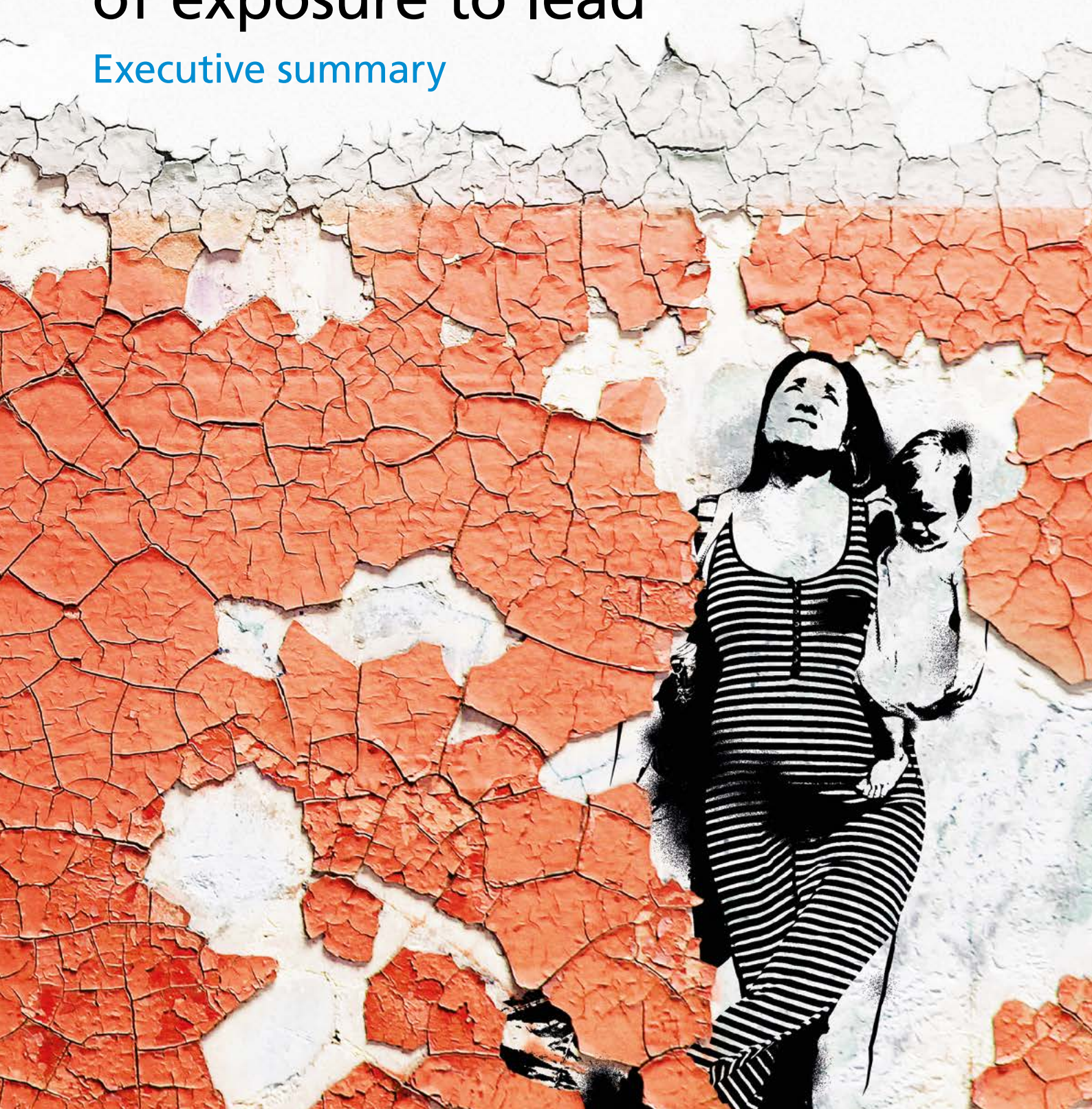
World Health Organization

WHO guideline for clinical management of exposure to lead

Executive summary



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WHO acknowledges the technical input of the guideline development group: Mohammad Abdollahi (Department of Toxicology and Pharmacology, Tehran University of Medical Sciences, Islamic Republic of Iran), Maha Khalid Al Mazrou'a (Regional Poison Control Centre-Dammam, Saudi Arabia), Yona Amitai (Department of Management, Bar Ilan University, Israel), Mary Jean Brown (Harvard Chan School of Public Health, Boston (MA), United States of America (USA)), Chulathida Chomchai (Mahidol University, Nakhon Pathom, Thailand), Paul Dargan (Guy's and St Thomas' National Health Service Foundation Trust, London, United Kingdom), Aruna Dewan (Centre for Education, Awareness and Research on Chemicals and Health, Ahmedabad, India), Amalia Laborde (Centre for Toxicological Information and Advice, Faculty of Medicine, Clinical Hospital, Montevideo, Uruguay), Philip J Landrigan (Schiller Institute for Integrated Science and Society, Boston College, Boston (MA), USA), Byung-Kook Lee (Institute of Environmental and Occupational Medicine, Soonchunhyang University, Seoul, Republic of Korea), Angela Mathee (Environment and Health Research Unit, South African Medical Research Council, Johannesburg, South Africa), Nguyen Trung Nguyen (Poisons Centre, Bach Mai Hospital, Hanoi, Viet Nam), Orish E Orisakwe (Toxicology Unit, Faculty of Pharmacy, University of Port Harcourt, Nigeria), Natalie Thurtle (St George's Hospital, Sydney, Australia) and Thuppil Venkatesh (National Referral Centre for Lead Poisoning in India, Bangalore, India). Particular thanks go to David Bellinger (Harvard Medical School Children's Hospital, Boston (MA), USA) for ably chairing the meetings of the guideline development group.

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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. Remarks The dosage should be sufficient to bring the total calcium intake to national guidelines for calcium in pregnant women or to the WHO/FAO-recommended nutrient intake value (1.2 g) *(25)*. This should be given as soon as the pregnancy is recognized, for the duration of the pregnancy.	**Strong** *(moderate-certainty evidence)*

Lactating women

1	Initiation or continuation of calcium supplementation is suggested for lactating women who have a blood lead concentration of ≥ 5 µg/dL. This should be for the duration of lactation.	**Conditional** *(low- to very low-certainty evidence)*

No.	Recommendation	Strength of recommendation *(certainty of evidence)*
Chelation therapy in individuals exposed to lead		
Children ≤ 10 years of age		
1	For a child (≤ 10 years) with a blood lead concentration ≥ 45 µg/dL, oral or parenteral chelation therapy is recommended.	**Strong** *(very low-certainty evidence)*
2	For a child (≤ 10 years) with a blood lead concentration of 40–44 µg/dL, when there is doubt about the accuracy of the measurement, a persistently elevated blood lead concentration in spite of measures to stop exposure or significant clinical features of lead poisoning, oral chelation therapy should be considered.	**Conditional** *(very low-certainty evidence)*
3	For a child ≤ 10 years with a blood lead concentration ≥ 70 µg/dL, there should be close monitoring for signs of clinical deterioration, including regular neurological assessments, during and after chelation therapy while the concentration remains high.	**Good practice statement**
4	For a child (≤ 10 years) with lead encephalopathy, urgent hospital admission and parenteral chelation therapy are recommended.	**Strong** *(very low-certainty evidence)*
Non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentration 45–70 µg/dL		
1	For a non-pregnant adolescent girl or woman of child-bearing age who has a blood lead concentration of 45–70 µg/dL but who *does not* show clinical features of lead poisoning, oral chelation therapy should be considered.	**Conditional** *(very low-certainty evidence)*
2	For a male patient aged ≥ 11 years or a woman who is no longer of child-bearing age who has a blood lead concentration of 45–70 µg/dL but *who does not* show clinical features of lead poisoning, chelation therapy is not indicated. The patient should, however, be re-evaluated within 2–4 weeks to ensure that the blood lead concentration is decreasing and the patient remains well.	**Conditional** *(very low-certainty evidence)*

No.	Recommendation	Strength of recommendation *(certainty of evidence)*
3	For a non-pregnant adolescent or adult with a blood lead concentration of 45–70 µg/dL and who *has mild–moderate* clinical features of lead poisoning (such as abdominal pain, constipation, arthralgia, headache, lethargy), chelation therapy is suggested.	**Conditional** *(very low-certainty evidence)*
Non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentrations of > 70–100 µg/dL		
1	An adolescent or an adult with a blood lead concentration > 70–100 µg/dL should be closely monitored for signs of clinical deterioration, regardless of whether chelation therapy is given.	**Good practice statement**
2	For a non-pregnant adolescent or an adult with a blood lead concentration > 70–100 µg/dL but who *does not show significant neurological features of toxicity,* chelation therapy is suggested.	**Conditional** *(very low-certainty evidence)*
3	For a non-pregnant adolescent or adult with a blood lead concentration > 70–100 µg/dL and with *significant neurological features of lead toxicity* (e.g. irritability, drowsiness, ataxia, convulsions, coma) or *lead encephalopathy,* urgent parenteral chelation therapy is recommended.	**Strong** *(very low-certainty evidence)*
Pregnant women		
1	For a pregnant woman *with lead encephalopathy,* regardless of trimester, urgent chelation therapy is recommended. The preferred chelating agent depends on the stage of the pregnancy and available data on safety of use in pregnancy.	**Strong** *(very low-certainty evidence)*
2	For a pregnant woman with a blood lead concentration ≥ 45 µg/dL, with or without clinical features of lead poisoning, but *without lead encephalopathy:* i. in the first trimester: the guideline development group could not make a recommendation because of an uncertain balance of risks and benefits; ii. in the second or third trimester: chelation therapy is recommended.	**No recommendation** **Strong** *(very low-certainty evidence)*

The anticipated outcomes of these WHO recommendations are reduced likelihood, improvement in or resolution of lead-related health impacts. It is expected that these would be valued by the patient, their carer in the case of children and by society as a whole.

Health equity considerations include the fact that individuals in economically deprived and disadvantaged populations bear the greatest burden of lead exposure, particularly in low- and middle-income countries *(1, 26)*. Other sources of vulnerability may exacerbate the health impacts of lead exposure, including a high prevalence of nutritional deficiencies. Addressing these will have important benefits, independently of termination of lead exposure, but is not a substitute for the latter. Pregnant women in low- and middle-income countries who are poor, not well educated and live in rural areas have lower coverage with health interventions and worse health outcomes than more advantaged women *(27)*. They are also more likely to have inadequate calcium intake *(27)*. Provision of calcium supplements, particularly if part of a programme of antenatal and postnatal support, could improve health outcomes. In settings where working with lead is an important livelihood, options for stopping exposure may be limited. This is particularly true where individuals or communities lack the necessary influence or power to improve their work or environmental conditions.

Feasibility considerations include lack of resources and expertise for the diagnosis and treatment of lead poisoning; the availability of chelating agents is limited in many low- and middle-income countries *(28)*, although the four recommended chelating agents are included in the WHO Model List of Essential Medicines *(29)*. The diagnosis of lead exposure requires access to analytical laboratory services; however, screening can be carried out by analysis of a capillary blood sample in a point-of-care analyser, which is relatively low-cost and simple to operate *(12)*. The feasibility and acceptability of terminating lead exposure depend on the source of exposure and availability and the costs of the required intervention(s). At low blood lead concentrations, the toxic effects will be mainly subclinical and, without understanding of the potential long-term impacts of exposure, there may be less motivation to take action.

Considerations for implementation of the recommendations

General considerations

Health-care providers, in particular family doctors, community health nurses, paediatricians, obstetricians and midwives, should be trained in identifying the risk factors for lead exposure and the prevention, diagnosis and management of lead poisoning.

Identification and confirmation of lead exposure require access to analytical equipment and laboratory services for measuring blood lead concentrations. WHO guidance is available on the selection of analytical methods and on establishing a laboratory service for this purpose *(12)*.

When lead exposure is suspected but the blood lead concentration is < 5 µg/dL, a follow-up measurement may be carried out after 6–12 months to rule out a continuing source of lead exposure.

Specific considerations

GI decontamination

The most appropriate method of GI decontamination varies from case to case. Factors to be taken into account include the size, nature and quantity of the lead object(s) or lead-containing material ingested, the time that the material has been in the stomach or other parts of the GI tract, evidence of lead absorption, the clinical condition of the patient and the availability of resources for the intervention.

Endoscopic procedures are standard practice for the removal of foreign bodies when there is a risk of harm to the patient, and evidence-based and evidence-informed clinical guidelines have been developed by national and international professional societies *(30–32)*. In the case of objects in the stomach, the use of oesophagogastroduodenoscopy may obviate surgery.

General skill in abdominal surgery (including laparoscopic methods) should be available at secondary and tertiary medical services. WHO guidance on appendectomy is available *(32)*.

WBI should be conducted only with an iso-osmotic polyethylene glycol-electrolyte solution.

Nutritional supplementation with iron and calcium

In all cases, nutrition counselling should be given to promote diet diversity and food combinations that improve calcium and iron absorption. This should be combined with counselling on methods for reducing lead exposure. For pregnant women, this information can be provided during routine antenatal care visits.

Calcium and iron may compete for absorption; therefore, if supplementation with both nutrients is required, they should be taken at different times of the day.

Calcium intake can be assessed by taking a dietary history and comparing intake with nationally recommended values. As the optimal dose for mitigating the effect of lead exposure is unknown, reference should be made to national intake value guidelines where possible or to WHO/FAO guidance *(25)*. Care should be taken in sourcing calcium supplements, as those derived from biological sources such as animal bone may be contaminated with lead. For children, it is suggested that their dietary calcium intake be

re-assessed after 3 months. If it is still inadequate and the blood lead concentration remains elevated, consideration should be given to a further period of supplementation. For pregnant women, calcium should be given for the duration of pregnancy and consideration given to extending administration into lactation.

Iron deficiency can be determined from an estimate of the serum ferritin concentration and a marker of inflammation (e.g. C-reactive protein or α1-acid glycoprotein) *(34)*. If this is not available, evaluation of anaemia is a non-specific marker of iron deficiency. Note that anaemia may also be a feature of lead toxicity. The optimal dose and duration of iron supplementation to mitigate the effects of lead exposure are unknown; therefore, reference should be made to WHO guidance for treating iron deficiency *(23, 24)*, which recommends a minimum treatment duration of 3 months, after which iron status should be re-assessed to evaluate continuation. In malaria-endemic areas, the possible harm of iron supplementation *(24)* should be balanced against the additional susceptibility of children with malaria to the neurotoxicity of lead *(35)* and the possibility that iron may be of benefit.

Chelation therapy

In application of these recommendations to individual patients, some room must be left for clinical judgement about potential vulnerability to lead toxicity, the circumstances, nature and chronicity of exposure, clinical features, the blood lead concentration or trends in concentrations, and the location of treatment. Some allowance may also be required for possible inaccuracy in the measurement of blood lead concentrations.

After chelation therapy, the blood lead concentration may rebound as lead stored in soft tissues and bone is released and the concentration in blood re-equilibrates. It is therefore important to re-check the blood lead concentration after a period for re-equilibration, to determine whether further chelation is necessary. An interval of 2–4 weeks is suggested, with the shorter interval for higher initial blood lead concentrations.

Admission to a treatment centre is advised in the following situations:

- The patient shows significant neurological features of toxicity, e.g. irritability, drowsiness, ataxia, convulsions, coma or lead encephalopathy.
- Parenteral chelation therapy is required.
- The patient is particularly vulnerable because of co-morbid conditions such as malaria.
- It is not otherwise possible to remove the patient from lead exposure, e.g. if their home environment is heavily contaminated and alternative accommodation is not available.
- It would otherwise be difficult to monitor the patient and the effectiveness of management measures, e.g. because of logistical issues.
- The ability of the patent to adhere to treatment is in doubt.

Selection of chelating agents

For non-pregnant patients, the evidence for the effectiveness of individual chelating agents and chelating agent combinations was of very low-certainty, and there were no good-quality studies in which chelating agents were compared alone or in combination.

For patients with severe lead poisoning, in particular lead encephalopathy, very low-certainty evidence suggests that chelation with succimer, sodium calcium edetate or dimercaprol, alone or in combination, could improve survival as compared with no chelation. It has been standard practice in some settings to treat lead encephalopathy with dimercaprol before giving sodium calcium edetate; however, the systematic evidence reviews did not find adequate evidence to determine whether this combination was more effective than alternative regimens. Penicillamine is used mainly for treating mild–moderate poisoning.

The availability and costs of chelating agents bear on the choice of agent for treating individual patients. The guideline development group made the following suggestions:

- for mild to moderate poisoning: succimer or penicillamine;
- for severe poisoning: sodium calcium edetate alone or in combination with succimer (if an oral medicine can be administered safely) or with dimercaprol.

For pregnant women in the first trimester, potential harm to the fetus by lead must be balanced against potential harm by the chelating agent. Limited data were available on the safety of chelation in pregnancy. The United States Food and Drug Administration categorizes the risk of fetal harm as follows: sodium calcium edetate is in category B (experimental animal studies do not demonstrate a risk to the fetus, and there are no adequate studies in pregnant women); succimer and dimercaprol are in category C (experimental animal data suggest a fetal risk); and penicillamine is in category D (known fetal risk) *(36)*.

In the second and third trimesters, teratogenicity is no longer a concern. On the basis of the available, but very limited, evidence and practical considerations, it is suggested that chelating agents be used on the same basis as in non-pregnant patients, described above. Ideally, chelation should be administered by or in consultation with medical practitioners experienced in the management of lead poisoning and the management of high-risk pregnancy.

While the decision to give chelation usually depends on measurement of the blood lead concentration, there may be circumstances, such as in an outbreak, in which there is strong evidence of widespread exposure to lead. In such circumstances, the guideline development group considered that it would be justified to initiate treatment in a patient of any age with encephalopathy while awaiting confirmation of the blood lead concentration.

The end-point of chelation therapy is not clear cut but should include resolution of clinical features of lead poisoning and a reduction in the blood lead concentration that is maintained on reassessment. Increases in blood lead concentration after chelation therapy are common and often related to remobilization of lead from bone stores, although it is also important to be alert to

potentially ongoing lead exposure. Some patients may require multiple courses of chelation therapy, and it is important to consider the risk–benefit of such therapy carefully, with input from an expert in the management of lead poisoning. If a patient has had four or five courses of chelation therapy and the blood lead concentration remains persistently > 45 µg/dL and has not fallen significantly from the baseline blood lead concentration, further investigation is strongly advised to determine whether measures to terminate exposure have been ineffective or whether there is a previously unrecognized source of lead exposure.

Integration and implementation of the recommendations in the management of lead poisoning

The WHO recommendations for specific aspects of the management of lead exposure should be integrated into an overall management plan for a case or cases of lead poisoning. Decisions about the management of lead poisoning should be made on the basis of the clinical condition of the patient, the circumstances of exposure, the blood lead concentration and the best interests of the patient according to the resources available for treatment.

Once lead exposure has been confirmed by measurement of an elevated blood concentration, the steps in management of exposure are:

- taking a history to identify the source(s) of exposure;
- evaluation of the severity of exposure by clinical examination and investigations;
- termination and mitigation of exposure, including improving nutrition;
- GI decontamination if indicated;
- chelation therapy if indicated;
- other supportive measures if required, for example for management of lead encephalopathy; and
- follow-up to determine whether further management measures are necessary.

Research implications

The systematic reviews of evidence identified very few good-quality studies of the effectiveness of the treatment interventions for lead exposure, and more evidence would increase the certainty of the recommendations. It is recognized, however, that, for some interventions, conducting RCTs would be ethically and/or practically difficult.

Gastrointestinal decontamination

Many variables influence the effectiveness of GI decontamination methods after ingestion of lead, and the number of cases of lead ingestion for which GI decontamination could be considered is probably small. This makes it difficult to accumulate a sufficient number of comparable cases for a meaningful study, and it is likely that any evidence of the effectiveness of methods of GI decontamination will continue to be based on case reports or small case series. These would be more useful if the interventions and outcomes were better documented.

Nutritional interventions

The available studies on nutritional interventions were conducted with patients who had relatively low blood lead concentrations, and they did not address the question of whether such interventions would be of benefit to patients with severe lead poisoning. In addition, there were no data on the value of combining nutritional supplementation with chelation therapy. This would be of interest, as chelating agents are known to also increase the elimination of some trace elements.

More and better studies are needed to determine whether the efficacy of increasing iron or calcium intake in the diet differs from that of supplements, as well as the optimal dose and duration of supplementation. Studies are also needed on the impact of calcium supplementation on outcomes other than blood lead concentration, e.g. neurocognitive development. Studies should also be conducted on whether different age groups, e.g. young children, adolescents or adults, benefit more.

Chelation therapy

Data are lacking on the impact of chelation therapy on longer-term outcomes, such as neurocognitive development, behaviour and cardiovascular disease. Also, the threshold blood lead concentration for chelation that is effective in improving outcomes in different age groups has not been established. More data are needed on adherence to treatment in out-patient settings and the link to outcomes. The safety of chelating agents in patients with glucose-6-phosphate dehydrogenase deficiency is not yet established. Better documentation of cases of chelation therapy in pregnancy should be provided.

Considerations for implementation of the guideline

WHO recognizes lead as one of 10 key chemicals of public health concern and is working with partners and policy-makers to raise awareness about the importance of preventing and managing lead exposure *(22)*.

To support implementation of this guideline, a derivative product will be developed that presents the recommendations in a format that can be more easily used by clinicians and that will be translated into other languages. A specific implementation plan will be developed, and the WHO regional offices and partners will take into account the challenges identified.

There are two important challenges to implementation of the guideline. The first is the limited availability of good-quality laboratory services for diagnosis of lead poisoning. WHO is advocating for greater availability of toxicology laboratories as a core capacity requirement under the International Health Regulations (2005). WHO's brief guide on methods for the analysis of lead in blood, published in 2020, is available in all six United Nations languages *(12)*.

The second challenge is the limited availability of chelating agents in many low- and middle-income countries, despite the inclusion of the four chelating agents on the WHO Model List of Essential Medicines. WHO will use the guidance to further advocate for greater availability of chelating agents as part of universal health coverage and improvements in the procurement of essential medicines through inter-country cooperation.

With regard to nutritional interventions, WHO is developing guidelines on single and multi-nutrient supplementation to improve the health of children and pregnant women. WHO is also working with FAO to update guidance on nutrient requirements for children.

WHO's initiative for strengthening and establishing poisons centres will be fully engaged in implementation of the guidelines, as these specialized centres are one of the target users.

Working with partners and, as resources permit, training workshops for health-care providers will be organized in selected countries on the identification of risk factors and the diagnosis and management of lead exposure, supplemented by online courses.

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World Health Organization

20 Avenue Appia • CH-1211 Geneva 27 • Switzerland

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