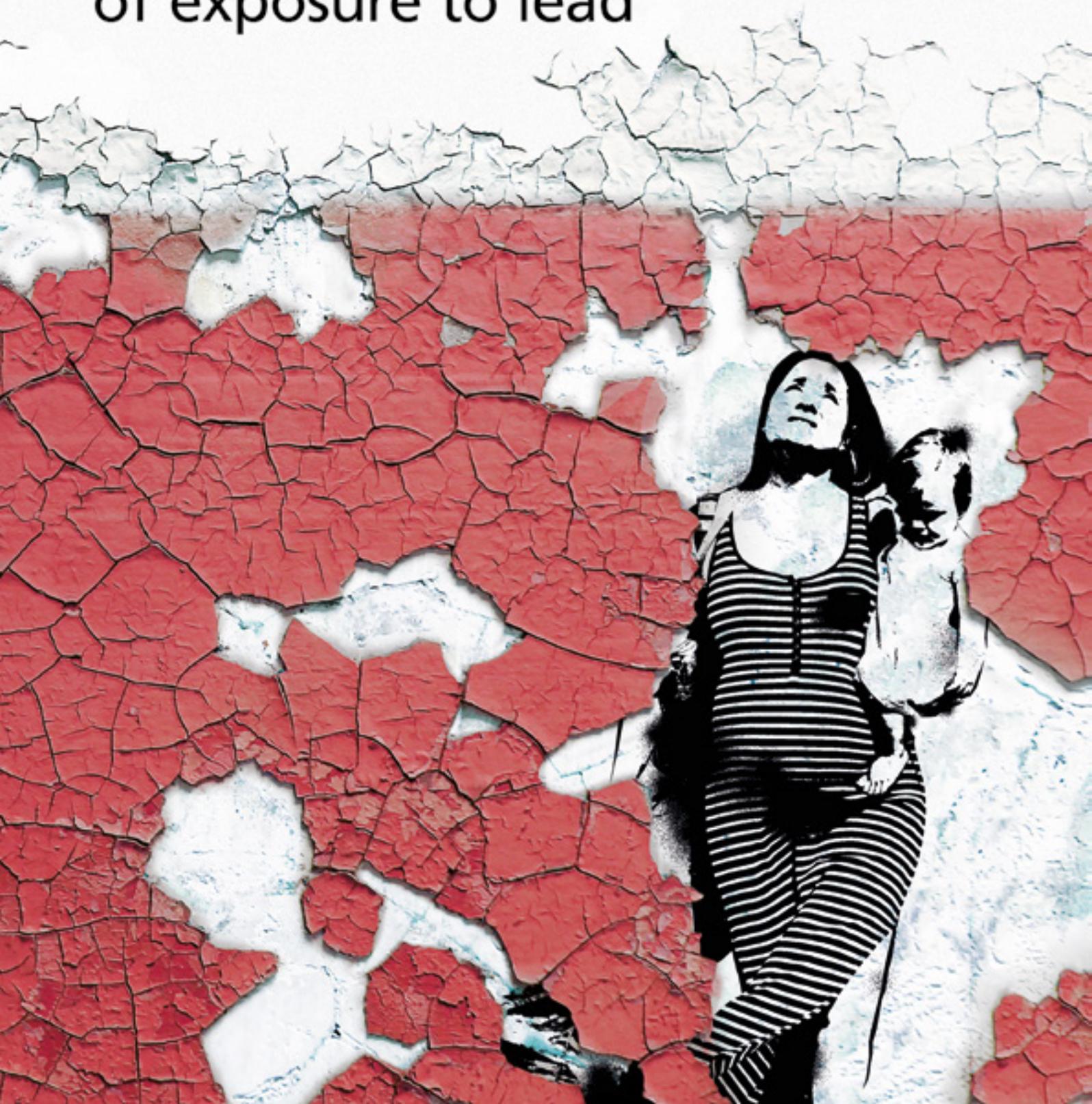




WHO guideline for clinical management of exposure to lead





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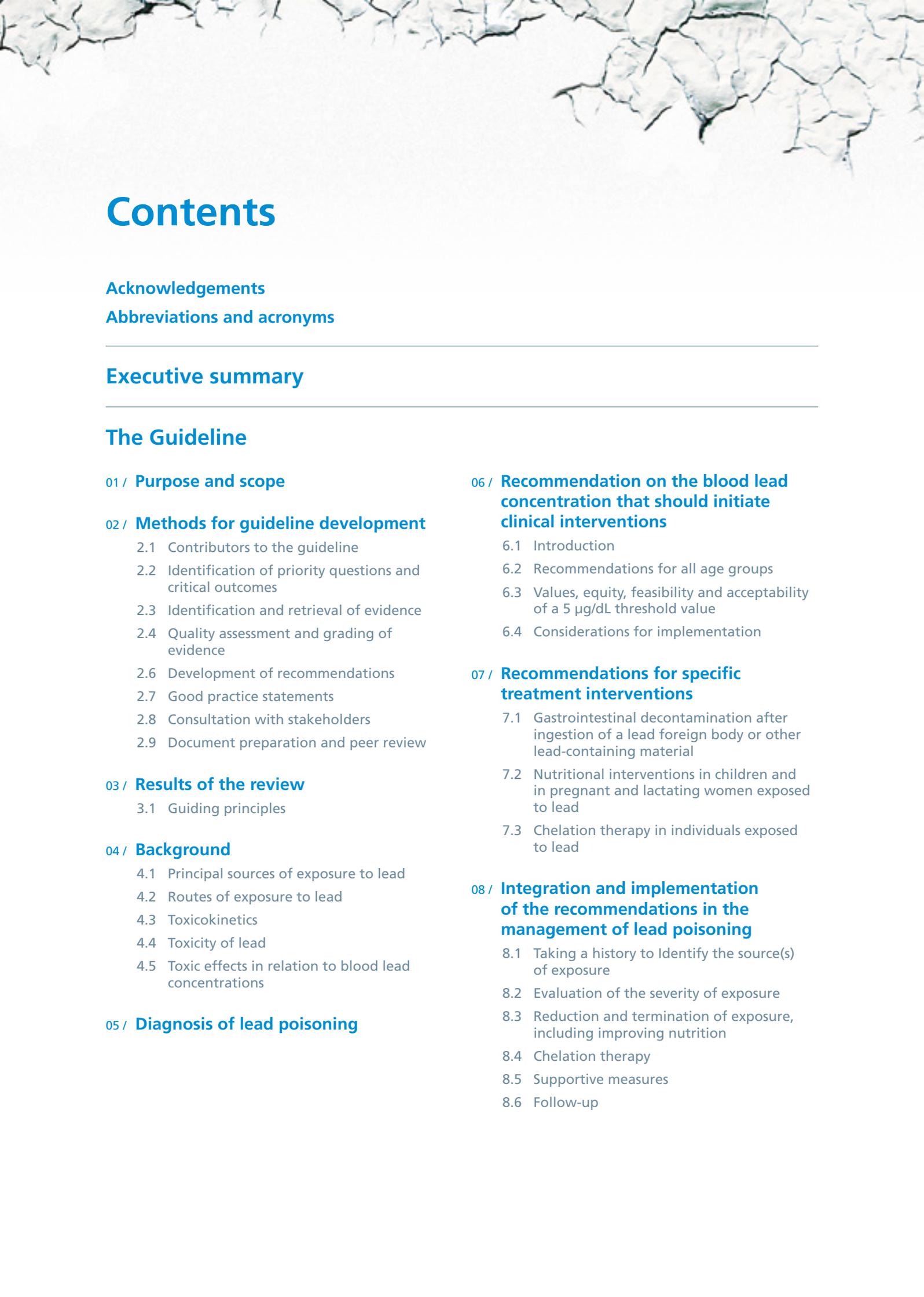
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Abbreviations and acronyms

CI	confidence interval
FAO	Food and Agriculture Organization of the United Nations
GRADE	grading of recommendations, assessment, development and evaluation
IQ	intelligence quotient
PbB	blood lead concentration
RCT	randomized controlled trial
TLC	treatment of lead-exposed children
WBI	whole-bowel irrigation

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. Children are particularly vulnerable, and WHO has estimated that lead exposure accounts for 30% of the global burden of idiopathic developmental intellectual disability. 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.

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*. 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://gradepr.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. Young children are particularly vulnerable to the neurotoxic effects of lead, which include impaired cognitive and behavioural development that can have life-long impacts. 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 sequelae 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.

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, 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. 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. 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. 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. 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. 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.

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. 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.
- 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

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 $\geq 5 \mu\text{g/dL}$, 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 a bullets, lead pellets, jewellery, fishing or curtain weights, that are <i>known to be in the stomach</i> .	Strong (very low-certainty evidence)
2	Consider whole bowel irrigation (WBI) for removing solid lead objects, such as a bullets, lead pellets, jewellery, fishing or curtain weights, that are <i>known to have passed through the stomach</i> . 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 a bullets or lead pellets, that are known to be in the appendix <i>if the patient shows clinical signs of appendicitis or an increasing blood lead concentration</i> . 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, <i>when this material is known to be dispersed in the gut.</i>	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 <i>who has, or is likely to have, inadequate calcium intake</i> , 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 <i>who has, or is likely to have iron-deficiency</i> , administration of iron supplementation is recommended. Remarks The dose should be in line with WHO guidelines or standard clinical practice.	Strong (very low-certainty evidence)

Pregnant women

	For a pregnant woman with a blood lead concentration of ≥ 5 µg/dL, <i>who has, or is likely to have, inadequate calcium intake</i> , 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). This should be given as soon as the pregnancy is recognized, for the duration of the pregnancy.	Strong (moderate-certainty evidence)
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Lactating women

	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)
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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 <i>does not</i> 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 <i>who does not</i> 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)
3	For a non-pregnant adolescent or adult with a blood lead concentration of 45–70 µg/dL and who <i>has mild–moderate</i> clinical features of lead poisoning (such as abdominal pain, constipation, arthralgia, headache, lethargy), chelation therapy is suggested.	Conditional (very low-certainty evidence)



No.	Recommendation	Strength of recommendation (certainty of evidence)
Chelation therapy in individuals exposed to lead <i>continued</i>		
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 <i>does not show significant neurological features of toxicity</i> , 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 <i>significant neurological features of lead toxicity</i> (e.g. irritability, drowsiness, ataxia, convulsions, coma) or <i>lead encephalopathy</i> , urgent parenteral chelation therapy is recommended.	Strong (very low-certainty evidence)
Pregnant women		
1	For a pregnant woman <i>with lead encephalopathy</i> , 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 <i>without lead encephalopathy</i> : <ul style="list-style-type: none"> 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 the above 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. 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. They are also more likely to have inadequate calcium intake. 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, although the four recommended chelating agents are included in the WHO Model List of Essential Medicines. 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. 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.

When lead exposure is suspected but the blood lead concentration is $< 5 \mu\text{g/dL}$, 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. 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.

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. 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 α 1-acid glycoprotein). 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, 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 should be balanced against the additional susceptibility of children with malaria to the neurotoxicity of lead 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 patient 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). 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 above 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.

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.

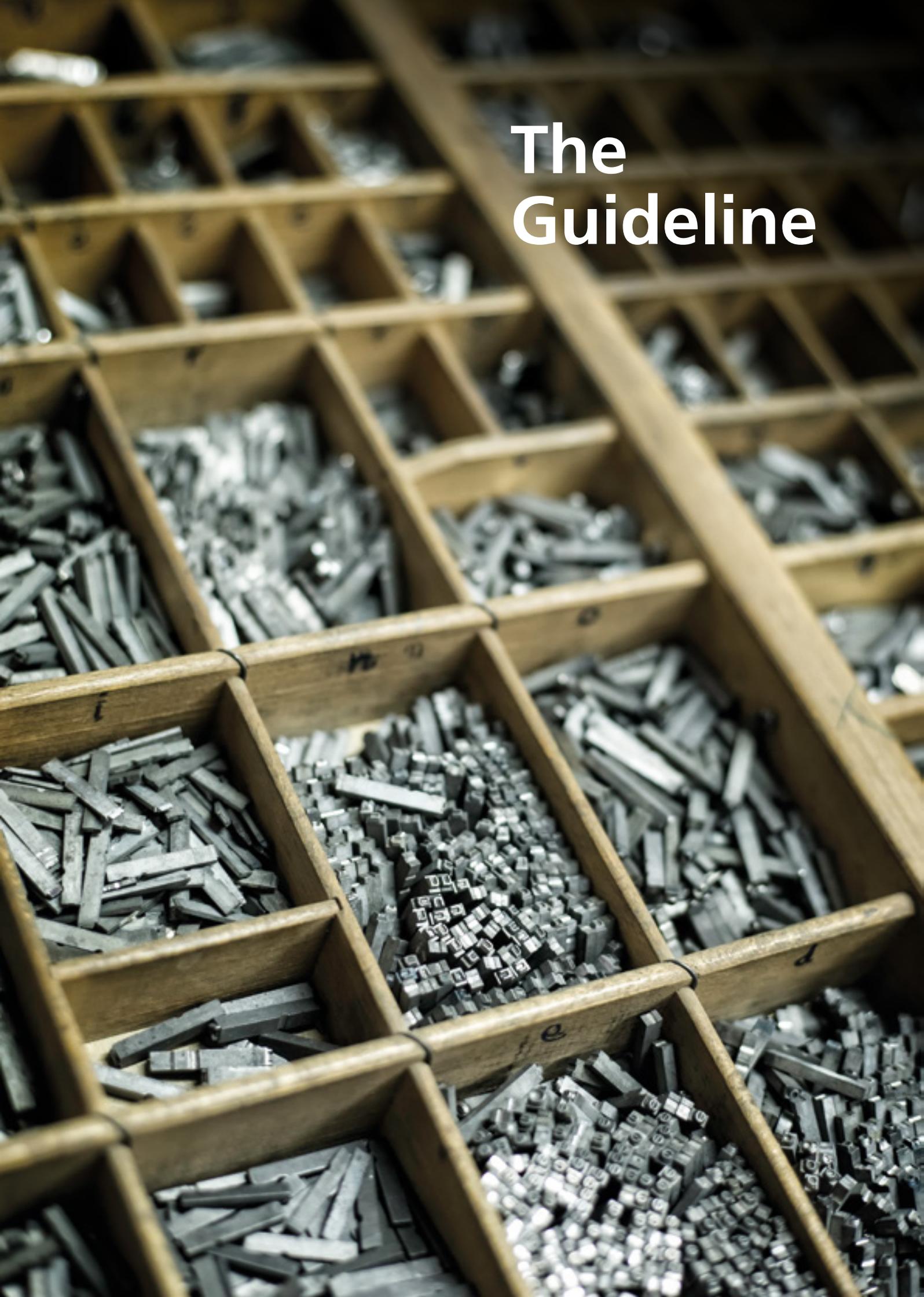
The second challenge is the limited availability of chelating agents in many low- and middle-income countries, despite the inclusion of the four chelating agents on the WHO Model List of Essential Medicines. WHO will use the guidance to further advocate for greater availability of chelating agents as 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.

The Guideline





Miner working in gold processing compound Zamfara State, Nigeria. Credit: Olga Victorie/MSF

01 /

Purpose and scope

Lead is a widely used but toxic metal that can give rise to life-threatening poisoning and cause long-term negative effects on health. Exposure can result from the ingestion of lead-containing substances or products, from inhalation of fumes during occupational exposure and from exposure to environmental contaminants. Individual cases of lead poisoning continue to occur owing to the many sources described in section 4. In addition, there have been a number of mass lead-poisoning events around the world, mostly related to environmental contamination or contamination of food (1–4). The morbidity and mortality associated with environmental exposures to lead can be very high. In northwest Nigeria in 2010, for example, an estimated 400 children died from environmental lead poisoning and over 1000 children < 5 years of age were treated with chelation therapy in a humanitarian response operation (4).

Lead exposure is a significant public health concern. It is estimated to have accounted for 0.90 million deaths from long-term health effects and 21.7 million disability-adjusted life years in 2019 (5). Children are particularly vulnerable, and WHO has estimated that lead exposure accounts for 30% of the global burden of idiopathic developmental intellectual disability (6).

The most important aspect of the management of lead exposure is identification and removal of the source of exposure. Depending on the circumstances and severity of exposure, other management measures that can be used are GI decontamination to remove material from the GI tract, nutritional supplementation to mitigate the

effects of lead poisoning and chelation therapy to facilitate elimination of lead from the body. In many countries, the management of lead exposure is difficult, particularly with regard to access to laboratory services for diagnosis, access to chelating agents for treatment and environmental services for source identification and remediation. Four chelating agents are in common use for lead poisoning: dimercaprol, penicillamine, sodium calcium edetate and succimer; however, these are not available in all countries.

The purpose of this guideline is to assist physicians in making decisions about the diagnosis and treatment of lead exposure for individual patients. The recommendations can be adapted for mass poisoning incidents. The guideline can be used to inform the development of national programmes for the diagnosis and management of lead poisoning. It can also be used by other groups to develop their own treatment protocols.

The guidelines present evidence-informed recommendations on:

- interpretation of blood lead concentrations,
- use of GI decontamination,
- use of nutritional supplementation and
- use of a chelating agent.

The guideline does not include discussion of methods for preventing lead exposure, such as environmental remediation, which will be the subject of a separate guideline document.

Methods for guideline development

This guideline was developed according to the procedure laid out in the *WHO handbook for guideline development* (7). Briefly, this involves:

- identification of priority questions and critical outcomes;
- retrieval of evidence;
- assessment and synthesis of the evidence;
- formulation of recommendations; and
- planning the dissemination, implementation, impact evaluation and updating of the guideline.

2.1 Contributors to the guideline

The guideline was developed with the assistance of a steering group, a guideline development group, an external review group, a systematic review team and methodologists.

WHO steering group

This group comprised members of staff from WHO departments concerned with public health and environment and food safety at headquarters and in four regions. The members are listed in Annex 1. This group drafted the initial scope and outline of the guideline and discussed the interventions and outcomes that would be researched. The group oversaw development of the guideline.

Guideline development group

The members of the guideline development group were proposed by the steering group. The guideline development group comprised 15 external experts from the six WHO regions. They are listed in Annex 2. This group provided expertise in clinical toxicology, children's environmental health, lead poisoning prevention and management, including in low-resource settings, and public health.

The guideline development group reviewed the proposed scope of the management guidelines and assisted in the identification and ranking of outcomes and the development of systematic evidence review protocols. The group then considered the systematic reviews of evidence for treatment interventions, assessed the certainty of evidence (see below), formulated the treatment recommendations and provided the supporting arguments for designating the recommendations as "strong" or "conditional".

Systematic evidence review team

A group at the Medical Toxicology and Information Services (now called ESMS Global) in London, United Kingdom, was commissioned to conduct systematic reviews of evidence for the management of lead poisoning. They first conducted a literature review to identify any existing systematic reviews on the management of lead poisoning; however, they found none. The GRADE¹ assessments were carried out with the support of a team at the Department for Evidence-based Medicine and Clinical Epidemiology at Danube University, Krems, Austria.

2.2 Identification of priority questions and critical outcomes

The WHO steering group drafted an initial list of possible interventions for the management of lead exposure. These were discussed with the guideline development group at its first meeting. The group also developed a set of research questions that would be used for the systematic evidence review. Through an iterative process, by email, a list of 18 outcomes relevant to the management of lead exposure was drawn up. The outcomes were ranked by the guideline development group as critical, important or unimportant. The research questions and the 12 critical and important outcomes are listed in Annex 3.

¹Grading of recommendations, assessment, development and evaluation

2.3 Identification and retrieval of evidence

In order to determine the threshold blood lead concentration for action, international and national assessments of the toxicity of lead were considered by the guideline development group (see section 4.4).

Evidence reviews were carried out for each of the interventions. The systematic review team, in collaboration with the WHO technical officer and the guideline development group, developed a review protocol based on the model used by the Cochrane Collaboration. This included the PICO² questions and the search strategies. Systematic searches were carried out in a number of bibliographic databases and also clinical trial registers. Details of the search strategies used and the criteria for including and excluding studies are described in the individual systematic reviews. There were no language restrictions. Each review was documented with the Cochrane Collaboration RevMan tool.³

For the literature searches for chelation therapy and GI decontamination there were no date limits, 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.

2.4 Quality assessment and grading of evidence

The quality of the body of evidence for each outcome was assessed with the GRADE approach (7). In this approach, the certainty of evidence for each outcome in the studies found was rated as “high”, “moderate”, “low” or “very low” on the basis of the criteria listed below. The final rating of the certainty of evidence was based on further consideration of these criteria.

Study design limitations

The risk of bias was first examined at the level of individual studies and then for all the studies that contributed to the outcome. For randomized trials, certainty was rated as “high” or was downgraded by one (“moderate”) or two (“low”) levels according to the minimum quality criteria met by the majority of the studies that contributed to the outcome. For observational studies, which in fact formed the majority of the evidence found, certainty was rated as “low” or “very low”, although the certainty of a study could be increased by one or two levels, as described below.

Inconsistency of the results

The similarity in the results for a given outcome was assessed by examining the magnitude of differences in the direction and size of effects observed in different studies. The certainty of evidence was not downgraded when the direction of the findings was similar and confidence limits overlapped but was downgraded when the results were in different directions and the confidence limits showed minimal or no overlap.

Indirectness

The certainty of evidence was downgraded when there was serious or very serious concern about the directness of the evidence, i.e. when there were important differences between the research reported and the context for which the recommendations were being prepared. Such differences were related to, for instance, populations, interventions, comparisons or outcomes of interest.

Imprecision

The degree of uncertainty about the estimate of effect is often a function of sample size and number of events. Therefore, studies with relatively few participants or events (< 300) and thus wide confidence intervals around effect estimates were downgraded for imprecision.

Publication bias

The rating of certainty could also be affected by perceived or statistical evidence of bias to underestimate or overestimate the effect of an intervention as a result of selective publication based on study results. A common practice is to downgrade evidence by one level if there is a strong suspicion of publication bias. In this review, however, there were insufficient studies for each intervention to allow numerical assessment of publication bias.

Rating up the certainty

The certainty of evidence was rated up if a large effect was reported (e.g. risk ratio > 2), there was a clear dose–response gradient or if all plausible confounding would have reduced the observed effect.

Evidence profiles were constructed for each outcome, which included the assessment and judgement of the criteria described above. This approach was used for chelation therapy in non-pregnant individuals and for nutritional interventions. For GI decontamination and chelation therapy in pregnancy, the reviews identified only case reports and small case series, which were automatically graded as being of very low certainty.

²Populations, interventions, comparisons and outcomes

³Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.

2.5 Management of conflicts of interests for external contributors

According to WHO policy, all experts must declare relevant interests before participating in WHO guideline development and meetings. All guideline development group members and external contributors were therefore required to complete a standard WHO declaration of interests form.

The technical officer consulted the WHO steering group about the declarations before finalizing invitations to experts to participate in guideline development. When any possible conflict of interest was declared, the technical officer reviewed the declarations with the departmental director to determine whether it was serious enough to affect the expert's objective judgement on the guideline development process and recommendations. To ensure consistency, the criteria for assessing the severity of conflict of interests in the *WHO handbook for guideline development* (7) and other internal WHO guidance were used. All findings from the declarations of interests received were managed in accordance with the WHO internal procedures for handling declarations of interests by WHO experts. Declarations of interests were judged case by case, and any issues arising were communicated to the experts.

Conflicts of interest that warranted action by WHO staff arose when experts had obtained funding from a body or an institution to perform primary research, could make a financial gain from any recommendations in the guideline or had performed a study or systematic review directly related to any of the guideline recommendations. The only commercial products considered in this guideline were the chelating agents. A person who had a personal or secondary (e.g. through a close family member) financial conflict relating to these products would not have been allowed to participate in the guideline development group.



Children's playground equipment painted with lead paint presents a hazard. Credit: WHO / Blink Media - Daiana Valencia

Before each guideline development group meeting, a webpage was created on the WHO website that presented the list of guideline development group members and short biographies. An email address was provided for communication of any concerns about individual experts. No such communications were received by WHO.

At the start of each guideline development group meeting, the WHO technical officer reminded the group of the reasons for requiring a declaration of interests and the scope of interests that could give rise to a conflict, including financial and intellectual interests. Each group member was asked to read out their declaration of interests and to provide any additional relevant information, which was noted in the meeting record. Meeting participants were invited to state whether they saw a potential or actual conflict of interest. If a conflict was identified, either in prior screening by the steering group or by meeting participants, the options were as follows. If the conflict was not considered to be significant, no action was required, apart from noting the conflict in the published guideline. If a conflict could have a bearing on the guideline development group member's decisions about a recommendation, depending on the perceived severity of the conflict, the concerned expert could have been allowed to participate in discussions but not in formulating a recommendation or could have been excluded from both processes.

The guideline development group members were selected because of their expertise in the toxicity of lead and/or their experience in managing lead exposure. Eight group members declared one or more interests, which are summarized in Annex 2. The interests fell into the following categories: providing expert testimony on the toxicity of lead and its impacts on the health of exposed people, in particular children (three experts); providing clinical advice to a national government and a nongovernmental organization on the diagnosis and management of lead exposure due to environmental contamination (one expert); clinical management of a mass lead poisoning event (one expert); involvement in the development of national policy on lead (one expert); management of a national lead poisoning prevention programme and technical input (in her professional capacity) to the development of a commercial point-of-care device for measuring blood lead concentration (one expert); and involvement in lead poisoning prevention campaigns (one expert). In the case of the mass lead poisoning event, four group members were co-authors of a publication describing the outcomes of a chelation intervention that was considered with other studies as evidence for the guideline.

None of the guideline development group members were considered to have a conflict that barred them from participating in the discussion and formulation of recommendations. The group had a balance of experience in the management of lead poisoning in low- and high-resource settings.

2.6 Development of recommendations

The following procedure was used 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, most of which was of very low certainty, formulated recommendations and decided on the strength of each recommendation.

By default, the strength of the recommendations discussed was aligned initially with the certainty of the evidence; i.e. at the start of the discussion, “strong recommendations” were based on evidence of “moderate” and “high” certainty, while “conditional recommendations” were based on evidence of “low” and “very low” certainty. 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. Consideration of values and preferences was based on the experience and opinions of members of the guideline development group. Cost evaluation relied on reported estimates obtained during evidence retrieval as well as the experience of members of the guideline development group. GRADEPro guideline development tool evidence-to-decision tables⁴ were used to note and synthesize these considerations and record the reasons for changes made to the default strength of the recommendations.

The interpretation from the perspectives of different decision-makers is shown in Table 1.

Each recommendation was adopted by consensus – defined as the agreement by at least 80% of the group, provided that those who disagreed did not feel strongly about their position. Strong disagreement would have been recorded as such in the guideline. If the participants were unable to reach consensus, the disputed recommendation, or any other decision, was put to a vote. Voting was by a show of hands by members of the guideline development group, and a recommendation was adopted if more than half the votes were in favour. If the majority was marginal, there was further discussion to try to obtain a stronger majority. This process did not apply if the disagreement related to a safety concern, in which case the WHO secretariat would choose not to issue a recommendation at all. WHO staff at the meeting, external technical experts involved in the collection and grading of the evidence and observers were not eligible to vote. If the issue to be voted on involved primary research or systematic reviews conducted by any of the participants who had declared an academic conflict of interest, the participant in question was allowed to participate in the discussion but was not allowed to vote. This situation did not, however, arise.

Recommendations were drafted in a series of face-to-face meetings of the guideline development group and finalized in a series of online meetings and email discussions.

Recommendations were designated as “strong” or “conditional” as follows:

Strong recommendation:

The group is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

Conditional recommendation:

The group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects but is not confident of this interpretation.

Table 1. Interpretation of strong and conditional recommendations for an intervention

Decision-maker	Strong	Conditional
Patients	Most people in your situation would want the recommended course of action, and only a small proportion would not.	The majority of people in your situation would want the recommended course of action, but many would not.
Physicians	Most patients should receive the recommended course of action.	Be prepared to help patients to make a decision that is consistent with their own values.
Policy-makers	The recommendation can be adopted as a policy in most situations.	Substantial debate and involvement of stakeholders are necessary.

Source: Ref. 7

⁴<https://grade.pro/>

2.7 Good practice statements

In discussing the recommendations, the guideline development group decided that three good practice statements were required. These were not developed through systematic evidence retrieval, synthesis and grading but were considered good clinical practice and are based on clinical experience in the management of patients exposed to lead.

2.8 Consultation with stakeholders

No formal consultation was held with potential users of the guideline; however, informal consultations took place at two technical meetings. An early version of the draft recommendations was presented to a group of experts on lead at a national meeting on the prevention and management of lead poisoning, organized by the Indian Council of Medical Research National Institute of Occupational Health in Ahmedabad, India, in June 2017. This meeting provided an opportunity to identify considerations for local implementation of the guideline.

After feedback from the meeting, the recommendations were simplified and reviewed again by the guideline development group. A discussion was held about the threshold blood lead concentration for action at a regional meeting of environmental health and public health specialists held in Cairo, Egypt, in December 2018 to explore the implications of the threshold value.

2.9 Document preparation and peer review

The guideline text was drafted by the WHO technical officer and circulated to the guideline development group. The finalized draft was then sent to eight external peer reviewers, who are listed in Annex 4. All the external reviewers completed a WHO declaration of interests form before being accepted as a reviewer. The reviewers' comments were discussed with the guideline development group, and 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. The external reviewers included clinicians who would potentially be users of the guideline when managing cases of lead exposure.



E-waste can be a source of lead exposure. Credit: WHO / Blink Media - Tali Kimelman

Results of the review



Pathology specimen. Credit: MSF

Five systematic reviews of evidence and two narrative reviews provided the evidence base for this guideline (8–14). Tables summarizing the findings for each intervention are available online (14). For chelation therapy, there were very few randomized controlled studies, and other types of controlled study were generally subject to a high risk of bias, for example because of use of historical controls. For nutritional interventions, several randomized studies were identified. For GI decontamination and the use of chelation in pregnancy, evidence was available only from case reports and small case series. There were insufficient studies for a meta-analysis of the evidence for any of the interventions, and the reviews were qualitative. Because the evidence was largely of low or very low certainty, some recommendations were based on the expert opinion of the guideline development group. The basis for the decision on each recommendation is given in the evidence-to-decision tables available online (*Web Annex*).

No studies were found that addressed the acceptability, feasibility or impact on equity and human rights of any of the interventions in the context of lead poisoning; however, some indirect evidence was found for interventions in pregnancy. These issues were considered by the guideline development group, and their remarks are included in the text, where relevant.

3.1 Guiding principles

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

1. When lead exposure has been confirmed, action should be taken as soon as possible to terminate or reduce the exposure. Lead has no physiological role in the body, and no level of lead exposure has been identified that does not have a deleterious effect (15, 16). As long as exposure continues, lead will be absorbed, with consequent negative effects on health (see section 4.4). Lead is also stored in tissues and bone, forming a sink from which it can be remobilized into blood (see section 4.3). All exposure due to the use of lead or environmental contamination with lead is potentially preventable.
2. Chelation therapy is of limited value if exposure continues. As a life-saving measure, however, it may be necessary to chelate children who have severe clinical effects of lead poisoning and 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.
3. As the clinical management of individuals with lead exposure 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.

04 /

Background

Lead is a naturally occurring heavy metal present in the earth's crust. Some lead is released into the environment through geophysical processes such as the weathering of rocks and volcanic activity. This is of minor importance, however, as compared with human activities to extract, process and use lead, which account for most of the lead in the environment (17). Once lead is released into the environment, it is deposited on surface soil and water. Lead remains in soil indefinitely unless it is remobilized or removed (18).

Lead has a number of properties, such as resistance to corrosion, malleability and high density, that make it useful for a wide range of purposes (19). The main use of lead is in storage batteries (e.g. for motor vehicles, solar power and for uninterrupted power supply). Lead is also used extensively in the construction and chemical industries. It is used in ammunition, shielding systems against ionizing radiation and for lining tanks and pipes. Metallic lead is a major component of many alloys such as those used for solders, type metal, speciality steel, brass and bronzes.

It may also be used as a weight in ballasts and as wheel weights in motor vehicles. Inorganic lead salts are used in pigments, paints, enamels, glazes, glass, plastics and rubber compounds (17). Lead is also included in some cosmetics and traditional medicines (20).

Organic lead compounds (tetraethyl and tetramethyl lead) were used extensively between the 1930s and the 2000s as anti-knocking additives to petrol to improve engine performance (17). Leaded petrol is now banned in all countries, and the use of organic lead compounds has consequently greatly decreased (21). Tetraethyl lead, however, continues to be used in some aviation fuel (Avgas) for piston engine aircraft (18, 22).

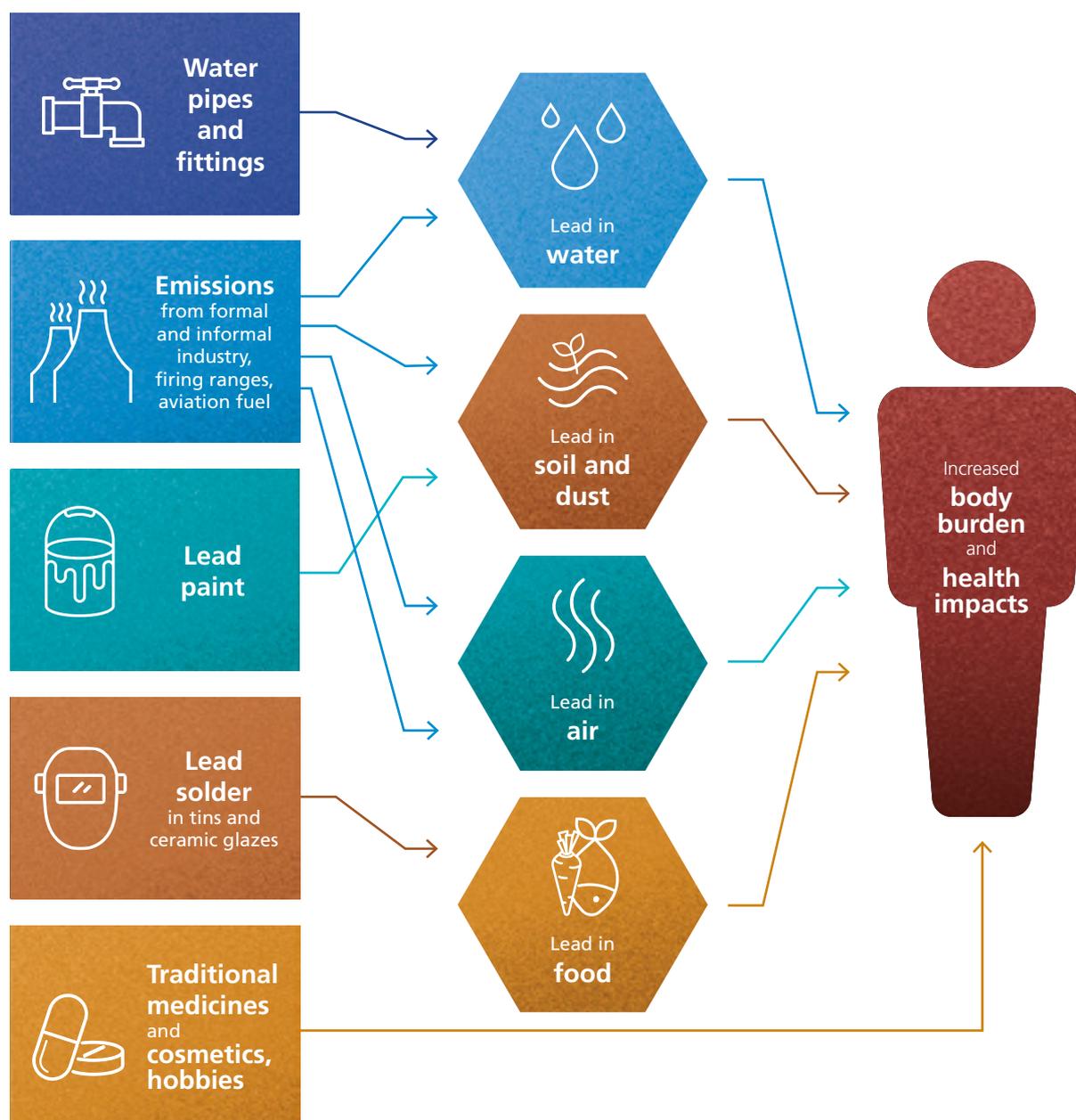


Water pipes can be a source of lead contamination.

4.1 Principal sources of exposure to lead

Because of the wide range of uses for lead and its environmental persistence, there are multiple sources and pathways of exposure (Fig. 1). Some important sources include lead paint, lead emissions from industries, leaded water pipes and fittings, lead-containing traditional medicines and cosmetics and lead-glazed food vessels. More information on sources is provided below. The relative importance of each source varies from country to country.

Fig. 1 Principal sources and pathways of exposure to lead



Source: adapted from Ref. 23

Environmental exposure

The environment may be contaminated with lead around mines, smelters and factories that process lead when emission controls are inadequate (24–26). Informal, small-scale industries such as recycling lead-acid batteries, lead smelting to make fishing weights and gold mining can also result in significant exposure to lead, both directly and from environmental contamination (3, 27–29).

Lead paint is a source of environmental contamination in and around the home when deteriorating paint crumbles and flakes to form part of household dust (30). Stripping of lead paint by burning or abrasive methods also contaminates the environment and can be a source of exposure of both those engaged in paint-stripping and people living in the vicinity (30). Outdoor structures such as steel bridges and flyovers painted with lead paint may contribute to the lead content of surrounding dust and grit (31). Repair and repainting of metal structures and demolition of old buildings can release large amounts of lead particles into the air and onto soil in surrounding areas, and this lead can then be blown or tracked into homes (32, 33).

Leaded petrol is no longer a significant source of exposure for the world's population (21). Continued use of lead in some aviation fuels, however, exposes populations around airports to lead (22).

Lead released as fumes and particulates is deposited into soil and water, where it can be taken up by food crops and animals and enter the human diet (34).

Food and drink

Since the considerable reduction in lead emissions from petrol, food and water have become more important sources of lead exposure (15, 18, 35). Lead in drinking-water is usually the result of leaching from household plumbing systems rather than a natural contaminant (35). The sources include lead pipes and fittings, brass fittings and lead leached from soldered connections in copper piping. Acidic water (below pH 8) and higher temperatures increase the solubility of lead from pipes and fittings (36, 37).

Food and beverages can be contaminated when they are prepared or stored in lead-containing utensils or vessels. These include cooking pots made from recycled metal (38), lead-ceramic-glazed pottery (39–41), some glassware (42) and food tins with lead solder (43). Ingestion of sweets (candy) contaminated by lead-containing dyes used on wrappers has also resulted in lead exposure (44). Lead poisoning from consumption of illicit alcohol ("moonshine") distilled in car radiators soldered with lead has been reported in the USA (45). Crops grown on contaminated land and animals that forage on the land may accumulate lead, thereby becoming sources of exposure for consumers (46, 47).

Hunted game shot with lead ammunition is a potential source of exposure of people who regularly eat this meat. Lead from ammunition can contaminate the flesh of the animal, and lead shot embedded in the flesh may also

be eaten, retained in the GI tract and absorbed (48, 49). Outbreaks of lead poisoning have been caused by flour ground with millstones fixed with lead components (1, 50, 51). Spices may be deliberately adulterated with lead compounds (52) or be contaminated by other means (53).

Traditional medicines and cosmetics

Traditional medicines may contain lead as an intended ingredient or as a contaminant, and there have been numerous reports of poisoning in children and adults (54–64). These medicines may be used for a wide range of conditions, including GI complaints (55), skin conditions (59, 60), infertility (61), erectile dysfunction (59, 62), epilepsy (63) and diabetes (64), or may be taken as tonics or aphrodisiacs (59). The use of lead-containing traditional cosmetics such as surma, kohl and sindoor has caused toxic effects, particularly in children (65–67).

Lead objects

Children can be exposed to lead by mouthing toys painted with lead paint or brass keys and may accidentally swallow lead objects such as fishing or curtain weights and lead jewellery (68–70). Adults may also ingest lead foreign bodies, either intentionally (71) or accidentally, for example as lead shot in hunted game (48). Ingestion of ground lead-glazed pottery by pregnant women can cause both maternal and fetal lead poisoning (72).

Occupational exposure

Lead is the most widely used non-ferrous metal, and a large number of occupations are therefore associated with risk of exposure. The industries include mining, smelting and refining operations, high-temperature lead applications such as welding and spray-coating, lead grinding and cutting, battery manufacture and recycling, scrap metal recycling, production of paints, pigments, ceramics, glazes, enamels and rubber, building renovation and decoration, construction and demolition, and plumbing and tank cleaning (73, 74).

Other, smaller-scale occupations that involve lead exposure include gunsmithing, glass polishing, brass polishing, locksmithing and making jewellery, pottery and stained glass (73, 75). Firing ranges are another source of exposure (76).

Para-occupational exposure can occur when people who work with lead bring home lead dust on their bodies and clothing (77).

Miscellaneous sources

Lead toxicity has also been associated with a variety of other substances, including lead-contaminated opium and other drugs of abuse (78–80) and lead nipple shields used by a mother of a breast-fed infant (81). Poisoning has been reported after ingestion of snooker cue chalk (82), lead roofing plates (83) and solder (84). Ingestion of soil or clay by pregnant women is a source of lead exposure in some communities (85). Lead poisoning can also arise from retained bullets and shrapnel (86).



Some traditional cosmetics can be a source of lead exposure. Credit: Matt Hahnewald / Shutterstock.com

4.2 Routes of exposure to lead

The most important routes of exposure to lead are ingestion and inhalation. Acute lead poisoning may occur after ingestion of a toxic amount of lead salts such as lead acetate or lead tetraoxide (87, 88). Most cases of oral lead poisoning, however, result from regular ingestion of small amounts of lead-containing material such as contaminated dust or soil, flakes of lead paint, contaminated food, lead-containing traditional medicines or from ingestion of a lead foreign body.

Young children are particularly likely to ingest contaminated soil and dust because they spend a lot of time in one place, tend to play on the ground, have frequent hand-to-mouth contact and mouth objects that may contain or be contaminated with lead (20). Children with pica may persistently eat flakes of leaded paint or lead-contaminated soil.

Inhalation of lead as fumes or particles is a major occupational route of exposure. Inhalation may also occur in the home if there is airborne dust contaminated with lead, for example as a result of paint stripping (89).

Dermal exposure can occur occupationally or through the use of cosmetic products containing lead, but this is considered a minor route (34).

Injection of lead compounds has occasionally been reported (90).

4.3 Toxicokinetics

Absorption

Absorption of lead from the GI tract is affected by dietary factors, age, nutritional status, genetic factors and the form of the lead (15, 34). In adults, approximately 3–10% of ingested lead is absorbed, and the remainder is eliminated in the faeces (34). Infants and young children absorb a greater proportion of ingested lead, in the order of 40–50% (34). Fasting and dietary deficiencies of iron or calcium are reported to enhance absorption (34). The impact of dietary zinc intake on lead absorption is unclear (34, 91).

Absorption of particulate lead by inhalation depends on particle size, concentration and ventilation rate (34). Age is also a factor: children may have higher exposure than adults as they breathe proportionately more air per unit of body weight (20). Small particles of lead (< 1 µm) are deposited in the lower respiratory tract, from where the lead is almost entirely absorbed, while larger particles (1–10 µm) are likely to be deposited in the upper airways, transferred by mucociliary transport to the oesophagus and swallowed (34). Models have been developed to estimate the blood lead concentration associated with different levels of airborne occupational exposure to lead (e.g. 34, 92).

Dermal absorption is minimal for inorganic lead and much greater for organic lead compounds (93).

Retained lead fragments such as gunshot pellets or bullet fragments may become a source of lead absorption. Risk factors include prolonged contact of the fragments with synovial, pleural or cerebrospinal fluid, position of the projectile near a bone or joint or an associated bone fracture, particularly a tarsal bone fracture (86, 94, 95). Absorption is also greater if the projectile is fragmented or there are numerous pellets, as both increase the surface area for absorption (86, 94, 95). The time between injury and raised blood lead concentrations is highly variable, ranging from 3 months to over 50 years in published reports (86).

Distribution

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 (34, 93). The highest soft tissue concentrations in adults are in the liver and the kidney cortex (34). Lead is also distributed to teeth and hair.

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. Most blood lead is in erythrocytes and the remainder, typically < 1%, in plasma (34). It is the latter fraction that interacts with cells in tissues throughout the body. The binding sites on erythrocytes are saturable; consequently, as more lead is absorbed, a larger proportion is available in plasma to distribute to tissues (93).

In individuals who are exposed chronically, bone contains > 90% of the body burden of lead in adults and > 70% in children (96). Lead forms stable complexes with phosphate and can replace calcium in hydroxyapatite, which forms the main crystalline matrix of bone. Lead can therefore deposit in bone during growth and remodelling (93). A labile pool of lead in bone readily exchanges with lead in plasma. As lead is excreted from blood by normal processes or after chelation therapy, it is replenished from the store in bone (93). Lead can also be released from bone during metabolic processes that increase bone turnover, such as occur during pregnancy, lactation, the menopause, hyperthyroidism, bone cancer and immobilization due to bone fractures (34, 97–99). Lead accumulates in bone over life up to the age of 50–60 years, followed by a decrease due to age-related changes in diet, hormonal concentrations and metabolism (98).

During pregnancy, the blood lead concentration increases due to increased resorption of maternal bone to meet the calcium needs of the developing fetal skeleton. There is a decrease in the second trimester due to haemodilution, and the blood lead concentration rises again in the third trimester and continues for a period post-partum, particularly in lactating women (93, 100). There is no placental barrier to lead, and maternal and fetal blood lead concentrations are similar (34).

Lead is present in breast milk from exogenous sources or remobilized from skeletal stores. There is a non-linear relation between the concentrations of lead in blood and breast milk, with milk lead concentrations increasing disproportionately at blood lead concentrations > 40 µg/dL (101). No cases of lead poisoning resulting from exposure to lead in breast milk alone have been identified.

Metabolism

Inorganic lead is not metabolized but is reversibly bound to amino acids, proteins and sulfhydryl compounds (93). Organic lead compounds are metabolized to inorganic lead. Alkyl compounds such as tetraethyl lead and tetramethyl lead undergo oxidative dealkylation to form the highly neurotoxic compounds triethyl and trimethyl lead, respectively (93).

Elimination

Absorbed lead is eliminated primarily in urine and faeces. Small amounts are excreted in sweat, saliva, hair, nails and breast milk (93).

Lead is eliminated from blood and soft tissues fairly rapidly, 50–60% being eliminated from blood in 30–40 days (34, 102). Lead is eliminated slowly from bone stores, the half-life depending on age and the intensity of exposure (34). As children's bones are still growing, the bone compartment is more labile than that of adults, and lead moves faster from bone to blood, the half-life for cortical bone being estimated to range from 0.23 years at birth to 3.7 years at 15 years of age and 23 years in adults (34). In individuals with an elevated bone lead burden, cessation of lead exposure typically results in an initial fairly fast decrease, with a half-life of several months, representing a reduction of lead in soft tissues, followed by a longer phase with a half-life of years, representing release of lead from skeletal tissues (34).

4.4 Toxicity of lead

4.4.1 Mechanisms of toxicity

The pathophysiology of lead is complex. It has been reviewed extensively (15, 18, 34, 93, 103) and is only summarized here.

Lead has no apparent physiological function. It has an affinity for sulfhydryl groups and other organic ligands in proteins and can mimic other biologically essential metals, such as zinc, iron and, in particular, calcium (18). As a result of these properties, lead has several modes of toxic action that depend on dose and target organ. The modes of action include changes in ion status and cell signalling, changes in protein binding, oxidative stress, inflammation, endocrine disruption, cell death and genotoxicity (34).

4.4.2 Toxic effects

The toxic effects of lead affect almost all body systems (15, 20, 34). 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. In addition, there is considerable inter-individual variation in dose–response relations for lead toxicity, and the presenting signs and symptoms are highly variable in both adults and children (93). The toxic effects may include GI, haematological, neurological and renal effects, as well as effects on the reproductive, immunological, endocrine and cardiovascular systems. In severe poisoning, life-threatening encephalopathy may occur (20, 104).

The features of acute and chronic poisoning are similar. In acute poisoning, GI and hepatic effects can occur within 1–2 days, followed by renal impairment and haematological and neurological effects over several days to weeks after exposure (105). After acute ingestion, some patients remain asymptomatic or show only mild effects, even with a high blood lead concentration, while others may develop severe poisoning (15). Retention of a lead foreign body can be a source of prolonged lead exposure.

Gastrointestinal effects

GI effects are common in lead toxicity but are non-specific. They include anorexia with weight loss, constipation, abdominal pain or discomfort, nausea, vomiting, diarrhoea and a metallic taste (93, 106). Lead colic (intense, painful, intermittent abdominal cramps) is associated with severe constipation and vomiting and can be mistaken for other conditions, such as acute abdomen, appendicitis, cholecystitis, intestinal obstruction or ileus (107).

Patients with poor dental hygiene may develop a “lead line” (Burton or blue line) along the gingival crest composed of dark granules of lead sulfide precipitated by the action of hydrogen sulfide (from bacterial degradation of organic matter) on lead. There may also be grey spots on the buccal mucosa and on the tongue (108).

Lead pellets consumed when eating hunted game or by intentional ingestion of shotgun pellets can accumulate in the appendix. In some cases, this results in lead toxicity and/or appendicitis (93 [Appendix C], 109, 110).

Neurological effects

Lead exerts toxic effects on all parts of the nervous system. Many of the effects are irreversible (34). Lead poisoning can cause life-threatening encephalopathy in people of all ages, although young children are particularly vulnerable (20, 34, 111). The initial signs include sporadic vomiting, loss of appetite, behavioural changes, with aggression, irritability and agitation, headache, clumsiness and intermittent lethargy. These symptoms may progress to persistent vomiting, ataxia, tonic-clonic convulsions, opisthotonus, severe cerebral oedema, raised intracranial pressure, coma and death (20, 93, 104, 112). Optic neuropathy associated with raised intracranial pressure has been reported (113). Death may occur within 48 h of the first convulsions in patients who do not receive intensive supportive therapy (114). Concurrent malaria appears to increase susceptibility, with severe neurotoxicity seen at lower blood lead concentrations (see Fig. 2 in section 4.5) (111).

Severe lead poisoning can result in cognitive and neurological deficits, seizure disorders, blindness and hemiparesis (104, 115, 116). In the mid-twentieth century, when programmes to identify and manage lead exposure were just starting and treatment options were limited, the mortality rate in children with severe poisoning could be as high as 65%, and permanent brain damage was common (116). Such severe impacts are still seen in places where there is no ready access to diagnosis and treatment (3, 111).

Chronic lead toxicity may cause more subtle changes in neurological function in children and adults, and many publications have addressed the neurotoxicity of lead in children (see reviews in references 34, 93, 112, 117, 118).

Children may develop neurological and cognitive sequelae after exposure to even low levels of lead, associated with blood lead concentrations < 5 µg/dL (16). The sequelae include reduced cognition and behaviour scores, changes in attention (including attention deficit hyperactivity disorder), changes in visual-motor and reasoning skills and impaired reading ability and social behaviour (16, 34, 93). Neurological deficits associated with lead exposure have been shown to persist into later childhood and adulthood (93, 119–122).

Studies to date suggest that there may be no threshold blood lead concentration for neurotoxic effects in children. Moreover, a pooled analysis of data from seven prospective cohort studies of children followed from birth or infancy to 5–10 years of age found that the association between blood lead concentration and intelligence quotient (IQ) may be non-linear (123). The analysis indicated a steeper decrease in IQ in children with maximal blood lead concentrations < 7.5 µg/dL, and the decrease became less steep as the blood lead concentrations rose above 7.6 µg/dL. An extensive independent statistical re-evaluation of the data in this analysis reached similar conclusions (124).

Case reports and small studies of occupationally exposed adults describe higher incidences of malaise, forgetfulness, headache, fatigue, lethargy, irritability, dizziness, weakness, impotence and decreased libido (34, 93). Chronic exposure to lead may be associated with cognitive deficits that affect, in particular, spatial ability, executive functions, learning and memory and psychiatric symptoms (15, 34). Cognitive deficits in adults arising from cumulative exposure to lead may become more apparent in old age (93, 122).

Reduced nerve conduction velocity has been found in lead-exposed workers, and both motor and sensory neuropathies have been reported (93). In individuals with severe, chronic lead toxicity, clinically significant extensor motor neuropathy may be seen, with wrist drop and/or foot drop (20, 104, 125). Motor weakness usually resolves once the individual is removed from exposure, but this may not be the case for sensory neuropathies (126). Poor postural stability has been reported in children with mildly elevated blood lead concentrations (127) and in lead-exposed workers (93). Exposure to lead may also cause visual and auditory impairment (16, 93, 128).

Cardiovascular effects

There is a large body of evidence that lead exposure is associated with an increased risk of cardiovascular disease, including hypertension, ischaemic heart disease and stroke (34, 129, 130). The specific level of exposure to lead, its timing, frequency and duration associated with these effects are unknown. As these conditions have a long latency, they are likely to be influenced by high exposures to lead early in life, even if current blood lead concentrations are low (34). While the effect on an individual's blood pressure is small, it can be significant from a population viewpoint, resulting in increased morbidity and mortality rates for ischaemic heart disease and stroke (15, 23, 131). An analysis of data from the Third National Health and Nutrition Examination Survey in the USA suggested that an increase in blood lead concentration from 1.0 µg/dL to 6.7 µg/dL is significantly

associated with mortality from cardiovascular and ischaemic heart disease (130). The authors estimated that reducing the blood lead concentration to 1 µg/dL or less would reduce mortality from both diseases by 37.4%.

Exposure to lead has been associated with changes in cardiac conduction, including increased QT and QRS intervals, and increased risks of intraventricular and atrioventricular conduction defects (34).

Hepatic effects

Liver toxicity, including in some cases liver failure, has been reported in patients with both acute and chronic lead poisoning (34, 86, 88, 90, 132).

Renal effects

Exposure to lead can cause acute and chronic nephropathy. In acute nephropathy, there is damage to the proximal renal tubules and impairment of renal function (Fanconi syndrome), resulting in proteinuria, aminoaciduria, phosphaturia, glycosuria and cellular casts (93, 133). Acute renal damage is usually reversible (116).

Chronic exposure to lead may cause progressive nephropathy, resulting in chronic renal failure, which is irreversible (133). The features include hyperuricaemia, which can increase the risk of gout, and hypertension (34). Because of the complex interaction between the renal and cardiovascular systems, with renal dysfunction increasing blood pressure and increased blood pressure causing kidney damage, effects on one or both systems can result in a cycle of worsening disease (34). The onset of lead-induced renal impairment is subtle, and patients may remain asymptomatic until there is significant renal dysfunction (133).

Endocrine and reproductive effects

There is some evidence that lead exposure affects the production of thyroid hormones, cortisol and vitamin D (34, 93). Exposure to lead has been associated with delays in growth and reduced growth (smaller stature and head circumference) in children as well as delayed sexual maturity in girls (93). Impotence and decreased libido have been reported in lead-poisoned patients (134). Lead exposure may reduce sperm quality and quantity and increase the risk of infertility (16, 18, 93).

Pregnancy

Lead has long been known to adversely affect reproductive outcomes in women and has been used as an abortifacient (135). Maternal exposure, even to low levels, is associated with reduced fetal growth, lower birth weight, hypertension and, potentially, preeclampsia, preterm birth and spontaneous abortion (16, 93, 136).

Haematological effects

Lead inhibits haem synthesis, resulting in anaemia, which increases in severity with increasing blood lead concentrations (20). This is frequently observed in children, and younger age and iron deficiency are risk factors (20). Leukocytosis is also seen, and haemolysis has been reported (106, 137). There may be coarse basophilic stippling; however, this is not found in all patients with lead poisoning.

Immunological effects

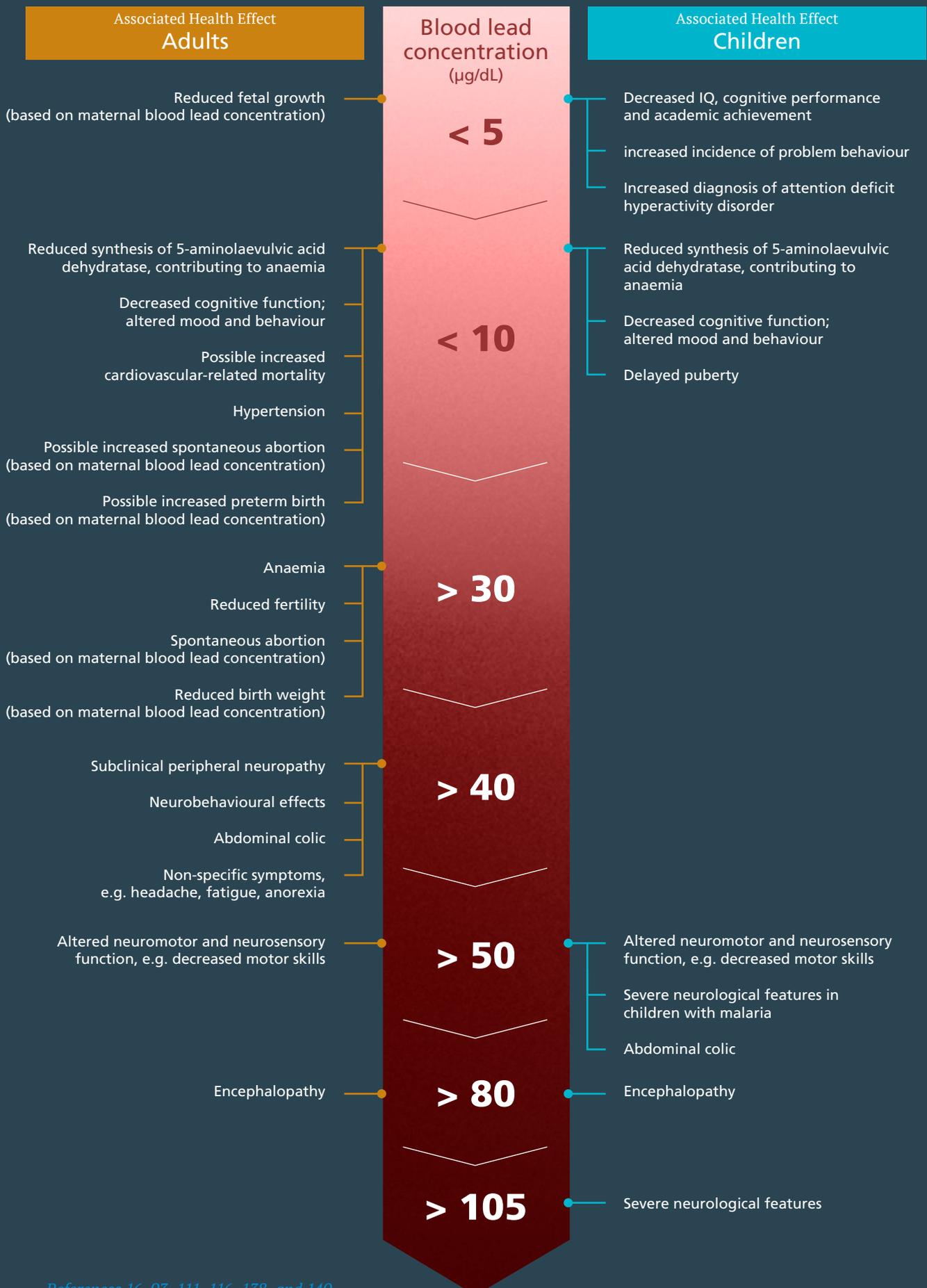
Prenatal and childhood exposure to lead may be associated with increased risks of asthma and allergy (34). Studies in experimental animals suggest that exposure to lead reduces host resistance to bacterial and viral infections (34).

4.5 Toxic effects in relation to blood lead concentrations

Blood lead concentration is the most commonly used measure of exposure, although it represents only about 1% of the total body burden of lead, the remainder being in soft tissues and bone (34). The concentration of lead in blood reflects recent exogenous exposure and endogenous redistribution of lead from bone (138). There is considerable inter-individual variation in the blood lead concentration at which specific signs of poisoning manifest (104). Some individuals may be apparently clinically well when they have blood lead concentrations that are associated with encephalopathy and death in others (116, 117, 139). In a review, the full spectrum of clinical effects, from no symptoms of poisoning to fatal

encephalopathy in children, were reported to occur within the range 100–200 µg/dL (116). The same variation applies to subclinical effects such as on IQ, so that children with the same blood lead concentration do not necessarily have the same risk of impaired neurodevelopment (117). Furthermore, a low blood lead concentration in adulthood does not necessarily indicate that lead exposure was always low. High exposures earlier in life might have caused organ damage that manifested only in adulthood. With those caveats in mind, Fig. 2 presents information about health effects in adults and children associated with specific blood lead concentrations, derived from reviews and large case series.

Fig. 2 Association of sub-clinical and clinical effects with blood lead concentrations





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Diagnosis of lead poisoning

Diagnosis of lead poisoning and treatment decisions are based on medical history, clinical examination and the results of investigations, including the blood lead concentration, biomarkers of effect such as 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, because there is a large body of evidence linking blood lead concentrations with clinical effects and treatment outcomes. Moreover, validated analytical methods and reliable blood quality-control and reference materials are available (141). While lead can also be measured in other matrices, such as plasma, urine, hair, teeth, nails and bone, these are not used clinically. WHO guidance is available on the analysis of blood samples for lead (142).

For diagnosis and treatment decisions, the blood lead concentration is best measured in a venous blood sample. Capillary samples, which are usually obtained by a finger-prick, are considered acceptable for screening purposes, and this is their main use (141–143). An elevated lead concentration measured in a capillary sample should be confirmed by laboratory measurement in a venous sample (141). In exceptional situations, when venous samples cannot easily be obtained and life-saving treatment would otherwise be delayed, capillary samples may be analysed for diagnosis, with a confirmatory laboratory analysis of venous samples as soon as possible.

Whether a capillary or a venous sample is collected, it is essential to take precautions to prevent lead contamination by thorough cleansing of the injection site and use of lead-free sampling equipment (142).



Measurement of blood lead forms part of a diagnosis of lead poisoning. Credit: WHO / Blink Media - Tali Kimelman

Recommendation

on the blood lead concentration that should initiate clinical interventions

6.1 Introduction

Lead exposure is confirmed by measurement of a venous blood lead concentration (*see section 5*). An elevated blood lead concentration may be due to a single acute exposure or to continuing exposure. Termination of lead exposure is an overarching principle of this guideline, as, without this action, lead will continue to exert toxic effects in target organs, with both short-term and long-term negative health effects (*see section 4.4*). Some examples of measures to identify and terminate exposure are described in section 8. For some cases of lead ingestion, it may be appropriate to use GI decontamination to stop further absorption, as discussed in section 7.1. Nutritional supplementation with calcium and iron may mitigate some of the effects of exposure, as described in section 7.2. When blood lead concentrations are high and/or the patient is showing significant features of lead toxicity, chelation therapy to facilitate lead excretion may improve health outcomes, as described in section 7.3.

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 have already been issued by international and national bodies, including WHO (*15, 16, 17, 34, 93, 103*). These document the adverse health impacts of lead particularly at exposure levels of 5 µg/dL and below, which is summarized in sections 4.4 and 4.5. The factors taken into account in this decision are described in an evidence-to-decision table available online (*Web Annex*).



Poison centres offer advice on the management and treatment of lead poisoning. Credit: WHO / Blink Media - Amanda Mustard

6.2 Recommendations for all age groups

- 1 / In all cases of suspected or confirmed lead exposure, the patient or carer should be given information about sources of lead exposure, methods for reducing exposure and the importance of good nutrition, in particular adequate dietary intakes of iron and calcium.

Good practice statement

Rationale

Providing health and preventive information to lead-exposed patients or their carer in the case of children is in line with WHO recommendations on the importance of health literacy in promoting good health (144) and is, therefore, considered to be good practice. Specific recommendations for improving calcium and iron intake are given in section 7.2.

WHO provides a range of information and advocacy materials on lead that can be adapted for local use (145).

- 2 / For an individual with a blood lead concentration $\geq 5 \mu\text{g/dL}$, the source(s) of lead exposure should be identified and appropriate action taken to reduce and terminate exposure.

Strong recommendation, high-certainty evidence of the toxicity of low-level exposure to lead

Rationale

There is consistent evidence from human observational studies and experimental animal data that exposure to lead even at low levels is associated with deleterious health effects (15, 16, 17, 34, 93, 103). As described in sections 4.4 and 4.5, a blood lead concentration below which there are no negative effects on health has not been identified; blood lead concentrations as low as $5 \mu\text{g/dL}$ and $10 \mu\text{g/dL}$ are associated with a range of effects, including impaired neurocognitive and behavioural development in children and cardiovascular disease in adults (Fig. 2). The health impacts of lead exposure in childhood may persist into adolescence and adulthood (119–122); therefore, terminating exposure is particularly important for this age group. The lack of a threshold blood lead concentration for toxicity implies that action should be taken if any lead is measured in blood. This is not necessarily practicable, however, because reliable measurement of very low blood lead concentrations requires advanced analytical equipment and a high level of technical skill (142), which are not available in all countries.

In high-income countries with effective regulatory control of sources of lead exposure, blood lead concentrations have been decreasing steadily over the past 10–20 years and are now very low in most people. Typically, the health authorities in those countries define excessive exposure to lead in relation to the reference value for the population as a whole. This is usually the blood lead concentration that characterizes that of the top 2.5% or 5% of the population, i.e. the 97.5th or 95th percentile, respectively. In France, for example, $5 \mu\text{g/dL}$ is the 98th percentile value for children < 7 years (146). Germany has adopted reference values of $3.5 \mu\text{g/dL}$ for children aged 3–14 years, $7 \mu\text{g/dL}$ for women and $9 \mu\text{g/dL}$ for men (147), which are based on the 95th percentile values (148). In the USA, a reference value of $5 \mu\text{g/dL}$ was established in 2012 based on the 97.5th percentile of blood lead concentrations observed in children

< 6 years during 2008–2012 (149). This concentration is also the reference value for adults (≥ 16 years) (150).

The guideline development group decided not to use a population-based measure such as a 95th or higher percentile value in a global guideline to determine whether clinical management interventions are necessary, for several reasons. Establishment of such a value requires data on blood lead concentrations from a sufficiently large, representative sample of the population. It also requires a quality-assured laboratory service that can accurately measure very low blood lead concentrations. The resources necessary for establishing a national reference blood lead concentration are not available in many low- and middle-income countries. Furthermore, in countries where there are continuing sources of high exposure for the general population, exposure from multiple sources and/or limited or ineffective control measures, a reference value based on a 95th percentile could result in a relatively high blood lead concentration being the threshold for initiating clinical interventions. This would offer less protection against the deleterious effects of lead on an individual's health.

In countries in which there is already a very low reference value, it may not be possible to reduce a person's blood lead concentration further with personal interventions; rather, population interventions might be required to reduce continuing sources of lead exposure. WHO is currently reviewing population-based interventions and non-clinical interventions as part of a future guideline on the prevention of lead exposure.

In view of the above and the extensively reviewed toxicological data and practical considerations, the guideline development group decided that a blood lead concentration of $5 \mu\text{g/dL}$ was a pragmatic value at which to initiate clinical interventions.

6.3 Values, equity, feasibility and acceptability of a 5 µg/dL threshold value

The anticipated outcome of this recommendation is a reduced likelihood of lead-related health, social and economic impacts. This would be expected to be valued by the person concerned, the carer in the case of a child and by society as a whole.

Health equity considerations include the disproportionate burden of lead exposure in economically deprived and disadvantaged populations, particularly in low- and middle-income countries (151–154). The United Nations Children’s Fund has estimated that about one in three children globally has a blood lead concentration > 5 µg/dL (151). In some settings, working with lead is an important livelihood, and options for stopping exposure may be limited. This is particularly true when individuals and communities lack the influence or power to improve their work or environmental conditions. When effective action is taken, however, a blood lead concentration > 5 µg/dL could improve health outcomes by reducing the short- and long-term adverse health and social impacts of lead exposure.

Blood lead concentrations \geq 5 µg/dL can be measured without highly sophisticated laboratory instrumentation (142). For screening purposes, a capillary blood sample can be analysed in a point-of-care analyser, which is relatively low-cost and simple to operate (142).

The feasibility of terminating lead exposure depends on the type of intervention required. This could be relatively simple, such as stopping sale of lead paints or more complicated and costly, such as remediation of contaminated land. Where the source of exposure is related to economic activities, such as lead recycling or mining, the feasibility and acceptability of terminating lead exposure will depend on whether working methods can be changed to reduce exposure or on the availability of alternative sources of income. This is a particular challenge in low-income communities engaged in small-scale artisanal industries (155). At low blood lead concentrations, the toxic effects are largely subclinical. Therefore, in the absence of understanding of the potential long-term impacts of exposure, governments may be less motivated to take action.

6.4 Considerations for implementation

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 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 for establishing a laboratory service for this purpose (142). As discussed in section 5, the venous blood lead concentration is the definitive biomarker of exposure and risk on which management decisions are routinely based; however, for screening purposes, use of capillary samples is acceptable.

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.



Lead poisoning and gold processing in Zamfara state, Nigeria, Ap.
Credit: Olga Victorie/MSF

Recommendations

for specific treatment interventions

This section provides WHO recommendations on specific aspects of the clinical management of patients with lead poisoning and descriptions of the type and strength of the evidence for each. The recommendations are for:

- GI decontamination after ingestion of lead;
- nutritional interventions in children and pregnant and lactating women; and
- chelation therapy in children, adolescents, adults and pregnant women.

The single most important action in the management of any lead exposure is to take measures to stop the exposure as quickly as possible. This alone will itself result in a reduction in the blood lead concentration and clinical improvement.

7.1 Gastrointestinal decontamination after ingestion of a lead foreign body or other lead-containing material

7.1.1 Introduction

The aim of GI decontamination is to remove lead objects or lead compounds from the GI tract and reduce or prevent absorption, thereby reducing the risk and severity of lead poisoning. The available methods for GI decontamination in the management of poisoning have been reviewed by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists. The methods are administration of activated charcoal (156), induced emesis (157), gastric lavage (158), administration of cathartics (159) and WBI (160). Not all of these methods are, however, applicable to the clinical management of lead ingestion, as discussed below. In addition, objects or materials can be removed from the gut by endoscopic or surgical procedures.

A number of factors bear on the efficacy of any of these methods, including the interval between ingestion and attempted decontamination, the quantity of toxic substance ingested, the physicochemical properties of the substance (e.g. whether it can bind to activated charcoal, its solubility) and the potential adverse effects of the decontamination technique in the context of the substance ingested (e.g. the risks of inserting a lavage tube if a corrosive substance has been swallowed).

Lead poisoning is most often associated with chronic ingestion of small amounts, e.g. in young children who ingest lead-contaminated dust through hand-to-mouth behaviour or some individuals with pica who eat large

quantities of lead compounds, e.g. paint flakes, over time. In such cases, there may be significant amounts of lead in the gut, which is often visible on an abdominal X-ray (161). Lead poisoning can also occur after acute ingestion of a lead object, e.g. a curtain weight or a fishing weight or sinker, which remains in the acidic environment of the stomach or in the intestines for days or weeks and from which lead is slowly absorbed (68, 69). More rarely, lead poisoning can result from intentional or unintentional acute ingestion of a toxic amount of a lead compound.

Evidence was sought for the impact of GI decontamination on the following outcomes:

Critical outcomes

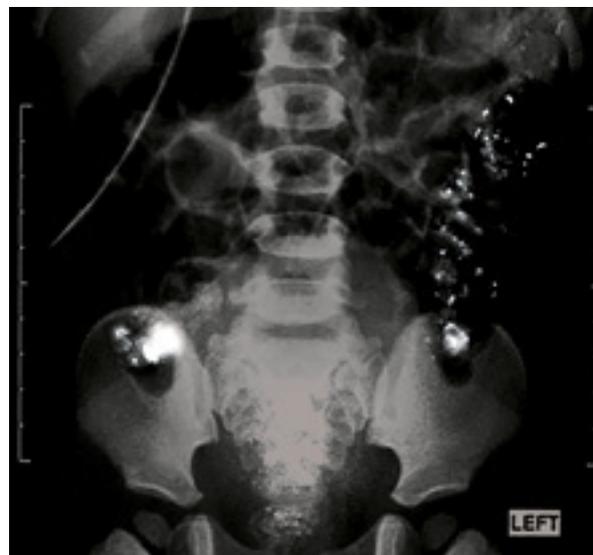
- blood lead concentration;
- neurological (cognitive, neurobehavioural and neuromotor) effects of lead poisoning measured in standardized, validated tests;
- mortality; and
- symptoms and signs of lead poisoning, e.g. abdominal colic and encephalopathy.

Important outcomes

- lead foreign bodies seen in vomitus, lavage fluid, stools or effluent; and
- adverse events of GI decontamination.

The search found only case reports and small case series describing GI decontamination following lead ingestion. There were no randomized or other controlled studies. In many studies, multiple methods of GI decontamination were used. The type and quantity of ingested material varied considerably. The most commonly reported outcome was removal of the material from the GI tract with a few studies reporting on adverse events (8). Patients with elevated blood lead concentrations were usually given chelation, which confounded any interpretation of the impact of GI decontamination on clinical outcomes. The evidence could not be evaluated with the GRADE approach; rather the level of the evidence was categorized according to a scheme adapted from the Oxford Centre for Evidence-based Medicine Levels of Evidence Working Group (2009) (157). As there were no randomized controlled studies, the certainty of evidence for all outcomes was categorized as very low. Tables summarizing the interventions and outcomes are provided in a supplementary online document (*Web Annex*). The basis for the recommendations below is described in the evidence-to-decision table provided online (*Web Annex*). No specific studies were identified that examined issues of values, equity, feasibility or acceptability with regard to GI decontamination following lead ingestion, however, some observations are made in section 7.1.3. Considerations for the implementation of these recommendations are given in section 7.1.4.

The recommendations below suggest use of medical imaging in certain circumstances to confirm the presence of and locate and monitor the movement of lead in the GI tract. The most commonly used technique is abdominal X-ray. WHO guidance is available on the factors to be considered in deciding on radiological imaging (162).



X-Ray image of pica in child's gastrointestinal tract. Credit: Courtesy of Paul Dargan.

7.1.2 Recommendations for all age groups

- 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 recommendation, very low-certainty evidence.

Rationale

The available evidence consisted of 13 case reports and was categorized as of very low certainty (8, *Web Annex*). Endoscopic procedures were the most commonly reported intervention (*Web Annex*); they were partially or fully successful in removing foreign bodies in nine cases and ineffective in two. One of the cases in which it was ineffective subsequently underwent surgery, and surgery alone was used in two cases. WBI was used in two cases, in combination with other methods of GI decontamination (*Web Annex*).

In four case reports of lead objects in the stomach, GI decontamination was not used (*Web Annex*). Three cases were fatal, as the presence of lead was either discovered when poisoning was at an advanced stage or post mortem. In the fourth case, the object was seen in the antrum of the stomach shortly after ingestion and had moved into the large intestine by day 5. The risk of severe lead poisoning is high when a lead object remains in the stomach as the acidic environment increases dissolution of lead, which is then absorbed. The longer the object remains in the stomach, the more likely it is that toxicity will occur. There is, however, insufficient evidence to establish how long a lead object can be left in the stomach without harming the patient, in view of many variables, including the nature

of the object (size, number and surface area) and patient characteristics (e.g. age, clinical status). When multiple small objects, such as pellets, have been ingested, the blood lead concentration can rise rapidly (163).

In spite of the very low certainty evidence, the guideline development group considered that the balance of harms and benefits favoured removal of a lead object to prevent potentially severe or fatal lead poisoning and advised a strong recommendation. Removal is particularly important if the blood lead concentration is increasing, there are features of lead toxicity, or the position of the object has been monitored and it has not moved for some time. Suggested methods are oesophagogastroduodenoscopy or surgery or, if these are not available, WBI. The decision on the approach to be used should be made for each case, usually in discussion with other specialist teams such as of endoscopists and surgeons.

The use of emesis or gastric lavage was considered unlikely to be effective owing to the weight, size and shape of most lead foreign bodies; moreover, emesis carries the risk that the object will cause choking. Metallic lead is not bound by activated charcoal (164).

2 / **Consider whole bowel irrigation for removing solid lead objects, such as a 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 recommendation, very low-certainty evidence.

Rationale

The only evidence identified was from 18 case reports and is categorized as very low certainty. The cases involved ingestion of lead pellets, bullets or fishing weights in numbers ranging from one to several thousand (8, *Web Annex*). In 12 cases, a combination of WBI and/or a cathartic and/or endoscopy and/or surgery was used. The duration of WBI varied from 6 h to 3 days. In four of five cases in which only a cathartic was used, expulsion of lead was reported over periods of 4–20 days. In six cases in which no GI decontamination was used, the lead objects cleared from the GI tract in 7–17 days (*Web Annex*). The diversity of the cases made it difficult to draw conclusions about the relative effectiveness of WBI, cathartics and allowing spontaneous elimination in preventing lead toxicity.

In view of the very low-certainty evidence, a conditional recommendation was made for WBI, on the grounds this method is that generally accepted for removing bulky or

poorly soluble toxic materials from the GI tract (160). The guideline development group took note of the evidence-informed joint position statement of the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists, which concluded that there was no evidence for the effectiveness of cathartics in the management of poisoning and advised against use of more than one dose of cathartic (159). On the basis of the limited available evidence and clinical experience, the guideline development group considered it unlikely that one dose of cathartics would remove a solid object from the gut.

Some solid objects pass through the GI tract of their own accord, and a decision to use WBI should be taken case by case. When WBI cannot be conducted or is unsuccessful and there is evidence of increasing toxicity, more invasive methods such as endoscopy or surgery may be considered.

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 recommendation, very low-certainty evidence.

Rationale

The evidence for this intervention is based on case reports and small case series on a total of 87 patients (8, *Web Annex*). Six patients showed lead toxicity and 13 developed appendicitis, including one with lead toxicity. Appendectomy was performed on 31 patients, including all those with lead toxicity, and the remainder were monitored. Only three patients were given chelation therapy. These cases suggested that the presence of lead in the appendix does not necessarily result in harmful effects.

In view of the very low-certainty evidence, a conditional recommendation was made. For a patient with no evidence of appendicitis or clinical or biochemical evidence of lead absorption, the guideline development group suggested monthly assessment for the first 3 months, followed by less frequent monitoring thereafter, provided the patient remains clinically well. It is recognized that some patients and physicians may prefer to remove the lead, even if it is not affecting health, as a preventive measure.

4 / Consider whole bowel irrigation for removing liquid or solid lead-containing substances, such as paint chips, lead-containing complementary or alternative medicines or ceramic glaze, *when the material is known to be dispersed in the gut.*

Conditional recommendation, very low-certainty evidence.

Rationale

Twenty case reports were identified, most of which involved ingestion of ceramic glaze or lead paint chips, shown on abdominal X-ray to be dispersed through the GI tract (8, [Web Annex](#)). In nine cases, several methods of GI decontamination were used, including gastric lavage, activated charcoal, WBI and cathartics. WBI was used alone in six cases, gastric lavage in four cases and cathartics in one case. WBI cleared the GI tract of ceramic glaze in all three cases in which it was used and lead paint chips in three of five cases. GI decontamination did not necessarily prevent an increase in blood lead concentrations.

Lead compounds are toxic, and absorption occurs mainly in the duodenum (93). The guideline development group considered that, when lead-containing materials are visible in the GI tract, GI decontamination is justified to reduce absorption and, potentially, the severity of poisoning. While the certainty of evidence for any method is very low, WBI is preferred over other methods as a means of clearing the whole of the GI tract. In view of the very low-certainty evidence, a conditional recommendation was made.

7.1.3 Values, equity, feasibility and acceptability of GI decontamination

Patients and children's carers would be expected to value the possibility of reducing the risk of potentially severe toxic effects through GI decontamination.

The identified evidence was from high-income countries, and it was recognized that the availability of equipment and trained staff to carry out more invasive procedures such as paediatric oesophagogastroduodenoscopy or surgery would depend on the setting. A patient might have to be transferred to a tertiary-care hospital. Polyethylene glycol-electrolyte solution, used for WBI, may be more readily available in lower resource settings as it has other medical uses, such as bowel cleansing before surgery or colonoscopy. This preparation is not, however, on the WHO Model List of Essential Medicines (165). Health equity would be improved if the necessary resources were available to provide appropriate GI decontamination interventions for ingestion of lead and other harmful or toxic agents.

Feasibility and acceptability would be influenced by the availability of resources for these interventions and the associated costs. Some patients, particularly young children, may find WBI difficult to tolerate, as it involves administration of a fairly large volume of polyethylene glycol-electrolyte solution, usually through a nasogastric tube. Home-administered WBI was used in a case of ingestion of lead foreign bodies, although no details were provided of the regimen used (166). No description of such use was found for lead compounds; however, as lead absorption is likely to be rapid, treatment at home may not be appropriate.

7.1.4 Implementation considerations for GI decontamination

The review of GI decontamination covered ingestion of various types and quantities of lead-containing material. Thus, the most appropriate method of GI decontamination differs 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.

GI decontamination is often considered in the management of poisoning. It is therefore important that medical personnel be trained in the appropriate use of GI decontamination methods. Medical personnel should also be trained in the diagnosis and management of lead poisoning. The management of lead poisoning requires access to laboratory services for measuring blood lead concentrations. WHO guidance is available on the selection of analytical methods and establishing a laboratory service for this purpose (142).

Endoscopic procedures are standard practice for removing foreign bodies when there is a risk of harm to the patient (167). National and international professional societies have developed evidence-based or evidence-informed clinical guidelines on the use of these procedures in children (168, 169) and adults (170). Oesophagogastroduodenoscopy is particularly applicable for large objects that will not easily pass the pylorus, and its use may obviate surgery.

General skills in the administration of abdominal surgery (including laparoscopy) should be available in secondary and tertiary medical services. WHO guidance is available on appendectomy (171).

WBI should be conducted only with an iso-osmotic polyethylene glycol-electrolyte solution, in order to avoid electrolyte or fluid imbalance in the patient during administration. A procedure for administering WBI is provided in Appendix 3 of the joint position statement of the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists (160).

The patient's clinical status and blood lead concentration should be monitored and additional interventions taken accordingly (see sections 7.2–7.3).

After GI decontamination, it is, of course, essential to ensure that the patient is not further exposed by taking appropriate preventive measures, for example removing lead paint and lead objects from the home or ensuring that they are kept out of sight and out of reach of children.

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

7.2.1 Introduction

Evidence from studies in experimental animals and humans indicates that nutritional factors, including intake of minerals and vitamins, alter susceptibility to lead (15, 34, 172). Possible mechanisms include modification of lead absorption, deposition in tissues and release from body stores and modification of the toxic effects of lead, for example through interaction with lead bound to cellular enzymes (34, 173, 174). The interactions of lead with dietary factors such as calcium, iron and zinc are complex.

Lead is thought to compete with calcium and iron for absorption from the gut, and low-calcium diets and iron deficiency have both been associated with higher blood lead concentrations (34, 175–181). Low calcium intake is associated with increased deposition of lead in soft tissues and bone (173). During pregnancy, lead can be remobilized from bone stores as calcium is taken to form the fetal skeleton (93, 100, 182). High calcium intake during pregnancy can reduce maternal skeletal-bone turnover (183, 184) and may therefore protect against an increased blood lead concentration. In the case of iron, there may be synergistic or additive effects between iron deficiency and lead toxicity, in particular with regard to anaemia and impaired cognitive functions (174, 185, 186). Low dietary intake of zinc is also associated with higher blood lead concentrations in young children; however, the mechanism has not been determined (34).

With regard to vitamin intake, vitamin D may have a protective effect, as it increases intestinal absorption of calcium and phosphate and is important for maintaining adequate serum concentrations for bone mineralization (187). Studies in experimental animals suggest that some antioxidant vitamins, such as vitamin C, have a protective effect against lead toxicity (188). A cross-sectional study in the USA of data from the Third National Health and Nutrition Examination Survey found an association between high serum levels of ascorbic acid and decreased prevalence of elevated blood lead levels (189).

Supplementation with minerals and/or vitamins may protect against or mitigate the toxic effects of lead. This may be particularly the case in economically deprived populations who are doubly burdened by nutritional deficiencies and high lead exposure (173).

The systematic review considered the following outcomes:

Critical outcomes

- blood lead concentration;
- cord blood lead concentration;
- neurological (cognitive, neurobehavioural and neuromotor) outcomes in children measured in standardized, validated tests;
- mortality in neonates and severely poisoned children and women;
- symptoms and signs of lead poisoning; and
- pregnancy outcomes, namely live birth and survival to one year, birth weight and neurological status of the neonate.

Important outcomes

- lead concentration in breast milk,
- mobilization of lead from bone (in women) and
- adverse effects of nutritional supplementation.



Good nutrition is important in protecting and mitigating against the toxic effects of lead. Credit: WHO

The systematic evidence review addressed the groups most vulnerable to lead toxicity, namely neonates, children, adolescents (< 19 years) and pregnant and lactating women. It was initially planned to include only studies in which participants had blood lead concentrations $\geq 5 \mu\text{g/dL}$; however, very few relevant studies were found, and it was decided to include studies in which participants had lower blood lead concentrations, although this resulted in some indirectness of the evidence.

A small number of RCT were identified of calcium supplementation for children and pregnant and lactating women and of iron and zinc supplementation for children. The outcomes reported after calcium intake were lead concentrations in blood, breast milk and bone; the outcomes reported after iron and zinc supplementation were blood lead concentrations and cognitive and behavioural outcomes. The studies with zinc provided moderate-certainty evidence of no benefit, and no recommendation was made. Small, individual studies, most including fewer than 100 subjects, were identified for combinations of calcium with vitamin A, C or D, but the evidence they provided was insufficient to make a recommendation. No studies that met the inclusion criteria were found for other vitamins or minerals.

The available studies 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 significant (blood lead concentration $> 45 \mu\text{g/dL}$) or severe (blood lead concentration $> 70 \mu\text{g/dL}$) lead poisoning.

The study populations included subjects judged to be deficient in the nutrient under study and subjects judged to have adequate nutrition. Overall, the certainty of the evidence was moderate to very low (9). GRADE summary-of-findings tables and evidence-to-decision tables are provided in supplementary online material ([Web Annex](#)).

No specific studies were identified that examined issues of values, equity, feasibility or acceptability with regard to nutritional supplementation after lead ingestion; however, some observations are made in sections 7.2.3 and 7.2.5. WHO recommendations are presented below for children and for pregnant and lactating women. Considerations for implementation of nutritional interventions are provided in section 7.2.6.

7.2.2 Recommendations for children ≤ 10 years of age

1 / **For a child (≤ 10 years) with a blood lead concentration $\geq 5 \mu\text{g/dL}$ who has, or is likely to have, inadequate calcium intake, administration of calcium supplementation is recommended.**

Remarks: The level of calcium supplementation should be sufficient to ensure that the total calcium intake meets the national age-appropriate recommended nutrient intake value.

Strong recommendation, very low-certainty evidence

Rationale

Evidence was provided by four RCTs, two of which were placebo-controlled. The studies were small, and the populations differed in age, blood lead concentration, calcium intake and calcium dose and were therefore not pooled (9, [Web Annex](#)). In the largest study (400 subjects, variable regular intake of calcium), the mean blood lead concentration in the intervention group was $5 \mu\text{g/dL}$ lower (95% CI, -6.42 ; $-3.58 \mu\text{g/dL}$) than that of the control group after 3 months of supplementation with 500 mg calcium, with a smaller effect in the group given 250 mg calcium (190). A treatment effect was still seen after multivariate regression analysis with control for nutritional status and dietary calcium intake. Two smaller studies (total number of subjects, 116) showed reductions in blood lead concentration (191, 192), but a study in children ($n = 88$) judged to have adequate calcium intake, who were given supplements to reach a daily intake of 1800 mg, showed no treatment effect (193). Adverse events were evaluated in three studies, and none were seen (191–193). The certainty of evidence provided by these studies was rated as very low because of risk of bias and imprecision.

The guideline development group noted the reduction in blood lead concentration associated with calcium administration in some studies and the lack of adverse events. It also noted that, in children whose daily calcium intake is below recommended values, increasing calcium intake has other health benefits, such as maintaining bone health (194). For these reasons, a strong recommendation was considered appropriate for children who have inadequate calcium intake, in spite of very low-certainty evidence. The group emphasized that this intervention is only one component of the general management of lead exposure, the most important being removal or control of lead sources.

Vitamin D is important for calcium absorption and homeostasis; therefore, it is also necessary to maintain an adequate vitamin D intake (195). Additional information on implementation is provided in section 7.2.6.

2 / For a child (≤ 10 years) with a blood lead concentration of ≥ 5 $\mu\text{g}/\text{dL}$ 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 (196, 197) or standard clinical practice.

Strong recommendation, very low-certainty evidence.

Rationale

Evidence for this intervention was from one small RCT ($n=135$) in children who were iron-deficient (serum ferritin, < 15 $\mu\text{g}/\text{L}$) and two larger RCTs in children, the majority of whom were not iron deficient (9, *Web Annex*). In the iron-deficient children, after 16 weeks' administration of either 15 mg of elemental iron in a daily fortified meal or an identical unfortified meal, the median blood lead concentration was 2.1 $\mu\text{g}/\text{dL}$ lower in the iron-fortified group (95% CI not calculable). Significantly fewer children in the iron group had a blood lead concentration ≥ 10 $\mu\text{g}/\text{dL}$, with a risk ratio of 0.52 (95% CI, -0.23 to 0.51) ($P < 0.001$) (198). This study provided very low-certainty evidence of a treatment effect.

In the two RCTs in mostly iron-sufficient children, who were given 9.75 mg or 8 mg of elemental iron, the difference in the reduction in blood lead concentrations was extremely small (199, 200). The mean difference in the decrease in blood lead concentrations between the treated and placebo groups was 0.14 $\mu\text{g}/\text{dL}$ (95% CI, -0.23 ; 0.51) in the larger study ($n=304$) (199) and 0.5 $\mu\text{g}/\text{dL}$ (95% CI not calculable) in the other ($n=227$) (200). Related studies

of cognitive and behavioural outcomes found no difference between intervention and placebo groups (200–202). These studies provided moderate-certainty evidence of no treatment effect.

In spite of the very low-certainty evidence for iron-deficient children, the guideline development group made a strong recommendation, for the following reasons: i) both iron deficiency and lead exposure are associated with anaemia and impaired cognitive development in children and there may be an additive or synergistic effect; ii) an existing WHO guideline recommends correction of iron deficiency in children to prevent anaemia (196); and iii) iron deficiency is associated with increased lead absorption in the GI tract and may increase the risk of pica, which may include lead ingestion (20, 203). Additional information on implementation is provided in section 7.2.6.

For children who were not iron-deficient, there was moderate-certainty evidence of no treatment effect, and the guideline development group did not make a recommendation.

7.2.3 Values, equity, feasibility and acceptability of calcium and iron supplementation in children

A reduction in blood lead concentration and the other health benefits of calcium and iron supplementation would be regarded as desirable outcomes and would be expected to be valued by children's carers.

Health equity considerations include the fact that children in economically deprived and disadvantaged populations bear the greatest burden of lead exposure, particularly in low- and middle-income countries (151). Nutritional deficiencies, including of calcium (194) and iron (197), are also prevalent in these populations, and addressing these deficiencies has important benefits independent of the termination of lead exposure. These interventions would therefore be expected to be acceptable to children's carers. Providing calcium or iron supplements could, however, cause harm if this was used as a substitute for reduction and removal from exposure to lead.

With regard to feasibility, while oral calcium preparations are not on the WHO Model List of Essential Medicines for Children (204), calcium supplements suitable for children are available at a range of prices (205). Iron supplements can cause constipation and abdominal discomfort, and these effects might reduce treatment adherence. The supplements are on the WHO Model List of Essential Medicines for Children for the treatment of iron-deficiency anaemia (204).

7.2.4 Recommendations for pregnant and lactating women

1 / For a pregnant woman with a blood lead concentration of $\geq 5 \mu\text{g/dL}$ who has, or is likely to have, inadequate calcium intake, administration of calcium supplementation is recommended.

Remarks: The dosage should be sufficient to raise the total calcium intake to the national guideline for calcium in pregnant women or to the WHO/FAO-recommended nutrient intake value (1.2 g) (204). This should be given as soon as the pregnancy is recognized, for the duration of the pregnancy.

Strong recommendation, moderate-certainty evidence

Rationale

The systematic review identified only one study that provided moderate-certainty evidence of an effect on blood lead concentration (9, *Web Annex*). This was a placebo-controlled RCT in 670 pregnant women given a daily supplement of 1.2 g of calcium carbonate (480 mg elemental calcium) for the duration of pregnancy. The women had a mean daily calcium intake before the study of 900 mg. The calcium supplement was associated with an 11% lower (95% CI, -17.8% to -3.7%) blood lead concentration, with a larger effect in women who adhered better to treatment (206). The study population had a geometric mean blood lead concentration $< 5 \mu\text{g/dL}$, and only 37% had a concentration $\geq 5 \mu\text{g/dL}$; however, analysis of this subgroup also showed a larger reduction (17%) than in the placebo group. The difference in blood lead concentrations was also greater in women who had a patella bone lead concentration $> 5 \mu\text{g/g}$ bone mineral, suggesting that calcium supplementation may reduce mobilization of lead from bone.

In formulating this recommendation, the guideline development group took account of the following factors. During pregnancy, the physiological demand of the mother for calcium is increased for formation of the fetal skeleton, and some of this demand is met by increased bone resorption. In lead-exposed mothers, this process releases lead from bone stores into blood, exposing both the mother and the fetus (100). Lead exposure is associated with adverse pregnancy outcomes, including increased risk of hypertension (16, 93, 136), reduced fetal growth (16, 136) and preterm birth (16, 34). The study provided moderate-certainty evidence that administration of a low dose of calcium is associated with a reduction in blood lead concentration, possibly by reducing mobilization of lead from bone. No evidence was identified for other prioritized outcomes, such as live births.

In pregnant women in general, an adequate calcium intake is important to protect against the risk of hypertensive disorders, including pre-eclampsia, and related problems such as preterm birth and neonatal death. There is low certainty evidence from a systematic review for pregnant women in general that high-dose calcium supplementation ($> 1 \text{ g/day}$) may reduce the risk of pre-eclampsia and preterm birth, particularly for women with low-calcium diets (207). This review also found limited evidence that

low-dose calcium supplementation may be associated with reductions in pre-eclampsia, hypertension and admission to neonatal high care.

The guideline development group took account of the moderate-certainty evidence of a benefit in reducing the blood lead concentration and potential wider benefits on pregnancy outcomes of providing calcium supplementation for women with low calcium intake and considered that a strong recommendation was justified. As the optimum dose of calcium is not established, the recommendation is for a dose sufficient to meet nationally established guideline intake values or the WHO/FAO recommended intake (195). Calcium supplementation should be started as soon as pregnancy is recognized and should continue throughout pregnancy. Additional information on implementation is provided in section 7.2.6.



Postnatal care in Nepal. Credit: WHO / Christopher Black

2 / Initiation or continuation of calcium supplementation is suggested for lactating women who have a blood lead concentration of $\geq 5 \mu\text{g/dL}$. This should be for the duration of lactation.

Conditional recommendation, low- to very-low certainty evidence

Rationale

Only one RCT was identified, which provided low-certainty evidence of an impact on blood lead concentrations; a further, linked study provided very-low certainty evidence of an effect on breastmilk lead concentrations (9, *Web Annex*). In the RCT, 617 lactating women were given 1.2 g of elemental calcium or placebo for 6 months (208). The women had mean blood lead concentrations of about $9 \mu\text{g/dL}$. The group that received supplement showed a small decrease in blood lead concentrations, and the effect was greater in women who had $> 50\%$ adherence and had higher patella lead concentrations ($> 5 \mu\text{g/g}$ bone mineral), in whom the mean blood lead concentration was $1.16 \mu\text{g/dL}$ lower (95% CI, -2.08 to -0.23) than in the placebo group. In the linked study of lead in breastmilk, there was no significant difference in lead concentrations at different times between women given calcium and those given placebo; however, the rate of decrease was 5–10% higher in the calcium group during lactation (209). In addition, very low-certainty evidence suggested that calcium supplementation was associated with reduced release of lead from bone in

breastfeeding women (208). The evidence of a benefit of calcium supplementation was very limited, although there was a suggestion of greater benefit in women with higher past exposure to lead and significant bone lead stores. No evidence was identified for other prioritized outcomes.

Bone resorption continues during lactation, and blood lead concentrations have been shown to rise during this period (100). In addition, a small amount of lead is secreted from blood into breastmilk (101). There is uncertainty about the role of dietary calcium in preventing bone resorption during lactation and the WHO/FAO guidance on mineral requirements in lactating women does not make a recommendation for calcium intake (195). The interaction between lead and calcium is complex, however, and, as there could be a more general benefit for the women's health, the guideline development group advised a conditional recommendation to give calcium supplementation to lactating women.

Additional information on implementation is provided in section 7.2.6.

7.2.5 Values, equity, feasibility and acceptability of calcium supplementation in pregnant and lactating women

No studies were found that specifically addressed these issues in lead-exposed women; however, some evidence was available for pregnant women in general. A qualitative systematic review of women's expectations of antenatal care found that women in high-, middle- and low-resource settings valued a positive pregnancy experience, including effective clinical practices such as nutritional supplements and relevant, timely information on diet and nutrition (210).

Health equity considerations include the fact that the greatest health burden of lead exposure is in economically deprived and disadvantaged populations, particularly in low- and middle-income countries. Women in these countries who are poor, least educated, and live in rural areas have less coverage with health interventions and worse health outcomes than more advantaged women (211). They are also more likely to have inadequate calcium intake (211). Provision of calcium supplements, particularly if part of a programme of antenatal and postnatal support, could improve health equity, provided the interventions was not used as a substitute for environmental remediation of lead hazards.

With regard to feasibility, calcium preparations are on the WHO Model List of Essential Medicines (165) and on 64% of national essential medicines lists (212). While calcium tablets tend to be large and may be unpalatable to some women, in the above RCTs over 80% of subjects had $> 50\%$ adherence in taking the supplement (205, 208).

7.2.6 Implementation considerations for supplementation with calcium and iron

Health-care providers, particularly 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. Management of lead poisoning requires access to laboratory services for measuring blood lead concentrations. WHO guidance is available on selecting analytical methods and establishing a laboratory service for this purpose (142).

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 sources of lead exposure and methods for reducing exposure. For pregnant women this information can be provided during routine antenatal care visits (213).

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 (187).



Chelating agents are antidotes for lead poisoning and included in WHO Essential List of Medicines.
Credit: WHO / Blink Media - Amanda Mustard

Calcium

Calcium intake can be assessed by taking a dietary history and comparing intake against national recommended values (195). As the optimal dose for mitigating the effect of lead exposure is unknown, the guideline development group decided to refer to recommended daily intake values. It is recognized that calcium requirements may be different in different dietary cultures; therefore, national guidelines should be used when possible (195). When determining a dosage for a pregnant or lactating woman, health-care providers should consider the woman's calcium intake from other sources, such as medications (e.g. antacids) (211).

While the evidence supported use of calcium supplements, calcium intake can also be improved by increasing the amount of calcium-rich foods in the diet, use of fortified foods or traditional supplements such as dried fish. As calcium supplements may be manufactured from natural sources such as animal bone, they may be contaminated with lead, and care should be taken in sourcing products (214, 215).

Vitamin D is important for calcium absorption and homeostasis; therefore, it is also necessary to maintain an adequate vitamin D intake. In the case of pregnant women, WHO does not recommend routine vitamin D supplementation, and women should be advised that sunlight is the most important source of vitamin D (216). If vitamin D deficiency is suspected, vitamin D supplements may be given at the current recommended nutrient intake of 200 IU (5 µg) per day (216).

In children, it is suggested that 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. If necessary, the source of lead exposure should be investigated further.

In pregnant women, calcium should be given for the duration of pregnancy and consideration given to extending supplementation into lactation.

Iron

Iron deficiency can be determined by estimating the serum ferritin concentration and a marker of inflammation (e.g. C-reactive protein or α1-acid glycoprotein) (217). If serum ferritin cannot be measured, 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 for mitigating the effects of lead exposure are unknown; therefore, reference should be made to WHO guidance for treating iron deficiency (196, 197), which recommends a minimum treatment duration of 3 months, after which the iron status should be re-assessed to evaluate continuation (197). In malaria-endemic areas, iron supplementation may be harmful to children who do not have regular access to malaria surveillance and treatment services (196). Children with malaria may, however, be more susceptible to the neurotoxic effects of lead when they are exposed to high levels (111). These two considerations should be taken into account when deciding on iron supplementation.

Inclusion of vitamin C will improve iron absorption from the diet and from iron supplements (195).

7.3 Chelation therapy in individuals exposed to lead

7.3.1 Introduction

Chelating agents are pharmaceuticals that, by physicochemical means, bind to lead and other trace elements and facilitate their excretion from the body (218). The aim of chelation therapy is to facilitate renal excretion, thereby decreasing the lead body burden and, potentially, resolving toxic effects and improving clinical outcomes by decreasing the availability of lead for binding at its sites of action. Four chelating agents were reviewed: dimercaprol, penicillamine, sodium calcium edetate and succimer (10–13). In evaluating the efficacy of chelation therapy, the following critical and important outcomes were considered:

Critical outcomes

- blood lead concentration;
- neurological (cognitive, neurobehavioural and neuromotor) effects of lead poisoning measured in standardized, validated tests;
- mortality;
- symptoms and signs of lead poisoning, e.g. abdominal colic and encephalopathy; and
- long-term health outcomes that may be affected by lead exposure, such as cardiovascular and renal effects.

Important outcomes

- urinary excretion of lead,
- mobilization of lead from bone and
- adverse events associated with chelation therapy.

In view of the importance of preventing the harmful effects of lead in children without overt lead poisoning, studies in children with blood lead concentrations < 45 µg/dL were analysed separately for the outcomes for which data were available.

The evidence review found very few randomized or non-randomized controlled studies, and most of the data found were from retrospective or prospective case series. The latter studies did not include control for the confounding effect of removal from lead exposure, which is an essential aspect of management. This made it difficult to differentiate the impacts of chelation and of removal from exposure on the studied outcomes. The certainty of the evidence for most outcomes was therefore very low.

The only blinded, randomized, placebo-controlled trial of chelation was the treatment of lead-exposed children (TLC) Trial, conducted with children with blood lead concentrations < 45 µg/dL treated with succimer.

GRADE summary of findings tables for chelation in children, adolescents and non-pregnant adults and evidence-to-decision tables are provided in supplementary material online ([Web Annex](#)).

The evidence identified for chelation therapy in pregnancy is described in section 7.3.7.

7.3.2 Overview of recommendations for chelation therapy

The recommendations for chelation therapy are differentiated according to threshold blood lead concentrations, age, sex, and severity of lead poisoning. The management of pregnant women is described in section 7.3.7. Chelation therapy is not usually indicated for individuals with blood lead concentrations < 45 µg/dL, and this is discussed in the recommendations below. Further information on the use of chelation, including criteria for hospital admission and selection of chelating agents, is given in section 7.3.9.

As described in section 4.3, absorbed lead is distributed to blood, soft tissues and bone. In chronic poisoning, bone stores of lead are significant, and the lead may remain there for many years. Only some of the lead in bone is directly mobilizable by chelating agents. After chelation therapy, a rebound increase in the blood lead concentration may be seen 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 allowing a period for re-equilibration, to determine whether further chelation is necessary.

The following principles apply:

- *As 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.
- In applying these recommendations to individual patients, room must be left for clinical judgement according to potential vulnerability to lead toxicity, the circumstances, the nature and chronicity of exposure, clinical features, the blood lead concentration or trends in concentrations and location of treatment. Some allowance may also be required for possible inaccuracy in measurements of blood lead concentrations.
- If possible, chelation should be administered by, or in consultation with, a clinical toxicologist or other medical practitioner experienced in the management of lead poisoning.
- The blood lead concentration should be re-checked 2–4 weeks after the end of chelation, with the shorter interval for higher initial blood lead concentrations. This is necessary to determine whether there is continuing lead exposure and/or whether chelation has been effective in reducing the blood lead concentration. Follow-up treatment depends on the blood lead concentration, as specified in this guideline.

7.3.3 Recommendations for 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 recommendation, 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 recommendation, 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 recommendation, very low-certainty evidence.

Rationale

The evidence for these recommendations was derived from a suite of studies from the TLC trial that specifically addressed the effect of chelation in children with blood lead concentrations $< 45 \mu\text{g/dL}$, and small quasi-randomized studies, small case series and studies with historical controls involving children with higher blood lead concentrations (10–13, Web Annex).

The TLC trial was a randomized, double-blinded, placebo-controlled study of succimer involving 780 children aged ≤ 3 years. Both treatment and placebo groups were removed from lead exposure. A suite of studies investigated short-term and long-term outcomes (219–224). The trial provided moderate-certainty evidence of an initially faster decrease in blood lead concentration in the first 6 months that did not persist to 12 months. There was low- to moderate-certainty evidence of no benefit for other critical or important outcomes, such as cognitive, behavioural and neuromuscular development. A statistically significant association between a fall in blood lead concentration and increased cognitive scores was seen only in the placebo group, in whom there was an increase of four points per $10 \mu\text{g/dL}$ fall in the blood lead concentration (223). Chelation with succimer was associated with slightly reduced growth at age 7 years (224). Overall, the guideline development group considered that the balance of risks and benefits in children with blood lead concentrations $< 45 \mu\text{g/dL}$ favours not giving chelation therapy, as removal from lead exposure is considered to be adequate.

No equivalent studies were found for use of other chelating agents in treating children with blood lead concentrations $< 45 \mu\text{g/dL}$; however, the guideline development group considered it unlikely that other agents would provide different results in terms of benefits, and chelating agents with significant adverse event profiles may be more harmful (see Box 1 in section 8.4).

Blood lead $\geq 45 \mu\text{g/dL}$

For children with a blood lead concentration $\geq 45 \mu\text{g/dL}$, there were no studies equivalent to the TLC trial for individual chelating agents or chelating agent combinations, and the evidence for all outcomes was of very low certainty (10–13, Web Annex). Lack of a control group in most of the studies meant that the results were confounded by the effect of removal from lead exposure. Rapid decreases in blood lead concentrations to values ranging from 39% to 79% of the baseline value and increased urinary excretion of lead were reported. In the few studies that reported symptoms and signs of lead poisoning, resolution or improvement was noted. In cases of severe neurotoxicity, some children were left with sequelae such as mental retardation and convulsive disorders, although there were fewer than among controls who had not been chelated (225–227).

Despite the limited availability of chelating agents in many low- and middle-income countries, the guideline development group decided that a strong recommendation

for chelation therapy in children with blood lead concentrations $\geq 45 \mu\text{g/dL}$ was justified, whether or not the child had clinical features of lead poisoning. This is because children are particularly vulnerable to the neurotoxicity of lead, with possible long-term neurological, cognitive and behavioural impairment (see section 4.4). Active elimination of lead from the body could confer an additional benefit to that of removal from lead exposure.

Blood lead 40–44 $\mu\text{g/dL}$

The guideline development group made a conditional recommendation for oral chelation in children with borderline but persistently elevated blood lead concentrations. This reflected concern about the accuracy of blood lead measurement, which depends on the method used, the equipment and whether the laboratory has adequate quality control. This is particularly likely to be a consideration in low- and middle-income countries where laboratories are often poorly resourced, but it may also be an issue in high-resource settings. In the USA, for example, the federal requirement for acceptable analytical performance in the measurement of blood lead concentrations is an accuracy of $\pm 4 \mu\text{g/dL}$, although many laboratories have better accuracy (228). In addition, the blood lead concentration provides only a partial guide to the risk of toxicity, and there is some variation in the health impacts of lead at specific concentrations. Thus, chelation is suggested for children with a blood lead concentration of 40–44 $\mu\text{g/dL}$, persistently elevated blood lead concentrations after removal from exposure, symptoms and signs of lead poisoning or doubt about the accuracy of the blood lead measurement. A decision to chelate should be made case by case, ideally guided by discussions with a clinical toxicologist or other medical practitioner experienced in the management of lead poisoning. An oral chelating agent is suggested, as it is less invasive than parenteral treatment and the child is unlikely to require hospital admission.

Blood lead $\geq 70 \mu\text{g/dL}$

Young children with very high blood lead concentrations ($\geq 70 \mu\text{g/dL}$) are more likely than adults to develop severe neurological toxicity, including lead encephalopathy, and they can quickly deteriorate, particularly if there is continuing lead exposure (115). It is considered good clinical practice to closely monitor such children, including through regular neurological assessment, to detect any signs of deterioration. Depending on the circumstances, this may be done as an in- or an outpatient, as discussed in section 7.3.9.

Any sign of lead encephalopathy in children can be life-threatening and is associated with permanent neurological damage such as mental retardation and seizure disorder (115). For this reason, although the evidence was of very low certainty, the guideline development group advised a strong recommendation for hospitalization and parenteral chelation therapy (see section 7.3.9 on selection of chelating agents).

7.3.4 Recommendations for non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentrations of 45–70 $\mu\text{g}/\text{dL}$

- 1 / For a non-pregnant adolescent girl or woman of child-bearing age who has a blood lead concentration of 45–70 $\mu\text{g}/\text{dL}$ but who *does not* show clinical features of lead poisoning, oral chelation therapy should be considered.

Conditional recommendation, very low-certainty evidence

Rationale

The evidence on the use of chelation in adolescents and adults was largely from uncontrolled case series (10–13, *Web Annex*). Most adult cases involved occupational exposure in men. Older age groups are less vulnerable to developing serious neurological toxicity than children, and chelation is usually given for high blood lead concentrations.

The guideline development group considered that a special case could be made for chelation therapy in girls and women of child-bearing age with a blood lead concentration in the range 45–70 $\mu\text{g}/\text{dL}$, even if there are no clinical features of lead poisoning. The rationale is that enhancing the elimination of lead could reduce the amount of lead available for deposition in bone and, for individuals with chronic exposure, might also release some

lead from bone into the chelatable pool for elimination. This could be a protective measure for the future when the girl or woman becomes pregnant, when lead is released into blood from bone stores, thereby exposing the fetus and re-exposing the mother. As a clinically well patient does not require hospital admission, an oral chelating agent is preferred (*see selection of chelating agents in section 7.3.9*). It was also recognized that not all girls or women would wish to have chelation therapy if they were asymptomatic of lead poisoning. The recommendation was therefore conditional. The use of chelation should be decided after a discussion between the physician and the patient about potential benefits and harms.

For chelation in pregnancy see section 7.3.7.

- 2 / For a male patient aged ≥ 11 years or a woman who is no longer of child-bearing age with a blood lead concentration of 45–70 $\mu\text{g}/\text{dL}$ but who does not show clinical features of lead poisoning, chelation therapy is not indicated. The patient should, however, be re-evaluated after 2–4 weeks to ensure that the blood lead concentration is decreasing and the patient remains well.

Conditional recommendation, very low-certainty evidence.



Exposure to lead can cause difficulties in learning at critical stages in life. Credit: WHO / NOOR / Sebastian Liste

3 / For a non-pregnant adolescent or adult with a blood lead concentration of 45–70 µg/dL who has mild–moderate clinical features of lead poisoning (such as abdominal pain, constipation, arthralgia, headache, lethargy), chelation therapy is suggested.

Conditional recommendation, very low-certainty evidence.

Rationale

The evidence for this group of patients was from small case series, usually with no control group. The patients had a range of blood lead concentrations, and specific ranges and outcomes could not be distinguished (10–13, Web Annex). There were very few cases in adolescents, and most of the adult exposures were occupational. Chelation therapy was associated with a variable but rapid reduction in blood lead concentrations to values ranging from 9% to 95% of the pre-treatment value and an increase in urinary excretion of lead. Some studies noted considerable inter-individual and intra-individual differences in urinary excretion during chelation. Most symptoms and signs of lead poisoning improved within 1.5–14 days, although some neurological features, such as weakness, took longer. No evidence was found on the effect of chelation therapy on the longer-term impacts of lead exposure, such as increased risks of cardiovascular and renal disease.

For patients without symptoms or signs of lead poisoning, the balance of benefits and harms of chelation therapy

with removal from lead exposure alone is unclear. The guideline development group considered that emphasis should be placed on removal from exposure rather than chelation therapy. The blood lead concentration and clinical status of the patient should, however, be re-evaluated after 2–4 weeks to ensure that exposure has terminated. They made a conditional recommendation, as some physicians and patients might prefer chelation therapy to be given.

When patients have mild–moderate clinical features of lead poisoning, the benefits of chelation therapy as compared with removal from exposure were also unclear. As chelation therapy is associated with rapid improvement in symptoms, some patients might prefer to be treated. A conditional recommendation for chelation therapy was made, as, ultimately, a decision on chelation depends on the specific case. Information on selection of chelating agents is provided in section 7.3.9.

For chelation in pregnancy see section 7.3.7.

7.3.5 Recommendations for non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentrations of > 70–100 µg/dL

1 / An adolescent or 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

Rationale

Some patients with blood lead concentrations > 70–100 µg/dL can deteriorate suddenly, without necessarily showing prodromal symptoms and signs. It is considered good clinical practice to closely monitor the clinical status and blood lead concentrations of these patients on an in- or out-patient basis (see section 7.3.9). Patients who are deteriorating, or in whom there is no or a slow decrease in blood lead concentration despite removal from exposure, should be reassessed for chelation therapy if this has not been given.

2 / For a non-pregnant adolescent or 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 recommendation, 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 recommendation, very low-certainty evidence.

Rationale

The evidence for this group of patients was from small case series, usually without control groups, and was therefore of very low certainty (10–13, *Web Annex*). The patients had a range of blood lead concentrations, the highest being 710 µg/dL, and it was not possible to distinguish specific ranges and outcomes. As described above, chelation therapy was associated with a rapid decrease in the blood lead concentration, increased urinary excretion and improvements in symptoms and signs of lead poisoning. Lead encephalopathy is unusual in adults, and only three cases were identified, all of whom improved after chelation.

No significant neurological features

For patients who are clinically well or show only mild–moderate features of lead toxicity but no significant neurological features in spite of high blood lead concentrations, the guideline development group recognized that not all physicians would give chelation.

Depending on the circumstances of exposure and the severity of poisoning, some physicians would wait to see whether removal from exposure alone resulted in improvement. For this reason, a conditional recommendation was made for chelation therapy.

Significant neurological features

For patients who show significant neurological features of lead toxicity, in particular encephalopathy, very low-certainty evidence suggested that chelation could improve survival. Despite the limited availability of chelating agents in many low- and middle-income countries, the guideline development group decided that a strong recommendation for chelation therapy was justified, as lead encephalopathy is a life-threatening condition.

For chelation in pregnancy see section 7.3.7. Information on selection of chelating agents is provided in section 7.3.9.

7.3.6 Values, equity, feasibility and acceptability for chelation in children and non-pregnant adolescents and adults

It was considered that carers of lead-poisoned children and adolescents and lead-exposed adults would value resolution of toxic effects and improved survival. Evidence from economic modelling in a high-income country indicated that parents would be willing to pay for chelation to reduce a child's lead body burden; however, the applicability of the modelling to other settings is unknown (229).

Health equity considerations include the greater prevalence of lead exposure in economically deprived and disadvantaged populations (151) and in settings where regulatory control of lead exposure, e.g. from environmental sources, is weak. Impaired neurocognitive development can have high personal and societal costs in terms of lost earnings, lost tax revenue and increased risk of antisocial behaviour (121, 230). While there is a consistent association between chelation therapy and enhanced elimination of lead, evidence is lacking for prevention of the long-term cognitive and behavioural impacts of lead; therefore, the impact on health equity is unclear. Provision of chelation therapy to these groups could cause harm if the therapy is given as a substitute for measures to terminate lead exposure, such as identifying and removal from source of exposure.

The four chelating agents are on the WHO model lists of essential medicines (169, 204); however, the availability of chelating agents in countries varies. An analysis in 2019 of 137 national essential medicines lists provided to WHO showed that penicillamine was listed in 70 (51%), dimercaprol in 59 (43%), sodium calcium edetate in 41 (30%) and succimer in only 8 (6%). All four chelating agents were listed in only four countries (212). This finding bears on the feasibility of the recommendations.

Factors that might influence the acceptability of chelation therapy include the duration of treatment and whether it is given on an in- or out-patient basis, as these factors have impacts on cost and convenience. In the case of mild-to-moderate poisoning, when hospital admission is not necessarily required for clinical reasons, children's carers and patients might prefer oral to parenteral therapy because it is less painful and can be given at home. Ensuring adherence to treatment for prolonged courses of chelation may be difficult, particularly if it requires repeated stays in or visits to medical facilities.

7.3.7 Recommendations for chelation in pregnancy

Exposure to lead during pregnancy is known to have negative effects on both the mother and the fetus. These include an increased risk of hypertension and possibly pre-eclampsia and reduced fetal growth, lower birth weight, preterm birth and spontaneous abortion. The risks are greater with higher blood lead concentrations (16, 34, 136). During pregnancy, calcium is mobilized from bone to form the fetal skeleton, which also releases stored lead, thereby re-exposing the mother and exposing the fetus (100).

The only evidence identified was from case reports, which were compiled in a narrative review (14, Web Annex). Some of the cases were poorly documented, and the main outcomes reported were the maternal and newborn blood lead concentrations. It was not possible to draw conclusions about the impact of chelation on other outcomes such as reversal of toxic effects in the fetus. For pregnant women, the certainty of the evidence was very low.

In the recommendations below, a distinction is made between pregnant women who have lead encephalopathy, for whom there is a strong case for chelation regardless of trimester, and women who are not encephalopathic,

in whom the trimester of pregnancy influences treatment decisions. Considerations for selecting a chelating agent are provided in section 7.3.9.

In all cases, regardless of the blood lead concentration, it is important to identify and remove the source(s) of exposure and to monitor the blood lead concentration. In addition to occupational and environmental sources, important sources of lead exposure of some pregnant women are pica (i.e. ingestion of soil, clay or other lead-containing materials) and use of traditional medicines and tonics (136). After treatment, the mother should be returned to an environment from which sources of lead exposure have been removed.

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.

Note that the mother's blood lead concentration can vary during pregnancy, with a decrease due to haemodilution in the second trimester and an increase in the third trimester and post-partum (93).

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 recommendation, very low-certainty evidence.

Rationale

The only evidence for use of chelation in pregnant women was from case reports, most of which concerned women in the third trimester of pregnancy; only two cases (in non-encephalopathic women) were found of chelation during the first trimester (14, Web Annex). The only evidence on use of chelation therapy in pregnant women with lead encephalopathy was from one case report of a woman in the third trimester with chronic lead exposure (231). Lead encephalopathy is a life-threatening condition, and the survival of both mother and fetus may be at risk. There is very low-certainty evidence in other patients with lead encephalopathy that chelation therapy is associated with improved survival. The guideline development group decided that the balance of potential benefits and harms favoured giving chelation therapy, and they advised a strong recommendation.

A decision on which agent to use depends on the circumstances (e.g. trimester of pregnancy, availability of the chelating agent), adverse effects of the chelating agent, including the risk of fetal harm in the first trimester, the setting (e.g. availability of treatment facilities) and clinical judgement (e.g. which chelating agent(s) can most safely and effectively be administered). In the first trimester, precedence should be given to the patient's preference if she can express it.

2 / For a pregnant woman with a blood lead concentration $\geq 45 \mu\text{g/dL}$, 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 uncertainties in the balance of risks and benefits (see Rationale):

No recommendation.

(ii) in the second or third trimester: chelation therapy is recommended.

Strong recommendation, very low-certainty evidence.

Rationale

The only evidence identified was from case reports of the treatment of 18 women, most of whom were in the third trimester of pregnancy (14, [Web Annex](#)). Some of the cases were poorly documented, and the main outcomes reported were maternal and newborn blood lead concentrations; no evidence was identified for other outcomes such as reversal of toxic effects in the fetus. The only data on use of chelation during the first trimester were from two cases involving succimer that were known to a member of the guideline development group (14, [Web Annex](#)).

First trimester

For pregnant women who do not have life-threatening lead encephalopathy and in the absence of data for an evaluation of the harms and benefits of chelation, the guideline development group could not make a specific recommendation and concluded that each case should be considered individually. A decision about chelation should be taken in consultation with the pregnant woman. Factors that should be considered include the severity of poisoning and the availability of specific chelating agents, as the risk of adverse effects in the fetus varies. According to the US Food and Drug Administration (232), the safest agent for use in the first trimester of pregnancy is sodium calcium edetate (category B: experimental animal studies do not demonstrate a risk to the fetus, and there are no adequate studies in pregnant women). The use of penicillamine should be avoided in the first trimester.

Second and third trimesters

For second and third trimester pregnancies, case reports provide very low-certainty evidence that chelation is associated with a reduction in the maternal blood lead concentration and does not appear to harm the fetus (14, [Web Annex](#)). Data are lacking on whether chelation improves fetal or neonatal outcomes. In spite of the lack of evidence and the limited availability of chelating agents in many low and middle-income countries, the guideline development group decided to advise a strong recommendation for chelation. This was because the fetus is particularly susceptible to the toxic effects of lead and

there is a known risk of adverse pregnancy outcomes associated with lead poisoning. It was considered that the more rapid reduction in the maternal blood lead concentration associated with chelation therapy would be likely to benefit both the mother and the baby.

The threshold blood lead concentration at which chelation should be given could not be derived from the available evidence. The guideline development group decided to use the same threshold as for children ($45 \mu\text{g/dL}$) in view of the vulnerability of the fetus. The blood lead concentration should be monitored regularly and further chelation given if the blood lead concentration exceeds $45 \mu\text{g/dL}$.



Antenatal care in Jamaica. Credit: WHO / Aphiluck Bhatiassevi

7.3.8 Values, equity, feasibility and acceptability for chelation in pregnant women

The intended outcomes of chelation therapy in a pregnant woman are survival of the mother and the fetus, in the case of lead encephalopathy, and more generally, improvement in clinical features of lead poisoning and reduction of lead exposure of the fetus. Most cases of lead poisoning in pregnancy are a consequence of unintended exposure, such as use of a traditional medicine containing lead, pica or environmental contamination. The guideline development group considered that the intended outcomes would be valued by most women.

Health equity considerations include the fact that economically deprived and disadvantaged populations have the greatest lead exposure (149), particularly in low- and middle-income countries. Women in these countries who are poor, least educated and live in rural areas may have less health intervention coverage and worse health outcomes than more advantaged women (211). Improvements in symptoms and signs and in survival from severe lead poisoning contribute to health equity. There is, however, lack of evidence for improved pregnancy outcomes and for prevention of the cognitive and behavioural impacts of lead exposure that can adversely affect an individual's economic productivity and social status later in life. Provision of chelation therapy could worsen health outcomes if it was given as a substitute for measures to terminate lead exposure.

As described in section 7.3.6, the availability of chelating agents in low- and middle-income countries is limited, penicillamine being the most commonly available (212). This agent is contraindicated in first-trimester pregnancy because of its teratogenicity. The availability of chelating agents bears on the feasibility of the recommendations.

Factors that might influence the acceptability of chelation therapy include the availability of a suitable chelating agent, e.g. an alternative to penicillamine for a woman in the first trimester, and the duration of treatment and whether it is given on an in- or out-patient basis, as these factors affect cost and convenience.

7.3.9 Implementation considerations for chelation therapy

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 in the prevention, diagnosis and management of lead poisoning. Management of lead poisoning requires access to laboratory services for measuring blood lead concentrations. WHO guidance is available on the selection of analytical methods for measuring blood lead concentrations and on establishing a laboratory service for this purpose (142). As discussed in section 5, the venous blood lead concentration is the definitive biomarker of exposure and risk on which management decisions are routinely based.

Removal from, or termination of, exposure is an essential first step in the management of lead poisoning.

Location of treatment

Lead-poisoned patients can be managed as out- or in-patients. 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-morbidities 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.
- There are doubts about the ability of the patient to adhere to treatment.

Selection of chelating agents

Succimer and penicillamine are given orally and sodium calcium edetate and dimercaprol parenterally. Sodium calcium edetate is sometimes given with succimer or dimercaprol in cases of severe poisoning. All four chelating agents are on the complementary list of the WHO Model List of Essential Medicines (165), indicating that specialized diagnostic or monitoring facilities, specialist medical care and/or specialist training are necessary. Dimercaprol, sodium calcium edetate and succimer are also on the WHO Model List of Essential Medicines for Children (204). Inclusion on the Model Lists indicates that the four agents have been evaluated for their public health relevance, safety, efficacy and comparative cost-effectiveness. In spite of listing, however, the availability of chelating agents in many low- and middle-income countries is limited (212).

Non-pregnant patients

The evidence for individual chelating agents and chelating agent combinations was of very low certainty, and there were no good-quality studies in which chelating agents or chelating agent combinations were compared. In addition, there were very limited data on use of penicillamine in patients with severe poisoning; most published data were for patients with mild–moderate poisoning.

For patients with severe lead poisoning, in particular lead encephalopathy, very low-certainty evidence suggested 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, because it was suggested that the latter increases distribution of lead to the brain (218). The systematic evidence reviews did not find adequate evidence to determine whether this combination was more effective than alternative regimens, and the evidence for a distribution effect is considered to be weak (104). The guideline development group therefore decided that use of sodium calcium edetate alone or in combination with dimercaprol or succimer was acceptable for patients with lead encephalopathy. Case reports from the 1950s described use of dimercaprol alone in severe poisoning; however, such use is considered less optimal than use of other agents.

Parenteral administration of chelation therapy is safer in encephalopathic patients who have an unprotected airway. A patient with adequate airway protection could, however, be given an oral chelating agent, provided there was no concern about impaired GI absorption. Some limited evidence from a large case series in a low-resource setting suggests that succimer can safely be used alone in children with severe lead poisoning, including those with encephalopathy (4).

The guideline development group recognized that the availability and costs of chelating agents vary by country and that this bears on the choice of chelating agent for treating individual patients. Other factors that influence the choice of chelating agent include whether parenteral rather than oral therapy is preferable and a preference for out-patient rather than in-patient treatment.

On the basis of the available, though very limited, evidence and practical considerations, the guideline development group made the following suggestions for the use of chelating agents.

- 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.

When treatment is provided to an outpatient and there is concern about adherence to treatment, consideration could be given to directly observed treatment (4).

Pregnant patients

In pregnant women in the first trimester, the potential for fetal harm caused by lead must be balanced against potential harm caused by the chelating agent. Data on the safety of chelation in pregnancy are very limited. Most data concern penicillamine, which has other indications and is therefore more widely used than other agents. The evidence review of chelation in pregnancy provided many reports of congenital malformations associated with penicillamine therapy for chronic conditions, although none for lead poisoning (14). The US Food and Drug Administration has categorized 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) (232).

In the second and third trimesters, teratogenicity is no longer a concern. On the basis of the available, though very limited, evidence and practical considerations, the guideline development group suggests that chelating agents can be used on the same basis as in non-pregnant patients, described above.

Other remarks applicable to all groups

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. Some patients with chronic lead poisoning and a significant store of lead in bone and soft tissues may require multiple courses of chelation therapy. Furthermore, there may be continuing exposure to lead in spite of efforts to terminate it, for example, when remediation has been incomplete. In one mass lead poisoning incident caused by environmental contamination, some children had five or more courses of chelation without achieving a blood lead concentration < 45 µg/dL. It was unclear to what extent persistently high blood lead concentrations were due to body stores of lead or to re-exposure.⁵ As chelation therapy can have adverse effects, in particular loss of essential trace elements, it cannot be given indefinitely. If a patient has already had four or five courses of chelation 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 effective or whether there is a previously unrecognized source of exposure. Expert advice on further management should also be sought.

⁵N. Thurtle, personal communication, December 2020

08 /

Integration and implementation

of the recommendations in the management of lead poisoning

Sections 6 and 7 provide recommendations for specific aspects of the management of lead exposure. These should be integrated into an overall management plan for cases of lead poisoning. As a general principle, 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 trends in 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 lead concentration ([section 6.2](#)), the steps in the management of exposure are:

- taking a history to identify the source(s) of exposure;
- evaluating the severity of exposure in clinical examination and investigations;
- reducing and terminating exposure, including improving nutrition;
- GI decontamination if indicated
- chelation therapy if indicated;
- other supportive measures if required; and
- follow-up to determine whether further management measures are necessary.



Children's playground equipment can be a source of exposure to lead paint. Credit: WHO / Sergey Volkov

8.1 Taking a history to Identify the source(s) of exposure

The many possible sources of exposure to lead are described in section 4.1. Identification involves taking a thorough environmental and/or occupational history and may involve environmental investigations such as measurement of the lead content in drinking-water, household paint or soil. Questions should be asked about the use of traditional medicines and cosmetics. In pregnant women, the possibility of pica leading to ingestion of soil, clay or other lead containing materials should be explored (136). Examples of approaches to history-taking are provided by WHO (20) and the US Agency for Toxic Substances and Disease Registry (233). In the case of occupational exposure, it may be necessary to investigate work practices and the existence and effectiveness of engineering controls and occupational hygiene measures.

When a case of lead exposure has been identified, it is important to investigate the possibility that others may also be exposed, such as siblings, other household members or work colleagues. This is particularly likely when the source is environmental or a consequence of inadequate occupational control measures.

8.2 Evaluation of the severity of exposure

The blood lead concentration provides an indication of the severity of exposure, but the patient should also be evaluated for symptoms and signs of lead poisoning. These 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. Young children with lead exposure should undergo a neurodevelopmental assessment.



Seams of lead ore in Uganda. Credit: WHO / Christopher Black

It is also important to take a dietary history to determine whether the patient has adequate nutrient intake, particularly of iron and calcium, as deficiency in these minerals is associated with increased absorption of lead and exacerbation of toxic effects (34, 172–174).

8.3 Reduction and termination of exposure, including improving nutrition

Means for terminating exposure depend on the source. In the case of lead ingestion, this may require GI decontamination (see section 7.1). In environmental exposure, identification of the source is important and may require the involvement of local public health or environmental health services. Measures to reduce and terminate exposure may include rehousing, remediation of contaminated soil or removal of lead paint, as well as longer-term measures such as implementation of environmental lead emission controls.

Occupational exposures may require temporary removal from work with lead. This should be followed by investigation of the cause(s) of exposure and implementation of the appropriate corrective measures. The regulatory limits for blood lead concentrations from occupational exposure vary around the world, some countries setting relatively high values. A review of national regulations showed that the concentration at which a worker should be removed from exposure ranged from 20 to 70 µg/dL for men and 10 to 70 µg/dL for women (234). The values are under review in some countries. In the European Union, for example, a limit of 15 µg/dL for men and avoidance or minimization of exposure for women of childbearing age have been recommended for adoption (235, 236). There are no WHO guideline values for this purpose.

The patient or carer should be given information about the harmful health effects of lead, about sources of exposure and how exposure can be reduced or avoided, including the importance of good nutrition, in particular adequate intake of iron and calcium and of vitamins C and D, as these facilitate absorption of iron and calcium, respectively (195). If necessary nutritional supplementation should be given (see section 7.2).

8.4 Chelation therapy

Issues in the choice of chelating agent for treatment are discussed in section 7.3.9. Table 2 provides a summary of information on chelating agents used for lead exposure. The systematic evidence reviews of chelating agents found that a variety of dosing regimens were used; however, the data were inadequate to compare the safety and efficacy of different regimens (10–14). The dose regimens listed in Table 2 are taken from WHO formularies, pharmaceutical reference books and summaries of product characteristics provided by manufacturers. Information on adverse effects is taken from the same sources and from the systematic evidence reviews in which this was reported.

Table 2. Background information about chelating agents for exposure to lead

Dimercaprol (Intramuscular injection)	
Dimercaprol (British Anti-Lewisite, BAL, dimercaptopropanol) is administered by deep intramuscular injection (218). It is usually formulated in a lipid solvent such as arachis or vegetable oil.	
Dose	A typical regimen is 2.5–3 mg/kg body weight intramuscularly every 4 h for 2 days, 3 mg/kg intramuscularly two to four times on the third day, then 3 mg/kg intramuscularly once or twice daily for 10 days or until recovery (237).
Adverse events	These include: rise in blood pressure, tachycardia, nausea and vomiting, which increase in severity with increasing doses, headache, a burning sensation in the lips, mouth and throat, a feeling of throat and chest constriction, conjunctivitis, lachrymation, blepharospasm, sweating, salivation, rhinorrhoea, tingling of the hands, abdominal pain, muscle pain and spasm, pain at the site of injection and occasional appearance of painful sterile abscesses (238–240). Fever may occur in children after the second or third injection and persist until treatment is stopped (239). Many of the adverse events are dose-related (10, 240). Transient elevations of liver enzymes may occur with higher doses (10). In patients with glucose-6-phosphate-dehydrogenase deficiency, haemolysis may occur (239, 241, 242). Exacerbation of lead toxicity has been reported (9).
Safety in pregnancy	Category C: Experimental animal data suggest a fetal risk (231).
Penicillamine (Oral)	
Penicillamine is a sulfhydryl amino acid product of the hydrolysis of penicillin, but it has no antibiotic properties. The pharmaceutical form is D-penicillamine, as L-penicillamine and the racemic mixture are toxic (243). Penicillamine is given orally.	
Dose	<p>Typical regimens are:</p> <p>Adult: 1–2 g by mouth daily in divided doses before food (236)</p> <p>Child (all ages): 7.5 mg/kg body weight three or four times daily (196) 15–20 mg/kg body weight per day in two or three doses (244).</p> <p>Some sources suggest starting at the lower dose initially, then increasing gradually, to reduce adverse effects (245).</p>
Adverse events	<p>Most of the information on adverse events is for patients on long-term therapy for hepatolenticular degeneration (Wilson disease), cystinuria or rheumatoid arthritis. These may be less frequent with the shorter courses of therapy required for lead poisoning.</p> <p>The most common adverse events are rash, anorexia, nausea, vomiting and taste disturbance (196). Uncommon events include fever, allergy, itching, urticaria, proteinuria and mouth ulcers. Rare events include haematuria, thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, nephrotic syndrome, lupus erythematosus, Goodpasture syndrome, hepatic dysfunction, pemphigus, dermatomyositis, myasthenia gravis, polymyositis and Stevens–Johnson syndrome (196, 237). People with penicillin allergy may be at risk for cross-sensitivity, but this appears to be rare (245).</p> <p>In the treatment of lead poisoning, the following adverse events have been reported: leukopenia, rashes, thrombocytopenia, eosinophilia, proteinuria and angioedema (11). These effects resolved on termination of treatment. Adverse events may be more likely at higher doses of penicillamine (11, 245)</p>
Safety in pregnancy	Category D: Known fetal risk (232)

Sodium calcium edetate (Intravenous or intramuscular injection)

Sodium calcium edetate (edetate calcium disodium, calcium disodium edetate, calcium disodium versenate) chelates a number of metals, including lead. It is given parenterally. This agent must not be confused with sodium edetate (edetate disodium), which can cause fatal hypocalcaemia (246).

Dose	A typical regimen is up to 40 mg/kg body weight twice daily intravenously or intramuscularly for up to 5 days. This can be repeated if necessary, after an interval of 48 h (237).
Adverse events	<p>Common adverse events include sneezing, nasal congestion, numbness, tingling, nausea, diarrhoea, abdominal cramps, fever, malaise, headache, myalgia, thirst and chills. Uncommon events include renal tubular necrosis, pain at the injection site, thrombophlebitis, lachrymation and transient hypotension. Rare events include mucocutaneous lesions (196). Nephrotoxicity appears to be dose dependent (247).</p> <p>Prolonged administration of sodium calcium edetate at a high dose may produce transient bone marrow depression and skin and mucous membrane lesions (including cheilosis), but these usually resolve on discontinuation of the drug (248).</p> <p>This drug may also cause increased excretion of trace elements such as zinc and copper (12, 246).</p>
Safety in pregnancy	Category B: Studies in experimental animals do not indicate a risk to the fetus, and there are no adequate studies of pregnant women (232).

Succimer (Oral)

Succimer (meso-2,3-dimercaptosuccinic acid, DMSA) is a water-soluble dithiol and is an analogue of dimercaprol. Succimer is usually administered orally (218).

Dose	A typical regimen is 10 mg/kg body weight or 350 mg/m ² orally every 8 h for 5 days, then every 12 h for an additional 14 days (245, 248, 249). The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks, unless blood lead concentrations indicate that more prompt treatment is necessary (245). Other regimens have been used, e.g. prolonging the overall treatment course to 21 or 28 days (4, 250).
Adverse events	<p>The most commonly reported adverse effects are GI disorders (nausea, vomiting, diarrhoea, loose stools), transient increases in serum transaminase activity, increased excretion of zinc or copper and skin eruptions, possibly affecting the mucosa (13, 249, 250). In a large case series, elevated alanine aminotransferase activity was seen in < 2.5% of children (4). Other reported effects include: flu-like symptoms, headache, drowsiness and dizziness (218, 245) and mild-to-moderate neutropenia (245).</p> <p>Hypersensitivity reactions with urticaria and angioedema have been reported rarely (245, 250). Haemolytic anaemia was reported in a patient with glucose-6-phosphate dehydrogenase deficiency (251), but succimer has been used in other patients with this condition without incident (252–254). Most adverse effects are mild to moderate and resolve on termination of treatment (13, 249).</p>
Safety in pregnancy	Category C: Data for experimental animals suggest a fetal risk (232).

8.5 Supportive measures

Patients with severe lead poisoning may have seizures, raised intracranial pressure, cerebral oedema and coma. Supportive management for these conditions should be provided in accordance with the usual hospital management protocols. WHO guidance on the management of obtundation and seizures in limited-resource settings is available (255, 256).

8.6 Follow-up

Whether or not chelation therapy has been given, it is important to re-evaluate the patient periodically, including the blood lead concentration, to determine the effectiveness of measures to terminate exposure and chelation and whether further action is necessary. If preventive measures are not successful, the blood lead concentration will continue to rise.

Chelation therapy removes lead from blood and soft tissues, but, if there are significant bone stores, remobilization occurs, and the blood lead concentration will rise again. The interval before re-evaluation of a patient depends on the severity of poisoning, the initial blood lead concentration (PbB) and whether the patient belongs to a vulnerable group. The following intervals were suggested by the guideline development group:

Children, adolescents and pregnant women:

- PbB > 30 µg/dL: after 2–4 weeks
- PbB 5–29 µg/dL: after 1–3 months
- PbB < 5 µg/dL: after 6–12 months if there is continuing concern about possible lead exposure

Other adults:

- PbB > 50 µg/dL: after 2–4 weeks
- PbB 30–50 µg/dL: after 1–3 months
- PbB 5–29 µg/dL: after 3–6 months

A shorter interval is suggested for severe poisoning, higher blood lead concentrations and for children, adolescents and pregnant women. As young children absorb proportionately more lead than adults, their blood lead concentrations may rise more rapidly (93). The fetal period and childhood are periods of particular susceptibility to the neurotoxic effects of lead. During pregnancy, physiological changes may result in an increase in blood lead concentrations and greater exposure of the fetus. The increased need for calcium for the developing fetal skeleton results in increased calcium absorption from the maternal GI tract and may also increase lead absorption. In addition, stored lead may be released as maternal bone is resorbed (182).

As children who have been exposed to lead may suffer impaired neurocognitive and behavioural development, the guideline development group advised periodic assessment for signs of difficulty in meeting developmental goals, ideally until the end of secondary education. These children should be given whatever support is available locally.



Doctor in Uruguay following-up and documenting her work. Credit: WHO / Blink Media - Tali Kimelman



Credit: MawardiBahar / Shutterstock.com

Research gaps

The systematic reviews of evidence identified very few good-quality studies of the effectiveness of any of the treatment interventions for lead exposure, and more evidence is needed for all the interventions. It is recognized, however, that conducting RCTs would, in most cases, be ethically and/or practically difficult. Observations are made below on the interventions considered in this guideline.

9.1 Gastrointestinal decontamination

A number of variables influence the effectiveness of GI decontamination methods after ingestion of lead. These include the form of lead ingested (e.g. foreign body, liquid glaze, paint flakes), the interval after ingestion, the physical condition of the patient and the resources available at the treatment centre. Furthermore, the overall number of cases of lead ingestion for which GI decontamination could be considered is probably small. It would be difficult, therefore, to accumulate a sufficient number of comparable cases for a meaningful study.

For these reasons, 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. While this evidence is considered to be of very low certainty, case reports would be more useful if they were better documented and guidance is available (257). In particular, when practical, more details of the effect (success or failure) of each method used, for example by stool collection, more frequent blood lead concentration monitoring or serial abdominal X-rays, would be helpful, provided they can be justified as part of patient management. The use of several methods in the same patient or administration of chelating agents will, of course, complicate interpretation of changes in blood lead concentrations and clinical condition, but this is unavoidable. The information could also be used to evaluate whether chelation should be withheld until GI decontamination is complete, as some have proposed (116, 258).

9.2 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 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.

9.3 Chelation therapy

While there is consistent evidence that chelation is associated with a reduction in the blood lead concentration and increased urinary excretion, there are still no data on longer-term outcomes, such as neurocognitive development, behaviour and cardiovascular disease, in patients with significant lead poisoning. Furthermore, the threshold blood lead concentration for chelation that is effective in improving outcomes in different age groups has not been established.

Oral chelating agents such as succimer can be given to outpatients, which offers economic and practical advantages when long courses of treatment are necessary. Directly observed treatment has been used in a low-resource setting (4), but more studies should be conducted of adherence to treatment in outpatient settings and the link to outcomes.

Very few reports were available of the use of chelating agents in patients with glucose-6-phosphate dehydrogenase deficiency, with mixed results. Therefore, the safety of these agents in this sub-group is not established.

No RCTs were found on use of chelation therapy in pregnancy, and it is difficult to see how such studies could be conducted, for ethical reasons. It is important, therefore, that cases in which chelation therapy is used in pregnancy be well documented and published in order to increase the body of knowledge about chelation in this patient group. Better national data are also needed on the prevalence of high blood lead concentrations in pregnant or lactating women.



Prevention of exposure to lead is vital to protect maternal and child health. Credit: MSF

Considerations for implementation of the guideline

WHO recognizes lead as one of 10 key chemicals of public health concern and is actively working with partners and policy-makers to raise awareness about preventing and managing lead exposure (259).

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

Two important challenges must be addressed in order to implement the guidelines. The first is the limited availability of good-quality laboratory services for the diagnosis of lead poisoning. WHO is advocating for greater availability of toxicology laboratories as a core capacity requirement under the International Health Regulations (2005) (260), and WHO's brief guide on methods for the analysis of lead in blood, published in 2020, is available in all six United Nations languages (142).

The second challenge is the limited availability of chelating agents in many low- and middle-income countries, as mentioned in section 7.3. The reviewed chelating agents are on the WHO model lists of essential medicines and of essential medicines for children (169, 196). WHO will use the guidance to further advocate for greater availability of chelating agents as part of universal health coverage and to improve procurement of essential medicines through inter-country cooperation. The WHO Regional Office for South-East Asia has launched the Initiative for Coordinated Antidotes Procurement in the South-East Asia Region to help countries in the Region to procure antidotes for a range of common poisons including lead (261, 262).

With regard to nutritional interventions, WHO is developing guidelines on single and multivitamin 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 key target users (263).

Working with partners and as resources permit, training for medical practitioners will be organized in selected countries in the diagnosis and management of lead exposure, supplemented by online courses.

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Annex 1

Members of the WHO Steering Group

Department of Public Health, Environmental and Social Determinants of Health

Joanna Tempowski (project manager until July 2020) – no longer with WHO

Annette Prüss-Ustün (2011–2013)

Marie-Noël Bruné Drisse

Department of Food Safety

Angelika Tritscher (2011–2018) – no longer with WHO

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Regional Office for the Americas: Agnes Soares da Silva, Ana Boischio (Department of Sustainable Development and Healthy Environment)

Regional Office for the Eastern Mediterranean: Mohamed Elmi (2011–2018) (Regional Centre for Environmental Health Action) – no longer with WHO

Regional Office for South-East Asia: Lesley Onyon (Department of Sustainable Development and Healthy Environment until 2020, then Department of Environment, Climate Change and Health, WHO Headquarters)

Regional Office for the Western Pacific: Rokho Kim (Department of Health and the Environment until 2020, then Department of Quality Assurance of Norms and Standards, WHO Headquarters)

Ukraine WHO Country Office

Dorit Nitzan (now Health Emergencies Programme, WHO Regional Office for Europe)

Gerry McWeeney (2011–2018) (now WHO Office for Representation at the European Union)

Annex 2

Guideline Development Group

Members of the guideline development group are listed below, by WHO region. Information is provided on affiliations and areas of expertise. All the members completed WHO declarations of interests forms before being admitted as a member of the group and before each meeting. The declared interests are summarized below.

Name	Organizational affiliation, address	Gender	Expertise
WHO African region			
Professor Angela Mathee	Director, Environment and Health Research Unit, South African Medical Research Council Johannesburg, South Africa	F	Public health; environmental epidemiology; lead poisoning in African children
Professor Orish E Orisakwe	Toxicology Unit, Faculty of Pharmacy, University of Port Harcourt Port Harcourt, Nigeria On roster of toxicological and epidemiological experts for Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011–2015	M	Environmental toxicology; analytical toxicology
WHO Region of the Americas			
Professor David Bellinger	Harvard Medical School Children’s Hospital, Boston (MA), USA Chair of the guideline development group On roster of toxicological and epidemiological experts for Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011–2015	M	Neurotoxic effects of lead; epidemiology; environmental health
Dr Mary Jean Brown	Previously: Lead Poisoning Prevention Branch (until August 2016), Centers for Disease Control and Prevention (CDC), Atlanta (GA), USA Now: Adjunct Assistant Professor, Harvard Chan School of Public Health Boston (MA), USA	F	Effects of lead on children’s health; prevention and management of lead exposure
Professor Amalia Laborde	Director Department of Toxicology, Centre for Toxicological Information and Advice, Faculty of Medicine, Clinical Hospital, Montevideo, Uruguay Director of WHO Collaborating Centre for Human Environmental Toxicology; member of WHO children’s environmental health network	F	Clinical and occupational toxicology; occupational and environmental exposure to lead; prevention of poisoning
Professor Philip J Landrigan	Previously: Icahn School of Medicine at Mount Sinai, New York City (NY), USA Now: Schiller Institute for Integrated Science and Society, Boston College, Boston (MA), USA Director of WHO Collaborating Centre for Children’s Environmental Health	M	Children’s environmental health; prevention of lead exposure



	Disclosure of interest	Conflict of interest and management plan
	None declared	None required
	None declared	None required
	<p>Acted as an expert witness in six litigation cases to provide an opinion on whether a child suffered neurodevelopmental harm as a result of exposure to lead, the severity of the harm and the period in which harm occurred. Depending on the facts of the case, Professor Bellinger sometimes supported the plaintiff and sometimes the defendant. This activity included acting as an expert witness for the Kennedy-Krieger Institute in Baltimore in litigation concerning the treatment of lead-exposed children study, which addressed the effectiveness of succimer therapy in preventing long-term effects of lead exposure. In this case, however, Professor Bellinger’s testimony did not concern the objectives or outcomes of the study.</p>	No conflict identified with respect to development of the guideline.
	<p>Responsible for developing and implementing policies in the USA on identification and treatment of lead poisoning in children. CDC was involved in the initial and continuing development of a point-of-care analyser for blood lead concentrations (LeadCare II), and, in her professional capacity, Dr Brown worked with the manufacturer on issues of the reliability and validity of the device.</p> <p>Is co-author of a paper describing the outcomes of a humanitarian intervention to provide chelation to children in a mass lead poisoning event in Zamfara, Nigeria.</p>	No conflict identified with respect to development of the guideline.
	Providing clinical advice to the NGO Vital Strategies and the Ministry of Health, Peru on the management of people exposed to lead from environmental contamination.	No conflict identified with respect to development of the guideline.
	Has provided expert testimony for the federal and state governments on childhood lead poisoning, taking the position that lead is dangerous to the health of children and that legal action is necessary to protect the health of children.	No conflict identified with respect to development of the guideline.

Name	Organizational affiliation, address	Gender	Expertise
WHO South-East Asia Region			
Dr Chulathida Chomchai (2011–2013)	Associate Professor of Paediatrics Consultant - Siriraj Poison Centre Mahidol University Nakhon Pathom, Thailand	F	Paediatric toxicology; public health; risk factors for lead exposure
Dr Aruna Dewan	Center for Education, Awareness and Research on Chemicals and Health, Ahmedabad, India	F	Clinical toxicology; analytical toxicology; lead poisoning from traditional remedies
Dr Thuppil Venkatesh	National Referral Centre for Lead Poisoning in India St John's National Academy of Health Sciences, Bangalore, India	M	Lead screening; prevention of lead exposure; analytical toxicology
WHO European Region			
Dr Yona Amitai	Department of Management, Bar Ilan University, Ramat Gan, Israel	M	Paediatric toxicology; injury and poisons prevention; children's environmental health
Professor Paul Dargan	Consultant Physician and Professor of Clinical Toxicology, Guy's and St Thomas' National Health Service Foundation Trust, London, United Kingdom	M	Clinical toxicology; management of lead poisoning in low-resource settings
WHO Eastern Mediterranean Region			
Professor Mohammad Abdollahi	Dean of Department of Toxicology and Pharmacology, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran	M	Clinical and analytical toxicology; epidemiology of poisoning; evidence-based medicine
Dr Maha Khalid Al Mazrou'a	Regional Poison Control Centre-Dammam, General Directorate of Health Affairs, Eastern Province, Ministry of Health, Dammam, Saudi Arabia	F	Clinical and analytical toxicology
WHO Western Pacific Region			
Dr Byung-Kook Lee	Emeritus Professor, Institute of Environmental and Occupational Medicine, Soonchunhyang University, Seoul, Republic of Korea Occupational health consultant, Korea Industrial Health Association	M	Occupational health; toxic metals; preventive medicine
Dr Nguyen Trung Nguyen	Director, Poisons centre, Bach Mai Hospital Hanoi, Viet Nam	M	Clinical toxicology
Dr Natalie Thurtle	Previously: Health Advisor, Zamfara Heavy Metal Poisoning, Medécins Sans Frontières–Operational Centre, Amsterdam, Netherlands Now: St George's Hospital, Sydney, Australia	F	Clinical toxicology; medicine in low resource settings; management of lead poisoning in low-resource settings

	Disclosure of interest	Conflict of interest and management plan
	None declared	No action required
	None declared	No action required
	None declared	No action required
	<p>None declared.</p> <p>Is co-author of a paper describing the outcomes of a humanitarian intervention to provide chelation to children in a mass lead poisoning event in Zamfara, Nigeria.</p>	No conflict identified with respect to development of the guideline.
	<p>Provided expert advice in support of a group legal action for compensation for the health impacts of lead exposure from environmental contamination in Kabwe, Zambia.</p> <p>Is co-author of a paper describing the outcomes of a humanitarian intervention to provide chelation to children in a mass lead poisoning event in Zamfara, Nigeria.</p>	No conflict identified with respect to development of the guideline.
	None declared	No action required
	None declared	No action required
	None declared	No action required
	Has been involved in campaigns on lead poisoning prevention and management in Viet Nam.	No conflict identified with respect to development of the guideline.
	<p>Was employed by Médecins Sans Frontières as a long-term consultant on the lead poisoning outbreak in Zamfara, Nigeria and led initial response activities.</p> <p>Is co-author of a paper describing the outcomes of a humanitarian intervention to provide chelation to children in Zamfara.</p>	No conflict identified with respect to development of the guideline.

Annex 3

Research questions and critical and important outcomes

Research question	Critical and important outcomes
Gastrointestinal (GI) decontamination	
In individuals (P) who have ingested a potentially toxic amount of lead or lead compounds, does use of a GI decontamination technique (gastric lavage, whole bowel irrigation (WBI), cathartics or activated charcoal, emesis) (I) reduce absorption of lead and/or result in clinical improvement (O) in comparison with no decontamination or another decontamination technique (C)?	<ul style="list-style-type: none">• blood lead concentration (critical)• mortality (critical)• symptoms and signs of lead poisoning e.g. abdominal colic, encephalopathy (critical)• neurological (cognitive, neurobehavioural and neuromotor) effects of lead poisoning measured in standardized, validated tests• lead foreign bodies in vomitus, lavage fluid, stools or effluent (important)• adverse effects of GI decontamination (important)
Chelation therapy	
In individuals with lead poisoning (P), does chelation therapy with dimercaprol, penicillamine, sodium calcium edetate or succimer alone or in combination with another chelating agent (I) improve health outcomes and/or increase elimination of lead (O) in comparison with other chelating agents or with no treatment (C)?	<ul style="list-style-type: none">• blood lead concentration (critical)• neurological (cognitive, neurobehavioural and neuromotor) effects of lead poisoning measured in standardized, validated tests• mortality (critical)• symptoms and signs of lead poisoning, e.g. abdominal colic, encephalopathy (critical)• long-term health outcomes that may be affected by lead exposure such as cardiovascular and renal effects (critical)• urinary excretion of lead (important)• mobilization of lead from bone (important)• adverse events associated with chelation therapy (important)
Nutritional interventions	
In children or women who are pregnant or lactating who have elevated blood lead concentrations (> 5 µg/dL) (P), does dietary modification and/or nutritional supplementation alone or dietary modification or nutritional supplementation in conjunction with chelation therapy (I) reduce the blood lead concentration and/or the adverse health impacts of lead exposure (O) in comparison with no dietary modification or nutritional supplementation (C)?	<ul style="list-style-type: none">• blood lead concentration (critical)• cord blood lead concentration (critical)• neurological (cognitive, neurobehavioural and neuromotor) effects of lead poisoning measured in standardized, validated tests (critical)• mortality of neonates and severely poisoned children and women (critical)• symptoms and signs of lead poisoning, e.g. abdominal colic, encephalopathy (critical)• pregnancy outcomes, namely live birth and survival to 1 year, birth weight and neurological status of neonates; bone lead (in women) (critical)• lead concentration in breast milk (important)• mobilization of lead from bone (in women) (important)• adverse effects of nutritional supplementation

P, problem; I, intervention; C, comparison; O, outcome

Annex 4

External reviewers

List by WHO region

African Region

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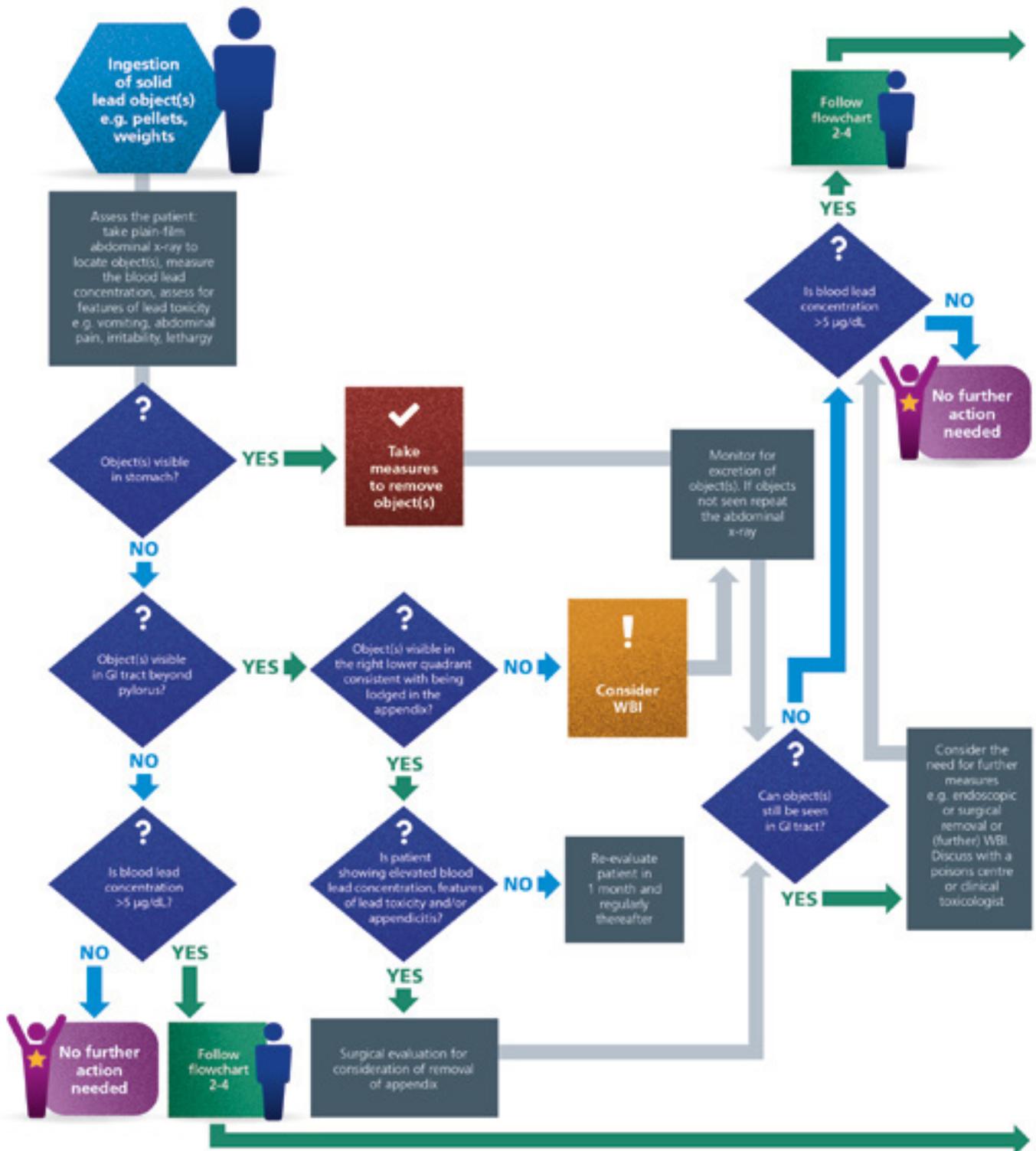
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Annex 5

Flowcharts summarizing aspects of patient management

1. Gastrointestinal decontamination after ingestion of one or more solid lead objects

Recommendations key	
✓	Strong recommendation
!	Conditional recommendation



3. Chelation therapy for an adolescent or adult with an elevated blood lead concentration

Recommendations key	
✓	Strong recommendation
!	Conditional recommendation
△	Good practice





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