Human health effects of benzene, arsenic, cadmium, nickel, lead and mercury

Report of an expert consultation

World Health Organization

European Region

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Abstract

Benzene, arsenic, cadmium, lead, mercury and nickel are ubiquitous pollutants in ambient air. The main sources are industrial processes, electricity generation and fuel combustion. The main routes of exposure are inhalation for benzene, and diet for arsenic, cadmium, lead, nickel and mercury. Inhalation of benzene, arsenic and cadmium is relevant for exposure in active tobacco smokers and people exposed to second-hand tobacco smoke. Epidemiological studies show that exposure to these pollutants is associated with adverse effects on the cardiovascular (cadmium, lead, mercury); haematological (benzene, lead); immunological, neurological and reproductive (benzene, lead, mercury); respiratory (cadmium, nickel); renal (cadmium, lead); and skeletal (cadmium) systems. Limited epidemiological evidence on ambient air pollution suggests adverse effects on the cardiovascular system (arsenic and nickel). Since benzene, arsenic, cadmium and nickel are classified as carcinogenic, the lowest possible exposure level is suggested to minimize the risk for cancer development in view of the no-effect threshold paradigm. Lead and methylmercury compounds are classified as possibly carcinogenic to humans. However, the available evidence is insufficient to warrant updating the air quality guidelines for these air pollutants. Evidence gaps are identified and these should guide future research efforts.

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Acknowledgements

Abbreviations

ALL	acute lymphoblastic leukaemia
AMAP	Arctic Monitoring and Assessment Programme
AML	acute myeloid leukaemia
ANLL	acute non-lymphocytic leukaemia
ANSES	*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* [French National Agency for Food, Environmental and Occupational Health and Safety]
APMMN	Asia-Pacific Mercury Monitoring Network
AQG level	air quality guideline level
ATSDR	Agency for Toxic Substances and Disease Registry
CAP	concentrated ambient particles
CD	cluster of differentiation
CI	confidence interval
CLRTAP	Convention on Long-Range Transboundary Air Pollution
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular diseases
DEFRA	United Kingdom Department for Environment, Food and Rural Affairs
DMA	dimethylarsinic acid
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe (project)
EMEP	European Monitoring and Evaluation Programme (full name: Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe)
EU	European Union
GEM	gaseous elemental mercury
GMOS	Global Mercury Observation System
IARC	International Agency for Research on Cancer
IQ	intelligence quotient
LOAEL	lowest adverse effects level
LOAEC	lowest adverse effects concentration
meta-OR	meta-analysis odds ratio
MMA	monomethylarsonic acid

NADP	(United States) National Atmospheric Deposition Program
NMMAPS	National Mortality and Morbidity Air Pollution Study
NOAEL	no observed adverse effect level
NOAEC	no observed adverse effect concentration
OEHHA	California Office of Environmental Health Hazard Assessment
PBM	particulate-bound mercury
PM	particulate matter
PM$_{2.5}$	particulate matter with an aerodynamic diameter lower than 2.5 µm
PM$_{10}$	particulate matter with an aerodynamic diameter lower than 10 µm
PPAR-ɣ	peroxisome proliferator-activated receptor gamma
REL	reference exposure level (California Office of Environmental Health Hazard Assessment) or recommended exposure limit (Occupational Safety and Health Administration)
REVIHAAP	Review of evidence on health aspects of air pollution (project)
RGM	reactive gaseous mercury
ROS	reactive oxygen species
RR	risk ratio (also called relative risk)
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme
URF	unit risk factor
US EPA	United States Environmental Protection Agency

Executive summary

Benzene, arsenic, cadmium, lead, mercury and nickel are ubiquitous in ambient air, and pose health concerns based on toxicological and epidemiological studies. Although each of these six pollutants has specific emission sources, most have several sources in common. These include fossil fuel combustion, energy generation, vehicle exhaust emissions, domestic heating and industrial processes. Non-exhaust emissions from road traffic are a source of most of these metals but the contribution to atmospheric pollution is minor.

Due to the health risks that these pollutants represent, authoritative bodies have issued air quality guidelines, limit values, target values or recommended values to mitigate exposure and protect populations. WHO air quality guidelines provide a reference to assist decision-makers in setting standards and goals for air quality, and have gained widespread influence among risk assessment institutions. In 1987 WHO published the first air quality guidelines, the *Air quality guidelines for Europe*, which initially covered 28 pollutants and was updated in 2000 to include some additional pollutants. The *Air quality guidelines: global update 2005* focused exclusively on particulate matter ($PM_{2.5}$[1] and PM_{10}[2]), ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2), and the 2021 *WHO global air quality guidelines: particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide* also covered carbon monoxide (CO) and certain other types of PM (black carbon, ultrafine particles, particles originating from sand and dust storms) in the form of good practice statements. WHO has also published indoor air quality guidelines for dampness and mould (2009), selected chemicals (2010) and household fuel combustion (2014).

In 2015 the expert group involved in the consultation on available evidence for the 2021 *WHO global air quality guidelines* recommended a review of the evidence for several air pollutants that had been included in previous guidelines but were not prioritized in the 2021 update. In response, an expert consultation was convened to identify and discuss the latest available evidence on the health effects of several air pollutants, including several metals or metalloids (arsenic, cadmium, lead, nickel and mercury) and benzene. This consultation aimed to support the revision of European Union (EU) Directive 2008/50/EC on ambient air quality and cleaner air for Europe, as well as similar policies in individual Member States.

The main findings of this review are that:

- there is insufficient new evidence to support a review of the current air quality guidelines for cadmium, mercury and nickel and the metalloid arsenic;

- lead exposure is associated with an increasing number of new health outcomes and warrants close follow-up – however, the current evidence does not yet justify updating the guidelines for lead;

- although it may be appropriate to review the existing air quality guidelines for benzene, the current air quality guidelines already state that there is no safe level;

- for the carcinogenic air pollutants (benzene, arsenic, cadmium and nickel):

  - the lowest possible exposure should be the aim to minimize the risk of cancer development, given the lack of a no-effect threshold; and

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[1]   PM with an aerodynamic diameter lower than or equal to 2.5 μm. Also called fine particles.
[2]   PM with an aerodynamic diameter lower or equal to than 10 μm. Also called coarse particles.

- a possible threshold effect in the dose–response relationship should be investigated, especially for arsenic, which is a non-genotoxic, non-stochastic[3] carcinogen; and

- for the non-carcinogenic air pollutants (lead and mercury), important health effects have been identified and guidelines are already in place and the available evidence does not support their review.

The evidence review identified knowledge gaps and proposed areas for future research, in particular policy-oriented research suitable for deriving or updating air quality guidelines. Similar knowledge gaps and research needs were identified for most of the air pollutants included in the expert consultation.

Based on the expert consultation, considerations for further research to derive health-based guidance values and guidelines are to:

- explore non-carcinogenic health end-points to provide a broader understanding of health outcomes, especially for (but not limited to) those affecting development and the cardiovascular and central nervous systems;

- conduct epidemiological studies on:

  - the low exposure levels of airborne pollutants that are experienced by the general population; and

  - susceptible populations who might be disproportionately impacted by exposures to these pollutants because of biological susceptibilities that increase the likelihood of health effects or of socioeconomic and lifestyle susceptibilities that increase exposure to these pollutants;

- conduct toxicological studies using environmentally realistic doses to identify the biological mechanisms underpinning the epidemiological observations, especially those related to development and the cardiovascular and central nervous systems;

- determine the shape of the dose–response function for each pollutant at the low concentrations experienced by the general population to provide new evidence for defining or updating the existing air quality guidelines, and investigate possible threshold effects for carcinogenic compounds that are not genotoxic;

- conduct exposure studies to:

  - characterize exposure to the six pollutants in the general population, especially in vulnerable populations and under different exposure conditions;

  - characterize the physicochemical properties of individual and mixtures of pollutants and assess their bioavailability and possible synergistic effects (such as inflammatory responses to oxidative stress) that are more likely trigger the observed health outcomes;

  - determine the physicochemical profiles of ambient and indoor-generated PM and their relative contributions on health effects; and

  - improve the usefulness of biomarkers of exposure by determining the equivalency between levels of the pollutants measured in biological matrices and in the air, especially those previously used to derive air quality guidelines;

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3 Non-stochastic effects are those for which incidence and severity depends on dose, but there is also a threshold dose.

– optimize monitoring programmes to help to protect populations from benzene and metal or metalloid exposure by establishing high-resolution networks in hot spots, providing comprehensive temporal and spatial trends or high-resolution spatiotemporal modelling, and sustained human biomonitoring programmes; and

• combine exposure, epidemiological and toxicological studies to explore the impact of climate change on the atmospheric levels, distribution and toxicity of the pollutants, taking into account any potential changes in population vulnerability.

In addition, the consultation suggested formulating questions to help those intending to update health-based values or guidelines for the general population.

1. Introduction

1.1 Background

Benzene, arsenic, cadmium, lead, mercury and nickel are chemicals of public health concern. Exposure to these pollutants contributes to the global burden of diseases attributable to modifiable environmental factors.

Benzene is a ubiquitous volatile air pollutant. It is a constituent of crude oil and petroleum products and is released via vaporization (1). Its main sources are combustion processes. Benzene and benzene homologues are important chemical precursors to the formation of ground-level ozone and secondary organic aerosol in the atmosphere. Natural sources of benzene are forest fires and volcanoes. However, the major environmental sources are anthropogenic, including industrial emissions, emissions from coal and oil combustion, motor vehicle exhaust emissions, and fuel evaporation (2). Sources of benzene emissions in indoor environments include carpets, new furniture, paint, personal and home care products, and activities such as smoking and cooking (3). Levels of benzene exposure are often greater indoors than in ambient air, even though in the absence of indoor sources the main contributors to indoor benzene concentrations are ambient sources.

Arsenic is a natural component of the earth's crust and is widely distributed throughout the environment in the air, water and soil (1). Arsenic is a ubiquitous, naturally occurring metalloid that is highly toxic in its inorganic form and is found as a contaminant of ambient air, cigarettes, drinking water, food, industrial emissions and occupational environments (4).

Cadmium is a soft, silver-white metal that in nature is usually found in combination with other elements (5). It occurs naturally in the earth's crust. Cadmium in the atmosphere is bound to aerosol particles (6). The main anthropogenic emission sources of cadmium are electricity production, industry and residential combustion (7).

Lead is a bluish-white, lustrous, highly malleable, dense and ductile metal. Anthropogenic sources are the main contributors to environmental lead (8). Activities such as mining and smelting, recycling and disposal of waste materials, fossil fuel combustion, and land application of fertilizer are now the main sources of airborne lead (9). Lead emissions to the atmosphere have considerably reduced since the use of lead in gasoline was banned (10,11).

Mercury is a silver-white metal that is liquid at room temperature and capable of long-range transport and bioaccumulation in ecosystems, leading to adverse effects on biota and human health (12). Industry is responsible for half of the total mercury emissions (13) and energy industries (mainly coal-fired power plants) for a third (14). Artisanal gold mining is another source of airborne mercury: emissions occur in restricted geographical areas but are globally distributed via long-range transport (15).

Nickel is a silvery-white, lustrous, hard metal that occurs naturally in the environment in air, water and soil (16). However, anthropogenic sources account for a large proportion of nickel compound emissions (17). The main sources of nickel emissions to the atmosphere are mining, combustion and industrial production processes (18). Emissions from coal and oil combustion predominantly comprise nickel sulfate (17).

In recent years, informal recycling of electronic waste has become a localized source of atmospheric heavy metals (including arsenic, lead, mercury and nickel) in developing countries (19).

In the atmosphere, benzene is found in the gaseous state and mercury is generally found as elemental mercury in the vapour phase, whereas arsenic, cadmium, nickel and lead are generally found either bound (i.e. adsorbed) to particles or internally mixed as constituents of airborne PM *(1)*. Their physicochemical properties define their atmospheric residence time. The half-life of benzene can range from 2 h to 8 days depending on the concentration of hydroxyl radicals in the atmosphere, with shorter residence times in locations with higher hydroxyl radical concentrations *(20)*. In contrast, inorganic mercury is very stable, with a residence time of approximately 12 months, which allows it to become globally distributed far from the emission sources and achieve uniform background levels *(12)*. Atmospheric residence times for arsenic, cadmium, nickel and lead depend on particle size, meteorological conditions and the industrial processes responsible for their release *(21)*. In general, submicron particles have a residence time between 100 and 1000 h, whereas particles of 1–10 μm in diameter have a residence time of 10–100 h *(22)*. Residence time influences the exposure of populations to atmospheric pollution beyond the vicinity of the source for pollutants that have a sufficiently large half-life to allow air pollutant transport. Lifetimes of between 2 h and 8 days could allow pollutants to be distributed across a city or even across a region or country. Hence, exposure to these pollutants can have health effects on populations far from the emission site. Therefore, the atmospheric residence times of air pollutants must be considered when setting appropriate air quality policies, including air quality guidelines.

In non-smoking, non-occupationally exposed populations, exposure to these chemicals can occur through inhalation, dermal exposure or ingestion. Inhalation is the major exposure route for benzene *(1)*. Lead exposure occurs mainly through ingestion of food and dust. The main exposure pathway to arsenic is via drinking contaminated water and to cadmium and nickel is via contaminated food intake. Diet is the main exposure route to mercury (as methylmercury), through consumption of contaminated fish and seafood. In occupationally exposed populations involved in industrial processes that use these chemicals, inhalation of vapours of benzene and mercury (as elemental mercury) or dust containing arsenic, cadmium, lead or nickel is the main source of exposure. Inhalation of benzene, arsenic and cadmium is relevant for exposure in active tobacco smokers and people exposed to second-hand tobacco smoke *(1)*.

A wide range of health effects have been documented: benzene, arsenic, cadmium and nickel compounds cause cancer and the other pollutants can affect the haematological and renal systems, produce reproductive and developmental problems or affect cognitive development *(1)*.

1.2 Relevant regional and global international treaties

The 1979 Convention on Long-Range Transboundary Air Pollution (hereafter referred to as the CLRTAP) was the first regional international treaty aimed at improving air quality *(23)*, and was signed by 51 Parties of the United Nations Economic Commission for Europe (UNECE). Since it entered into force in 1983, this international cooperation has successfully led to a reduction of air pollution emissions in the UNECE region. CLRTAP comprises eight protocols that address specific air pollutants. The 1998 Aarhus Protocol, ratified by 35 Parties, focuses on reducing emissions of heavy metals, in particular cadmium, lead and mercury *(24)*. The Protocol was amended in 2012 to include more stringent measures intended to further reduce emissions of cadmium, lead, mercury and PM. The amendments entered into force on 8 February 2022.

Building on the 1998 Aarhus Protocol on Heavy Metals, in 2013 the Minamata Convention on Mercury was adopted under the auspices of the United Nations Environment Programme (UNEP), thereby raising the profile of mercury to global level *(25)*. It has 138 Parties and 128 signatories and entered into force on 16 August 2017. The Minamata Convention is intended to protect human health and the environment from the adverse effects of mercury. It requires Parties to control anthropogenic release of mercury throughout the life cycle of the pollutant.

1.3 WHO air quality guidelines

WHO has a long history of synthesising evidence on air pollution and health. Starting from the 1970s, a series of Environmental Health Criteria reports dedicated to specific pollutants has been published. The first report was on mercury *(26)*, followed by reports on arsenic *(27)*, cadmium *(28)*, nickel *(29)*, benzene *(30)* and lead *(31)*.

Since 1987, the WHO Regional Office for Europe has been developing recommendations in the form of air quality guidelines. They are used as a reference for decision-makers in setting standards and goals for air quality. Table 1 shows the timeline of evolution of the WHO air quality guidelines for benzene, arsenic, cadmium, lead, mercury and nickel *(32)*.

Published in 1987, the *Air quality guidelines for Europe* covered 28 pollutants *(33)*. The guidelines included lifetime risks for benzene, arsenic and nickel and proposed guidelines for annual exposures for cadmium, lead and mercury. The air quality guidelines were updated in 2000, covering the same 28 pollutants and a few additional ones, and published as the *WHO air quality guidelines for Europe, second edition (1,32),* and then as the *Guidelines for air quality (34)*. The global guidelines were updated in 2005 with the publication of the *Air quality guidelines: global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide (36)*. However, this update did not include benzene, arsenic, cadmium, lead nickel or mercury.

Publication of a series of indoor air quality guidelines began in 2009 with the *WHO guidelines for indoor air quality: dampness and mould (37)*, followed by the *WHO guidelines for indoor air quality: selected pollutants (3)*, which included lifetime risk factors for benzene only. The 2014 *WHO guidelines for indoor air quality: household fuel combustion* included lifetime risk factors for benzene *(35)*, consistent with those of the indoor air quality guidelines for selected pollutants *(3)* and second edition of the air quality guidelines for Europe *(1)*.

The 2021 *WHO global air quality guidelines: particulate matter (PM$_{2.5}$ and PM$_{10}$), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide* is an update of the global guidelines applicable to both ambient and indoor air *(38)*. In addition to air quality guideline levels (AQG levels) and interim targets for six air pollutants, they include good practice statements for certain types of PM (black carbon, ultrafine particles, and particles originating from sand and dust storms) *(38)*. However, it does not provide guideline values for benzene, arsenic, cadmium, lead, mercury or nickel.

As shown in Table 1, the current air quality guidelines are that annual concentrations should not exceed 5 ng/m^3 for cadmium, 0.5 μg/m^3 for lead and 1 μg/m^3 for mercury. No safe levels can be suggested for benzene, arsenic or nickel because they are classified as International Agency for Research on Cancer (IARC) Group 1: carcinogenic to humans *(1)*. The estimated risk of leukaemia for a lifetime exposure to 1 μg/m^3 benzene is 6×10^{-6}.[4] The estimated risk of lung cancer for a lifetime exposure to 1 μg/m^3 arsenic is 3×10^{-3}.[5] The estimated risk of lung cancer for a lifetime exposure to airborne nickel compounds at a concentration of 1 μg/m^3 is 3.8×10^{-4}.[6]

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[4]   Representing six additional cases of leukaemia due to benzene exposure in a population of 1 million people.

[5]   Representing three additional cases of lung cancer due to arsenic exposure in a population of 1000 people.

[6]   Representing 3.8 additional cases of lung cancer due to arsenic exposure in a population of 10 000 people.

Table 1. Evolution of WHO air quality guidelines

Pollutant	1987 Air quality guidelines for Europe *(33)*	2000 Air quality guidelines for Europe *(1)*	2000 Guidelines for air quality *(34)*
Benzene	No safe level could be recommended because it is carcinogenic to humans Estimated risk of leukaemia for a lifetime exposure to a concentration of 1 µg/m³ is 4×10^{-6a}	No safe level could be recommended because it is carcinogenic to humans Estimated risk of leukaemia for a lifetime exposure to a concentration of 1 µg/m³ is 6×10^{-6}	No safe level could be recommended as it is carcinogenic to humans Estimated risk of leukaemia for a lifetime exposure to a concentration of 1 µg/m³ is $4.4–7.5 \times 10^{-6}$
Arsenic	No safe level could be recommended as it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 3×10^{-3b}	No safe level could be recommended because it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 1.5×10^{-3}	No safe level could be recommended because it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 1.5×10^{-3}
Cadmium	Guideline value recommends that annual concentrations should not exceed 1–5 ng/m³ in rural areas and 10–20 ng/m³ in urban areas without agricultural activities and in industrialized areas	Guideline value recommends that annual concentrations should not exceed 5 ng/m³	Guideline value recommends that annual concentrations should not exceed 5 ng/m³
Lead	Guideline value recommends that annual concentrations should not exceed 0.5–1 µg/m³	Guideline value recommends that annual concentrations should not exceed 0.5 µg/m³	Guideline value recommends that annual concentrations should not exceed 0.5 µg/m³
Mercury	Guideline value recommends that annual indoor concentrations should not exceed 1 µg/m³	Guideline value recommends that annual indoor and ambient concentrations should not exceed 1 µg/m³	Guideline value recommends that annual indoor and ambient concentrations should not exceed 1 µg/m³
Nickel	No safe level could be recommended because it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 4×10^{-4c}	No safe level could be recommended because it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 3.8×10^{-4}	No safe level could be recommended because it is carcinogenic to humans Estimated risk of lung cancer for a lifetime exposure to a concentration of 1 µg/m³ is 3.8×10^{-4}

[a] An estimated risk of leukaemia of 4×10^{-6} represents four extra leukaemia cases per 1 000 000 population for a lifetime exposure to 1 µg/m³ benzene. This corresponds to an excess lifetime risk for leukaemia of 10^{-4}, 10^{-5} and 10^{-6} for an airborne benzene concentration of 17 µg/m³, 1.7 µg/m³ and 0.17 µg/m³, respectively.

[b] An estimated risk of lung cancer of 3×10^{-3} represents three extra lung cancer cases per 1000 population for a lifetime exposure to 1 µg/m³ arsenic. This corresponds to an excess lifetime risk for lung cancer of 10^{-4}, 10^{-5} and 10^{-6} for an airborne arsenic air concentration of approximately 66 ng/m³, 6.6 ng/m³ and 0.66 ng/m³, respectively.

[c] An estimated risk of lung cancer of 4×10^{-4} represents four extra lung cancer cases per 10 000 population for a lifetime exposure to 1 µg/m³ nickel. This corresponds to an excess lifetime risk of 10^{-4}, 10^{-5} and 10^{-6} a nickel air concentration of approximately 250 ng/m³, 25 ng/m³ and 2.5 ng/m³, respectively.

Note: The 2010 WHO guidelines for indoor air quality: selected pollutants *(3)* and the 2014 WHO guidelines for indoor air quality: household fuel combustion *(35)* recommend the same air quality guidelines for benzene as in the 2000 Air quality guidelines for Europe *(1)*.

1.4 Scope and objectives

Development of the 2021 *WHO global air quality guidelines* was guided by the provisions set out in the *WHO handbook for guideline development (39)*, and involved planning and scoping of the guidelines, systematic reviews of evidence, grading of evidence, and development of recommendations. That highly structured and complex process engaged several expert groups (systematic review team, guideline development group, external review group, WHO steering group, methodologists).

Scoping of the guidelines covered the selection of air pollutants and of the critical health outcomes for each air pollutant in relation to durations of exposure.

In 2013, WHO published the report from the *Review of evidence on health aspects of air pollution* (REVIHAAP) *(40)* project, which reviewed evidence on a range of air pollutants, including arsenic, cadmium, lead, mercury or nickel that had been published since the *Air quality guidelines: global update 2005 (36)*. REVIHAAP found no new evidence for mercury and insufficient evidence for arsenic, but identified new evidence for cadmium, lead and nickel. In the case of cadmium and lead, it was advised to consider them in the update of WHO air quality guidelines.

In 2015 WHO organized an expert consultation to assist WHO in planning and establishing priorities for evaluation of the air pollutants to be considered in the update of the global air quality guidelines *(38)*. The experts grouped 32 air pollutants that had been included in previous air quality guidelines into four categories to reflect their relative importance for updating the guidelines. Since a large body of new health-related evidence had been published since the 2005 global update *(36)*, the experts suggested prioritizing the six pollutants ($PM_{2.5}$, PM_{10}, ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide) in the update).

After the formal initiation of the project to update WHO global air quality guidelines, the Guideline Development Group confirmed the selection of the six air pollutants and added some types of PM (black carbon/elemental carbon, ultrafine particles, and particles originating from sand and dust storms) to be followed up to identify more conclusive evidence. It also selected the critical health outcomes associated with these pollutants.

Six systematic reviews of evidence covering different pollutant–outcome–averaging time combinations were commissioned for the guidelines and published in a special issue of the *Environment International* journal *(41–46)*, together with other reviews that were discussed and used in the process *(47,48)*.

Whereas the 2021 update of the WHO global air quality guidelines covered six, classical air pollutants out of 32 evaluated during the expert consultation in 2015 *(38)*, the expert group advised to review the evidence on several other air pollutants that had been included in previous air quality guidelines but were not ultimately considered/included in the current update. In this context, the 2021 report, *Human health effects of polycyclic aromatic hydrocarbons as ambient air pollutants: report of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution*, presents a comprehensive review of the evidence on this group of air pollutants *(49)*.

For several other air pollutants, namely arsenic, cadmium, lead, mercury, nickel and benzene, an expert consultation was convened to identify and discuss the latest available evidence on their health effects. This consultation aimed to support the revision of the EU ambient air quality directive *(50)* and similar policies in individual Member States of the WHO European Region and beyond.

This report is based on overviews of the air pollutants collated in six working papers on sources and exposure levels, toxicological and epidemiological studies, causality determinations, and health-based guidance values from authoritative bodies for benzene, arsenic, cadmium, lead, mercury and nickel (Annexes 1–6).

The working papers were presented and discussed, and research gaps were identified at:

- the First Session of the Expert Consultation on Selected Air Pollutants, Bonn, Germany, 27 May 2022; and

- the Second Session of the Expert Consultation on Selected Air Pollutants, Bonn, Germany, 29 June 2022.

This report provides a summary and key findings on benzene, arsenic, cadmium, lead, mercury and nickel that was collected by the expert group during the consultation, as well as knowledge gaps and ideas for future research. It is not intended to provide a systematic, comprehensive review of exposure to the six pollutants or their health effects. Instead, it focuses on specific aspects relevant to health risk assessment, such as the characteristics of the pollutants, their sources and occurrence in the environment, environmental levels, and human exposures. It provides an overview of the absorption, distribution, metabolism and excretion of the inhaled compounds, and includes selected toxicological and epidemiological studies on the health effects, and information on causality determination and on health-based evaluation and guidance values from authoritative bodies. Lastly, it suggests areas of research for each pollutant to provide the evidence needed to update the air quality guidelines for benzene, arsenic, cadmium, lead, mercury and nickel.

2. Benzene

2.1 Background

Benzene is a ubiquitous volatile air pollutant that mainly arises from anthropogenic sources such as combustion processes *(3)*. It is found in crude oil and, hence, in petroleum products *(51)*. Atmospheric benzene and benzene homologues are important chemical precursors of ground-level ozone and secondary organic aerosol *(52)*.

2.2 Emissions and ambient exposure to benzene

Natural sources of benzene are forest fires and volcanoes, but anthropogenic sources are the major environmental contributors to atmospheric benzene. Benzene is primarily derived from petroleum and is used in the manufacturing of chemical intermediates and organic chemicals. Therefore, benzene exposure may occur in several industries and occupations, including those related to petroleum, chemicals, coke making and manufacturing *(2)*.

Benzene is also used as an additive in gasoline, although its content has been declining in response to regulatory pressure *(2)*. Therefore, industrial emissions, emissions from coal and oil combustion, motor vehicle exhaust emissions, and fuel evaporation are the major anthropogenic sources. There are numerous sources of benzene emissions in indoor environments, such as the use of personal and home care products, new furniture, carpets, paint and activities such as smoking and cooking *(53,54)*.

Benzene is present in the atmosphere primarily in the vapour phase. It reacts with other compounds, mainly hydroxyl radicals, resulting in an atmospheric residence time of hours to several days depending on the abundance of the hydroxyl radicals *(20)*. As a consequence, benzene has an atmospheric residence time of 2 h to 8 days *(20)*.

Benzene concentrations measured in ambient air are generally orders of magnitude lower than those reported in occupational environments. Benzene concentrations in ambient air have significantly declined over time in the United States of America and Europe (current annual average concentrations are < 5 µg/m³). Higher concentrations are measured in some urban environments in other regions of the world *(2)*.

Ambient air concentrations of benzene are 0–1.35 µg/m³ across the United States *(55)* and range from 0.57–0.89 µg/m³ (background levels *(56))* to 1.5–12 µg/m³ (urban areas) in Europe *(53,57,58)*. Concentrations are highest in Asia at 2.33–21.75 µg/m³ *(59)*.

Higher air concentrations are observed in some microenvironments such as those near to road traffic, gasoline service stations and petrochemical facilities and within homes. Benzene concentrations in personal exposure studies are higher than in ambient air: reported concentrations are 4.7–6.3 µg/m³ in Europe and the United States, 50 µg/m³ in India and up to 111 µg/m³ in Asian countries. A recent review suggests that ambient benzene has a significant, if not dominant, role in indoor concentrations globally *(60)*. However, indoor sources still have a strong impact on personal exposures to benzene.

In Europe in 2019 ambient concentrations were above the limit value for benzene (5 µg/m³) in only two European Monitoring and Evaluation Programme (EMEP)[7] monitoring stations (located in two of the 31 reporting countries *(61)*). At 93% of locations, annual mean concentrations were below the lower assessment threshold of 2 µg/m³. Out of all stations across 15 European countries, 11% reported benzene concentrations above the WHO reference level of 1.7 µg/m³ *(2)*.

2.3 Review of health effects and causality

Benzene exposure mainly occurs via inhalation, although skin absorption is also possible (62). It is rapidly distributed throughout the body and accumulates in fat-rich tissues, especially adipose tissue and bone marrow. Unmetabolized benzene is excreted in the breath and urine, but most benzene is metabolized to phenol, hydroquinone, catechol, (E,E)-muconic acid and S-phenylmercapturic acid (28).

Bone marrow damage is one of the first signs of chronic benzene toxicity. Most haematological effects have been associated with benzene inhalation exposures. Epidemiological studies have shown haematological effects (decreased leukocyte, platelet and blood cell counts) at benzene levels lower than those found in occupational exposures (i.e. ≤ 0.82 mg/m³) but higher than most ambient concentrations *(63–65)*.

IARC concluded that there is sufficient evidence that benzene causes cancer in humans: "benzene causes acute myeloid leukaemia in adults" *(2)*. This conclusion was supported by inhalation studies in humans, including several cohort studies on occupational exposures, and by inhalation studies in laboratory animals.

The mechanism(s) of benzene carcinogenicity appears to be multifactorial, complex and not yet fully understood: several modes of action are possible and could act synergistically. In the haematological system, DNA damage is likely to precede haematotoxicity and carcinogenicity. The European Chemicals Agency considers the main genotoxic effects to be clastogenicity and aneugenicity and indicated that benzene has only a weak effect in directly inducing DNA mutations and that adduct formation is unlikely to have a significant role in benzene-induced leukaemia *(66)*. A recent review underscored the potential importance of chronic inflammation as a mode of action *(67)*.

Benzene in ambient air is associated with higher risk for childhood leukaemia, with a much higher risk for acute myeloid leukaemia (AML) *(68,69)* than for acute lymphoblastic leukaemia (ALL) *(70,71)*, consistent with the previous findings in adults. Recent epidemiological data support an etiological relationship between ambient air pollution and childhood leukaemia risk, which appears to be mainly attributable to benzene, although a contribution from other pollutants that covary with benzene emissions is plausible, either alone or in mixture *(2)*.

Benzene has been characterized as a genotoxic carcinogen for which fully protective, health-based limit values cannot be derived. Recent reviews suggest that a threshold based on mode of action can be established for the risk assessment of benzene-induced adverse health effects *(66,67)*. The large interindividual variability in benzene metabolism suggests that exposure thresholds may vary across populations. If the mechanistic evidence is suggestive of sublinearity, then the excess risks obtained using a linear non-threshold approach might be overestimated in the low exposure range.

There is little evidence of a threshold for benzene exposure, especially for AML *(68)*.

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[7]   Full name: Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe.

The 2000 WHO *Air quality guidelines for Europe* proposed a unit risk of 4×10^{-4} per 1 µg/m^3 benzene based on linear extrapolations from an increase in leukaemia in a cohort exposed to benzene in the manufacture of Pliofilm *(1)*.

Health-based guidance values have been set for benzene inhalation. Of the three guidance values on chronic toxicity, only the most recent was below the current European air quality standard (5 µg/m^3) *(72)*. The California Office of Environmental Health Hazard Assessment (OEHHA) toxicological reference value (or chronic reference exposure level (REL)[8]) of 3 µg/m^3 *(73)* was based on a decreased lymphocyte count in workers who had been heavily exposed to benzene *(74)*.

Since the 2000 WHO *Air quality guidelines for Europe* proposed an excess lifetime cancer risk, or URF,[9] for leukaemia (4.4×10^{-6} to 7.5×10^{-6}, geometric mean: 6×10^{-6}) *(1)*, four new URFs have been identified, ranging from 2.2×10^{-6} to 2.9×10^{-5} *(76–79)*.

Two recent meta-regression analyses of occupational cohort studies *(2,80)* and one of case–control studies on benzene in ambient air *(68)* provided substantial information on the relationship between air exposure to benzene and the risk of leukaemia (in particular, AML). These analyses may be useful for deriving new URFs.

2.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO suggests no safe level for benzene *(1)*.

Annual air quality standards range from 3.25 µg/m^3 (as an air quality objective in Scotland and Northern Ireland (United Kingdom) *(81)*) to 5 µg/m^3 in the EU (as an annual limit value *(72)*) and England and Wales (United Kingdom; as an air quality objective *(81)*).

No air quality standard for benzene was identified in North America. According to a 2019 review, China and most other countries in Asia, Africa and South America (where benzene levels in ambient air are highest) do not have an air quality objective. However, the Russian Federation and some Asian countries (such as India) have annual limit values of 5 µg/m^3 *(82)*.

The first pan-European analysis of benzene exposures from the petrochemical industry recommended extending the European annual standard for benzene to an hourly or daily limit *(83)*.

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[8] Defined as the concentration at or below which adverse health effects are not likely to occur *(27,28)*.
[9] Defined as the additional lifetime cancer risk in a hypothetical population after a lifetime exposure to a compound at a given concentration *(75)*.

2.5 Knowledge gaps and research needs

The expert consultation found that the research needs to provide evidence to assess the requirement to change the current risk factors and air quality guidelines are to:

- conduct high-quality prospective studies on the relationship between benzene in ambient air and the risk of leukaemia (in particular, childhood leukaemia and AML and/or acute non-lymphocytic leukaemia (ANLL) leukaemia subtypes);

- conduct studies that aim to define the shape of the dose–response curve at low environmental benzene concentrations for leukaemia (in particular, childhood leukaemia and AML and/or ANLL subtypes) and haematological end-points;

- investigate benzene metabolism and its interaction with co-pollutants at exposure to low environmental concentrations; and

- monitor and model exposure to benzene and other air pollutants in people living close to petrochemical sites and gasoline/diesel service stations and inside their homes.

3. Arsenic

3.1 Background

Arsenic is a natural component of the earth's crust. It is a ubiquitous metalloid that is widely distributed throughout the environment in the air, water and soil *(1)*. Inorganic arsenic is highly toxic. Arsenic toxicity to humans is well established, with many historical examples *(84)*. Arsenic can be found as a contaminant of drinking water, cigarettes, food, industrial effluent, occupational environments, as well as in ambient and indoor air.

3.2 Emissions and ambient exposure to arsenic

Natural and anthropogenic sources emit arsenic to the atmosphere. The main anthropogenic sources are industrial processes that involve heating arsenic-containing materials to high temperatures, such as smelting metal ores and fuel combustion, and the use of arsenic-based pesticides *(4)*. Recently, informal recycling of electronic waste has become a significant source of environmental arsenic, especially in developing countries *(85–87)*.

In air, arsenic is primarily concentrated in the fine fraction of suspended particles (< 2.5 μm) and its atmospheric residence time will depend on the particle size and meteorological and emission conditions during its release *(21)*. Wet and dry deposition processes will contribute to the eventual removal of arsenic from the atmosphere.

There is a large variability of arsenic concentrations in air depending on the type of monitoring site. Worldwide, mean total arsenic concentrations in air range from 0.02 ng/m^3 to 4 ng/m^3 in remote and rural areas and from 3 ng/m^3 to 200 ng/m^3 in urban areas. Concentrations are considerably higher near industrial sources, such as arsenic-rich coal-fired power plants and non-ferrous metal smelters (> 1000 ng/m^3).

Worldwide simulations of mean atmospheric arsenic concentrations also show large regional variations, with the highest levels in Chile (largest copper producer) and China in 2015, and a large increase in India between 2005 and 2015. Arsenic concentrations in ambient air are 0–1.35 μg/m^3 in the United States *(55)* and range from 0.57–0.89 μg/m^3 (background levels *(56)*) to 1.5–12 μg/m^3 (urban areas) in Europe *(53,57,58)*. Concentrations were the highest in China (range: 2.33–21.75 μg/m^3) *(59)*. In Europe, arsenic air pollution is highly localized, usually associated with the emissions from specific industries. Exceedances of the target value of 6 ng/m^3 for arsenic in PM$_{10}$ samples were observed at only seven out of 645 stations in 27 European countries in 2017 and in six out of 665 stations in 28 European countries in 2018 *(88,89)*. High local levels are still recorded: for example, in 2019 arsenic levels of up to 550 ng/m^3 in PM$_{10}$ were observed near a copper production facility in Bor (Serbia), which is one of the most polluted regions in southeastern Europe *(88,89)*.

3.3 Review of health effects and causality

Of the various routes of arsenic exposure, drinking water is the largest source of arsenic poisoning in the general population worldwide. Arsenic exposure through ingestion usually comes from food crops grown in arsenic-polluted soils and/or irrigated with arsenic-contaminated water or from milk or seafood. For the general population, atmospheric arsenic exposure appears to be the least significant contributor (compared with drinking water and food) to total arsenic intake, representing less than 1% of the total dose in both heavily and lightly contaminated areas *(18)*.

After absorption, inorganic arsenic is widely distributed throughout the body and accumulates in keratin-rich tissues such as skin, hair and nails *(90)*. It is eventually excreted, mainly via urine.

A few observational studies on arsenic in ambient air identified positive associations with health effects, mainly cardiovascular end-points: heart attack and/or coronary events, impairments in heart rate variability and/or blood pressure, systemic oxidative stress and systemic inflammation *(90,91)*. Moreover, a broad range of health adverse effects are consistently related to high arsenic environmental exposure, mainly cardiovascular diseases (CVD) and cancer *(90)* but with emerging evidence of neurodevelopmental impairments *(91)*. However, these results may reflect the health effect of common arsenic sources or of other pollutants that covary with arsenic in mixtures rather than the intrinsic toxicity of the particular arsenic compound, and/or exposure through other routes than inhalation (i.e. drinking water, food).

Although the exact contribution of arsenic to ambient air is unknown, airborne levels of arsenic may affect levels in food and water, thereby increasing the overall level of exposure. Several variables may modulate or confound the relationship between arsenic environmental exposure and adverse health effects – these include exposure route; genetic susceptibility; ionizing radiation; levels of B vitamins, folate and selenium; malnourishment; sex; and smoking.

IARC concluded that there is sufficient evidence that exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite and arsenate, can cause cancer in humans, including lung, bladder and skin cancer *(4)*.

In 2000 WHO *Air quality guidelines for Europe* proposed a URF of 1.5×10^{-3} per 1 µg/m^3 arsenic based on linear extrapolations from the lung cancer risk related to cumulative exposure to arsenic in smelter cohorts *(1)*. Since then, several studies have suggested a higher or lower URF.

The biological mechanism associated with the carcinogenicity of arsenic and its inorganic compounds has not been identified, but it does not seem to involve direct DNA damage *(90,92)*. This suggests that a possible threshold exposure level may exist for arsenic carcinogenicity, but there is insufficient data to define this. Since the mechanistic evidence suggests a nonlinear effect, extrapolation outside the observed range would introduce uncertainties, with possible overestimation of the excess risks in the low exposure range.

Much of the evidence on health effects associated with arsenic exposure is based on ingestion as the main exposure route. Clearly, the health effects related to inhalation might differ. Therefore, further studies focused on inhalation as the main arsenic exposure pathway are needed to derive air quality guidelines.

Although inhalation is not the main exposure pathway, arsenic can remain in the lungs for years, and such chronic accumulation may result in lung cancer. However, there is insufficient evidence on arsenic bioaccumulation in the lungs, and evidence of risk from exposure to ambient air is insufficient to change guidelines compared with evidence of the risk from arsenic exposure through other exposure pathways.

In populations exposed to high geochemical background arsenic or soil pollution, the respiratory route is always a low or very low contributor. For chronic non-cancer effects, in the case of non-

acute but abnormally high atmospheric concentrations (e.g. ≥ 30 ng/m^3), a pragmatic suggestion would be to calculate an equivalent dose by the oral route due to respiratory exposure. This dose should be added to the oral exposure dose, with the total compared to an oral toxicological reference value.

3.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO recommends no safe level for arsenic *(1)*. Similarly, no arsenic air quality standard has been identified in North America, China or most other countries. However, the EU has set an annual target value of 6 ng/m^3 for the total arsenic content in the PM$_{10}$ fraction *(50)*.

The expert consultation stated that an effects screening level of 3 µg/m^3 for acute toxicity should be considered non-health based *(93)*; in general, values from the Texas Commission on Environmental Quality should be taken with caution.

The values proposed by Health Canada *(94)* were considered rather old and non-health based. This is consistent with the precautionary approach taken by most jurisdictions when looking at cancer, who opted for a linear extrapolation assuming the lack of a threshold rather than potentially underestimating the risk through using a threshold approach.

3.5 Knowledge gaps and research needs

The commission found that the research needs to provide evidence to assess the requirement to change the current risk factors and air quality guidelines are to:

- characterize the relationship between arsenic exposure biomarkers and air pollution;

- study the factors that determine the metabolism and kinetics of arsenic;

- identify the genetic and epigenetic determinants of susceptibility and the mode of action of arsenic; and

- investigate the mode of action through which arsenic may produce disease from chronic low-level inhalation exposures.

4. Cadmium

4.1 Background

Cadmium is a soft, silver-white metal that is generally found in nature combined with other elements *(5)*. It has important industrial properties such as high thermal and electrical conductivity, high ductility, a low melting temperature and excellent corrosion resistance. Based on these properties, cadmium is used in a wide range of industrial applications.

4.2 Emissions and ambient exposure to cadmium

Cadmium is found naturally in the earth's crust, and in the atmosphere is mainly bound to aerosol particles.

According to EMEP, the main anthropogenic emission sources of cadmium in the region are industry, electricity production and household fuel combustion for residential heating *(11)*. In Europe, industrial production processes emit about 39% of cadmium emissions, with a further 28% from public power and cogeneration (power and heat) plants. Informal recycling of electronic waste is becoming a significant localized source of environmental cadmium, especially in developing countries *(86,87,95)*.

Airborne cadmium can be adsorbed onto the surface or internally mixed within the core of PM. The atmospheric residence time depends on the particle size, meteorological conditions, and operating conditions of the industrial or combustion process responsible for its release *(96)*.

In 2020 the annual concentration of cadmium was 0.01–0.2 ng/m³ across most of the EMEP region *(11)*. Information collected from EMEP monitoring stations also shows that cadmium concentrations declined by 47% in 2000–2020 in the EMEP region *(11)*.

4.3 Review of health effects and causality

Although cadmium inhalation is a minor component of the total exposure *(97)*, ambient cadmium concentrations are an important source of soil deposition and, thus, indirectly contribute to dietary intake. Following inhalation, only 20% of cadmium is retained in the body, mainly in the kidneys *(98)*. Absorbed cadmium is excreted very slowly *(99,100)*; its efficient retention means that cadmium bioaccumulates with a half-life of 7–30 years *(97,99,100)*.

IARC has classified cadmium and cadmium compounds as carcinogenic to humans (Group 1) *(4)*. Based on its carcinogenicity, the United States Environmental Protection Agency (US EPA) has proposed an excess URF of 1.8×10^{-3} for developing cancer upon lifetime exposure to 1 µg/m³ cadmium *(101)*.

The evidence suggests that cadmium is a toxic element with harmful effects on the cardiovascular, renal and respiratory systems (1,40,102,103). Prenatal exposure to cadmium is associated with fetal growth restriction (104,105) and slower growth trajectories (106,107), learning disabilities and lower cognitive performance in children (108–110). Similarly, cadmium exposure in children is associated with adverse neurodevelopmental outcomes (111,112). Several studies have reported that childhood exposure to cadmium can affect renal function (113–115).

Given that cadmium is a highly ubiquitous and toxic trace metal (causing bone diseases, nephropathy, reproductive disorders and an increased cancer risk) that persists in the environment and bioaccumulates in organisms, cadmium exposure is of great concern to human health.

The 2000 WHO *Air quality guidelines for Europe* aimed to limit the cadmium concentration in air in order to reduce soil deposition and, thereby, prevent a further increase in dietary intake – the dominant exposure route (1). This rationale is supported by evidence that the average cadmium concentrations in the renal cortex in the general population in Europe (15–40 mg/kg) are very close to the critical level for renal effects (1). The need to reduce cadmium airborne emissions has been reiterated since the publication of the Guidelines (40,103). Therefore, in view of the narrow margin of safety for adverse effects on the bones and kidneys, every effort should be made to further reduce cadmium emissions to the atmosphere and reduce other types of cadmium input into soil (40,103).

In the WHO European Region, the cadmium input into agricultural soils is greater than the output, suggesting that cadmium intake will not decrease (103) and that current cadmium air concentrations are too high to reach cadmium equilibrium in soil (i.e. the present AQG level for cadmium is not sufficient to reduce cadmium deposition) (40,116).

The most recent evidence on the possible public health impact of long-term cadmium exposure in the general population goes beyond effects on kidney and bone, and now includes cancer (especially hormone related) (117) and CVD (118–126).

All of these factors should be considered in decision-making about whether the current WHO AQG level for cadmium should be updated.

4.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO proposed an air quality guideline that annual cadmium concentrations in air should not exceed 5 ng/m³ (1). This guideline was based on effects other than cancer and mainly aims to prevent a further increase in cadmium in agricultural soils, which is likely to result in increased dietary cadmium intake for future generations.

In the EU, the annual target value is 5 ng/m³ (50). However, no cadmium air quality standard was identified in North America or in China and most other countries.

4.5 Knowledge gaps and research needs

The more recent studies that suggest that low-level exposures to cadmium may increase the risk to the general population for atherosclerosis and CVD (including CVD mortality) indicate a need for further epidemiological studies at low exposure levels *(118–126)*. These should appropriately account for confounding by smoking and include a greater focus on never smokers. Further studies should also investigate developmental effects, including prenatal outcomes and neurocognitive developmental effects. The findings of such studies could inform an update of the guidelines.

More research into the respiratory effects (e.g. chronic obstructive pulmonary disease (COPD)) is also important for public health but remains a lower priority than research into the effects of cadmium exposure on the cardiovascular system.

Future epidemiological work should be supported by experimental studies to underpin the observed associations with biological mechanisms related to the disease etiology, progression or exacerbation.

The non-renal effects (e.g. effects on bone, cancer, CVD) should be considered in the health risk assessment of cadmium since they have wider implications for public health.

5. Lead

5.1 Background

Lead is a bluish-white, lustrous metal with distinct properties that make it useful for a wide range of applications, including a low melting point, corrosion resistance, ductility, high density and malleability *(8)*. It is used in storage batteries.

5.2 Emissions and ambient exposure to lead

Anthropogenic sources are the main contributors to environmental lead. Activities such as lead mining and smelting, recycling and disposal of waste materials, fossil fuel combustion, land application of fertilizer, and informal electronic waste recycling are the main sources of airborne lead *(127,128)*. In Europe, about 57% of lead emissions are released by the industry production sector, while each of the other sectors contributes a maximum of about 14% (including road transport (leaded gasoline)) *(11)*. lead emissions to the atmosphere have considerably reduced since the 1980s. Since 2000, EMEP stations have reported a 76% decrease in airborne lead concentrations *(11)*.

Lead in air is primarily adsorbed onto the surface of $PM_{2.5}$, from where it is removed from the atmosphere via wet or dry deposition *(129)*. Levels of airborne lead are variable: current concentrations are around 10 ng/m³ in Europe *(11)*, 30 ng/m³ in the United States *(130)*, 15–850 ng/m³ in China *(131)* and around 300 ng/m³ in Egypt *(132)*.

Potentially high levels of occupational lead inhalation have been reported in industrial settings such as lead smelting and refining plants, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, and printing industries *(133)*.

5.3 Review of health effects and causality

Direct inhalation accounts for a small proportion of lead exposure, with much from lead in dust. Occupational exposure is the most common source for adults *(133,134)*. The absorption of lead particles and fumes by inhalation is affected by particle size, concentration and ventilation rate. Lead is distributed to the soft tissues and bones, with the latter absorbing approximately 94% of the total lead burden. Inorganic lead is not metabolized but binds reversibly to proteins, amino acids and sulfhydryl compounds *(135)*. Lead is primarily excreted in the urine and faeces *(136)*.

Most human toxicity and epidemiological studies have focused on the effects of lead on the nervous, cardiovascular and haematological, renal, reproductive, and immune systems. However, a review of recent toxicity and epidemiological studies in both humans and animals suggests that lead toxicity may affect more organ systems *(137)*.

In 2013 US EPA assessed the causality of observed health effects on populations exposed to lead *(138)*. A causal relationship was determined for effects on the nervous system such as decrements in cognitive function and problems with externalizing behaviours such as attention decrements, impulsivity and hyperactivity in children. A likely causal relationship was established for other effects on the nervous system, such as externalizing behaviours in children and young adults related to conduct disorders, internalizing behaviours in children, decrements in auditory and motor function in children, and decrements in cognitive function and psychopathological effects in adults. The same assessment recognized that effects on the cardiovascular system (e.g. coronary heart disease) and haematological effects (i.e. decreased red blood cell survival and function, altered heme synthesis) were causal. Effects on the male reproductive system and fetal developmental were also causal. Lead was also determined to be likely causal for effects on the immune system, such as atopic and inflammatory responses and decreased host resistance.

US EPA also considered that there is a likely causal relationship between lead exposure and cancer *(138)*. In contrast, IARC has classified lead and inorganic lead compounds as possibly carcinogenic to humans (Group 2B) *(139)*. The German Research Foundation has classified lead as Category 2 "to be regarded a human carcinogen" *(140)*.

A review of epidemiological and toxicological studies found that most of the effects of lead in both children and adults occur at blood lead levels significantly lower (as low as 5 μg/L) than the WHO-recommended level for an exposed population (100 μg/L) *(1,137)*. In addition, based on studies that had reported cognitive impairment associated with blood lead levels of 100–150 μg/L in children, the 2013 REVIHAAP review proposed a critical level of 100 μg/L *(40)*. Therefore, regulatory and public health interventions must be developed and implemented in order to prevent and reduce occupational and environmental exposure to lead in the air.

The 2000 WHO *Air quality guidelines for Europe* proposed an annual mean lead concentration of 0.5 μg/m³ to ensure that blood lead concentrations remain below 540 μg/L *(1)*. However, blood lead levels as low as 5 μg/dL and 10 μg/dL are associated with a range of health effects, including impaired neurocognitive and behavioural development in children *(137,141,142)* and CVD in adults *(143–146)*. Since there might not be a threshold level for the neurobehavioral effects of lead in children, a conservative approach is justified from a policy perspective. Therefore, updated WHO air quality guidelines should take these effects into account, as well as additional research into the timing, frequency and duration of lead exposure in air.

5.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO has proposed an air quality guideline for annual concentrations of lead in air not to exceed 0.5 μg/m³ *(1)*. The same value was proposed in the EU, which set a limit value for airborne lead of 0.5 μg/m³ *(72)*. The value is lower in the United Kingdom, which has an annual air quality objective of 0.25 μg/m³ *(81)*. The United States has the lowest guideline, with an air quality standard of 0.15 μg/m³ measured quarterly (i.e. 3-month average) *(135,147)*.

An air quality standard for lead was not identified for China or most other countries.

5.5 Knowledge gaps and research needs

The current global burden of diseases caused by lead exposure is likely to be higher than estimated in the cited calculations *(148)*, indicating a knowledge gap that must be filled. Consequently, more research should be conducted to determine the global burden of disease caused by lead exposure.

Further research is needed into the acceptability, feasibility and impact on equity and human rights of any interventions to reduce lead poisoning. Programmes are needed to help to develop and implement policies to eliminate lead exposure.

Previous studies have shown an association between lead and CVD (i.e. hypertension *(143)*, ischaemic heart disease *(149)* and stroke *(145)*) *(150)*. However, further studies are needed to determine the specific level, timing, frequency and duration of lead exposure that is associated with CVD outcomes. Epidemiological studies are also needed to determine the prevalence of high blood lead concentrations in pregnant or lactating women and to investigate a possible association with congenital birth defects.

Most lead studies, whether in animals or humans, have focused on ingestion as the mode of lead exposure, and very few on inhalation. Consequently, research gaps exist on the contribution of lead inhalation to total lead exposure. Further studies should investigate possible connections between lead in the air, lead biomarkers in the blood, and health effects.

Most of the reviewed levels of lead (and of metals in general) were based on biomonitoring data. Therefore, it is important to determine the relationship between biomonitoring data and lead concentrations in ambient air. Similarly, some of the conventional biomarkers used in epidemiological studies might not accurately reflect chronic lead exposure. Therefore, research is needed on the applicability of different biological matrices to evaluate acute and chronic exposure to lead.

6. Mercury

6.1 Background

Mercury is a toxic pollutant with the potential to bioaccumulate in ecosystems. In the environment, inorganic mercury is transformed by methylation into organic forms, which are more bioavailable; these organic forms can bioaccumulate and are more toxic than inorganic forms of mercury (151). All forms of mercury have been associated with adverse effects on human health and biota.

Elemental gaseous mercury is typically unreactive and is not efficiently removed from the atmosphere by precipitation because of its relatively low solubility. Therefore, mercury has a relatively long atmospheric residence time (0.5–2 years) and is thought to be transported across long distances in the troposphere (152–154).

6.2 Emissions and ambient exposure to mercury

The industry production sector emits about 47% of total mercury emissions, followed by energy industries, which release 35% of total emissions, mainly from coal-fired power plants (11). Artisanal gold mining is another source of airborne mercury in restricted geographical areas (15). Following its release to the atmosphere and depending on its physical and/or chemical form, mercury can be either deposited in the vicinity of the emission source or subject to long-range atmospheric transport via air masses (153). Currently, various local, regional and national air mercury monitoring networks coordinated by UNEP are in operation to support the Minamata Convention on Mercury (25).

Emissions of mercury and mercury compounds have been declining in the United States (155) and the EU (156), but continue to grow in Africa, Asia and other industrializing regions (net growth of 1.8% per year between 2010 and 2015) (157).

The Global Mercury Observation System (GMOS), coordinated by UNEP, has been operating since 2016 (158). Long-term monitoring of mercury in Europe and the northern hemisphere is taking place in response to the Heavy Metals Protocol to the CLRTAP (24). Based on data reported by UNEP the mean gaseous elementary mercury concentration (annually averaged) is 1.3–1.6 ng/m³ at sites in the northern hemisphere and approximately 1.0 ng/m³ at sites in the southern hemisphere (159). The notably small variation in background levels is explained by the long atmospheric residence time for of mercury, which enables it to become evenly distributed in the atmosphere (152–154).

Mercury concentrations in air (measured as annually averaged values) are well below the available chronic health base values. However, caution is advised when interpreting annually averaged concentrations as surrogates of exposure because these values may not reflect shorter-term peak concentrations. This is especially important given the ability of methylmercury to induce adverse developmental effects over shorter timescales (such as in utero) (160).

Current gaps in the geographical coverage of monitoring locations (in Africa, Latin America and the Caribbean, and the Russian Federation) cause uncertainties about the potential exposures and health risks in these locations. However, information on mercury concentrations generated by the six existing monitoring systems *(158,161–165)* should help to fill the existing gaps *(158)*. This is especially important for developing countries with larger mercury emissions to air from artisanal gold mining, coal combustion and electronic waste recycling. Whereas artisanal small-scale gold mining is an important source of mercury in low- and middle-income countries *(166–168)*, crematoria are a major source of atmospheric mercury in Europe *(169)*. Dental amalgam workers have been identified as another group that may be occupationally exposed to mercury *(170)*. The EU is considering changing the legislation to protect these workers as part of their package of mercury regulations *(171)*.

6.3 Review of health effects and causality

Inhalation is the major contributor to total mercury exposure for most of the general population, with diet and dermal absorption only minor contributors. In countries with high consumption of marine food, such as Japan, Republic of Korea, Mediterranean countries, some parts of South America, and Arctic countries, diet is the main source of methylmercury exposure *(172–175)*. All forms of mercury are rapidly distributed throughout the body. The primary organs of accumulation are the brain (elemental mercury (Hg(0)) and organic mercury), kidneys (elemental mercury and mercuric mercury (Hg(II)) and liver (organic mercury). Elemental and mercuric mercury are mainly excreted in the faeces and urine, whereas organic mercury is mainly excreted in the bile and faeces *(160,176)*.

Mercury is a neurological, developmental and reproductive toxicant. Epidemiological and animal studies have consistently associated inhalation and oral exposure to all forms of mercury with neurological and renal effects. Many of these effects are seen with both acute and chronic exposures *(160)*. A 2022 assessment by the Agency for Toxic Substances and Disease Registry (ATSDR) highlighted effects on the central nervous system, as well as on the cardiovascular, immune, renal and reproductive systems, and developmental effects (other than neurodevelopment) *(160)*.

IARC has classified methylmercury compounds as possibly carcinogenic to humans (Group 2B) and metallic mercury and inorganic mercury compounds as not classifiable as to its carcinogenicity to humans (Group 3) *(177)*.

Mercury is distributed in environments at different scales, and toxicological effects have been observed with both acute and chronic environmental mercury exposures. Further research is needed to understand the effects of shorter-term exposures and to address gaps in the toxicological database that currently limit the development of acute and intermediate health-based values (which are required to assess health risks).

6.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO has proposed an air quality guideline that annual concentrations of mercury in air should not exceed 1.0 µg/m³ *(1)*. In the United States, the limit value is lower, at an annual air quality

standard of 0.3 μg/m³ *(178)*. However, no limit or target value for mercury has been set in the EU and no air quality standard was identified for China and most other countries.

The available health-based guidance values, guidelines and standards for elemental mercury (the main species in ambient air) range from 0.03 μg/m³ to 1.0 μg/m³. Health-based guidance values do not exist for other mercury species (inorganic and organic mercury) because toxicological data are lacking and inhalation is not likely to be a significant exposure route.

The 2022 ATSDR review of toxicological data *(160)* identified new occupational data on a specific neurological point of departure[10] (tremors) in a large population of chloralkali workers, with exposure levels extrapolated from urinary mercury levels) *(160)*. The resulting (provisional) chronic minimal risk level is similar to the chronic health-based value developed by US EPA in 1995 *(178)* but lower than the one developed by the California EPA owing to the use of different uncertainty factors. For effects related to acute exposures, the only corresponding health-based value is from California (United States) *(73,180)*.

However, the draft ATSDR protocol for deriving a chronic health-based value for mercury was questioned by the experts in the consultation *(160)*. ATSDR applied a steady-state mass balance model to convert urinary concentrations of mercury to equivalent exposure concentrations. It considered that urinary mercury concentrations more accurately reflect the total body burden than mercury concentrations in air (measured in room air or the breathing zone), which are likely to be highly variable. It also acknowledged that non-occupational sources, such as diet and mercury dental amalgams, might have contributed to the urinary mercury levels observed in the occupational studies used to derive the health-based guidelines. Despite this, it considered that occupational exposures was still likely to be the main source of urinary mercury in these studies. One study reported that urinary mercury alone is probably not a good biomarker for the contribution of gaseous elemental mercury (GEM) to the total body burden of mercury in some population groups *(181)*. Measurement of mercury levels in hair could be used as non-invasive matrix to distinguish the body burden associated with atmospheric mercury inhalation from that associated with mercury in the diet *(181)*.

6.5 Knowledge gaps and research needs

Uncertainties related to gaps in the geographical coverage of monitoring locations (e.g. in Africa, Latin America and the Caribbean, and the Russian Federation) prevent a full understanding of the potential exposures and health risks associated with mercury. This is especially important for countries with significant emissions to air from sources such as artisanal gold mining, coal combustion and electronic waste recycling.

Further research is needed to determine the mechanism of action, existence of a threshold, best biomarkers to characterize acute and chronic exposures, estimation techniques, and point of departure for calculating health-based exposure limits.

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[10] On a toxicological dose–response curve, the point of departure corresponds to an estimated low or no effect level *(179)*.

7. Nickel

7.1 Background

Nickel is a silvery-white, lustrous metal. Its chemical and physical properties (i.e. fair conductor of heat and electricity, hardness, ductility, malleability, high melting point and somewhat ferromagnetic) make nickel an appropriate base for several alloys; hence, it is widely used in industrial applications *(4)*.

7.2 Emissions and ambient exposure to nickel

Nickel is naturally found in the environment in air, water and soil. However, anthropogenic sources account for 1.5 times the amount released by natural sources *(96)*. Until recently, the main sources of nickel emissions to the atmosphere were fossil fuel combustion, mining and smelting, municipal incineration and production processes *(16)*. Emissions from coal and oil combustion are predominantly in the form of nickel sulfate. Recently, informal recycling of electronic waste in small industries or at home has become a localized source of nickel in developing countries.

Nickel in the atmosphere is adsorbed onto the surface or internally mixed within the core of PM. The atmospheric residence time of nickel $PM_{2.5}$ in the atmosphere depends on the particle size, meteorological conditions and emission factors related to the responsible industrial processes. Nickel-bound particles are removed from the atmosphere by wet or dry deposition *(21)*.

Airborne nickel concentrations vary by the type of area: typical nickel concentrations in air are 0.3–2 ng/m³ in rural areas, 1–13 ng/m³ in urban locations and up to 50 ng/m³ near to industrial sites *(86,95,182)*. A study in France found that personal exposure to nickel was 3 ± 4 ng/m³ in PM_{10} *(183)*, and concentrations measured in China were five times larger *(184)*.

7.3 Review of health effects and causality

Food is the major contributor to nickel exposure, with lower contributions from drinking water and inhalation. In the body, nickel is transported bound to proteins such as albumin and alpha-2-macroglobulin and can cross biological membranes. It is mainly excreted in urine.

IARC has classified all nickel compounds as carcinogenic to humans (Group 1) and metallic nickel as possibly carcinogenic to humans (Group 2B). This is consistent with the WHO classification of nickel compounds as human carcinogens. US EPA has also classified nickel from refinery dust and nickel subsulfide as carcinogenic to humans (Group A) and nickel carbonyl as probably carcinogenic to humans (Group B2).

Unit risk estimates *(1,185–187)* and target values *(50,188)* for airborne nickel are based on carcinogenicity data from occupational epidemiological studies. The 2000 WHO *Air quality guidelines for Europe* used lung and nasal sinus carcinogenicity observed in cohorts occupationally exposed to nickel as the critical health end-point to derive a unit risk for nickel subsulfide and nickel dust *(1)*. The Guidelines propose a unit risk of 3.8×10^{-4} per 1 µg/m³ nickel based on linear extrapolations from increased carcinogenicity in Norwegian nickel refinery workers *(189,190)*.

Despite being present at low concentrations in the atmosphere, nickel is a common constituent of PM and, alongside many other components, is suspected to contribute to the health effects attributed to $PM_{2.5}$. Indeed, potential associations between nickel exposure through ambient air and health effects have been described *(40,51,191)*. The most recent overall review reported that the highest level of health evidence[11] was obtained for cardiovascular and respiratory effects *(191)*. Some individual reviews have concluded that the metal content of $PM_{2.5}$ in ambient air has a large influence on the cardiovascular effects of $PM_{2.5}$ exposures. In particular, transition metals were suggested to be responsible for these effects, with nickel likely to be a key contributor *(193)*. Although it has been argued that reduction measures for transition metals are likely to improve public health, there are limited data on the effect of ambient nickel exposure on cardiovascular risks to allow their use in WHO air quality guideline standards *(40)*. However, it is difficult to identify the individual effects of transition metals because their concentrations are strongly correlated because of their shared sources, for example, industrial processes or combustion of petroleum products for iron, nickel and vanadium.

Experimental and epidemiological data suggest that it is important to consider nickel species when estimating health risks. Several physiochemical factors of the various nickel compounds (e.g. water solubility, particle size distribution, whether adsorbed onto the surface or internally mixed within the core of PM) could affect bioavailability and, hence, their toxicity and impact on human health *(18)*. Unfortunately, current measurement techniques cannot provide sufficient information on which nickel species are present in ambient air and their physiochemical properties.

All of these factors should be considered when deciding whether the WHO air quality guidelines for nickel should be updated *(1)*.

7.4 Health-based evaluations and regulatory guidelines by authoritative bodies

WHO recommends no safe level for nickel *(1)*. Consistent with this, no air quality guideline for nickel could be found for China, the United States and most other countries. However, the EU has set an annual target value of 20 ng/m³. The United Kingdom has set the same target value as well as an annual guideline value of 20 ng/m³.

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[11]   Different systems are used to classify evidence into different levels *(192)*.

7.5 Knowledge gaps and research needs

It has been suggested that both the chemical composition and size of PM should be considered to better explain the observed health effects related to PM rather than size alone *(194)*. However, findings from epidemiological studies on specific chemical components of PM are inconsistent and may partly relate to limitations in exposure assessment.

More epidemiological studies are needed on potential associations between nickel (and different nickel species) in ambient air and health effects. These should include an accurate assessment of exposure to highly correlated components of ambient PM.

Since experimental and epidemiological data indicate that risk estimation depends on the particular nickel species, further studies to characterize which nickel species are present in ambient air and their physiochemical properties may be warranted.

Future epidemiological work should be supported by experimental studies using environmentally realistic doses to identify the biological mechanisms underpinning disease etiology, progression and exacerbation.

8. Discussion

The expert consultation aimed to assess whether there is sufficient evidence to update the air quality guidelines for benzene, arsenic, cadmium, lead, mercury and nickel.

The available evidence for benzene suggests that updating the air quality guidelines may be appropriate. In contrast, there is insufficient new evidence for arsenic and, especially, for cadmium, nickel and mercury to justify a review the existing air quality guidelines. However, the current air quality guidelines already state that there is no safe level for benzene, arsenic and nickel. Lead exposure has been associated with an increasing number of new health outcomes and warrants close follow-up; however, the current evidence does not justify updating the lead guidelines.

The evidence review identified similar knowledge gaps and research needs for most of the six air pollutants under consideration. In particular, there is a need for policy-oriented research upon which to derive air quality guidelines or update the existing ones.

More human studies are needed using different exposure conditions in order to disentangle the effect of specific pollutants from those of other pollutants. More experimental or quasi-experimental studies are needed in order to disentangle the effects of exposure via different routes and learn more about synergistic effects.

Epidemiological studies should aim to provide useful information upon which to define guidelines to protect more vulnerable populations by including those with a specific biological susceptibility such as genetic predisposition to certain health effects that might be aggravated by exposure. The studies should also include population groups with biological susceptibility due to immature human systems, including the immune system, occurring in utero and during infancy, childhood and adolescence, as well as older and chronically ill populations and those with disabilities, who have comorbidities and weaker immune systems and are, therefore, more vulnerable to pollutant exposures. Other susceptible populations include groups with elevated exposures to these pollutants: for example, socioeconomic status might lead to some ethnic groups living close to pollutant sources or might prevent them from adopting implementing costly measures to reduce their exposure; and children's breathing area is closer to vehicle exhaust emissions because of their height. The evidence on susceptible populations was mainly related to prenatal and childhood exposures. It showed that health effects are related to prenatal and childhood exposure to benzene *(195,196)*, cadmium *(104–106)*, lead *(9,142,197–203)* and mercury *(160,204)*. Benzene exposure is associated with an increased prevalence of AML, chronic lymphoid leukaemia, chronic myeloid leukaemia, multiple myeloma and non-Hodgkin lymphoma in children *(2)*. Prenatal exposure to cadmium is associated with fetal growth restriction *(104,105)* and slower growth trajectories *(106,107)*, learning disabilities and lower cognitive performance in children *(108–110)*. Similarly, cadmium exposure in childhood is associated with adverse neurodevelopmental outcomes *(111,112)* and effects on renal function *(113–115)*. Chronic cadmium exposure has been linked to poor cognitive performance *(205)* and a higher risk of heart failure *(118)* in elderly populations. Prenatal lead exposure is associated with behavioural problems *(197)* and poor global cognition *(198,206,207)*. Lead exposure in childhood is associated with poor executive function *(199)*, poor global cognition *(200–202)*, behaviour problems *(142)* and neuropsychiatric disorders such as attention deficit hyperactivity disorder and antisocial behaviour *(197)*. Lead exposure in childhood is also associated with effects on the central nervous system *(203)* and brain volume in adulthood *(208)*. Lead exposure in elderly population is associated with frailty *(209)*. A systematic review concluded that the evidence is consistent with lead having a detrimental effect on neurodevelopment in children in low- and middle-income countries, but more evidence is needed for arsenic, cadmium and mercury *(210)*. Mercury exposure in utero and during childhood can result in neurodevelopmental and neurobehavioral alterations, including loss of motor abilities, loss of language skills, apathy, agitation, withdrawn mood, loss of social skills and personality changes *(211,212)*. Therefore, although there is some evidence for deleterious

health effects of exposure to the six pollutants under consideration, more evidence is required for different health end-points and susceptible populations.

Although the toxicological studies were somewhat dated and used non-realistic exposure concentrations, this general approach is often required to obtain a measurable response in small test populations. For some of the pollutants, more animal studies on long-term exposure and mechanisms of action could be useful. Studies into the mechanism of action should be based on specific research questions. For example, the available epigenetic studies have not generated useful evidence to derive new air quality guidelines.

It is also important to consider that previous guidelines were based on evidence from studies on occupational cohorts. These guidelines considered the healthy worker effect and refined uncertainty factors when extrapolating values. However, good quality epidemiological studies on populations exposed to ambient concentration levels of these pollutants are considered more important for defining new guidelines. For this, it is essential to have more detailed and comprehensive air quality monitoring, as well as good evaluations of policy measures and intervention studies that demonstrate the benefits of reducing atmospheric pollutant concentrations.

A better understanding of the metal content of aerosols and their environmental parameters is also needed, such as their size fraction distribution, whether they are absorbed onto the surface internally mixed within the core of PM, and their solubility.

More experimental evidence about what happens to the metals when they enter the body, their bioavailability, whether they are excreted effectively, and whether they are capable of driving oxidative and inflammatory reactions is also warranted. There is a need for directed experimental approaches using real-world exposure concentrations.

It was important to identify the most severe health outcomes before conducting systematic reviews of the available studies. For example, for nickel these could be hypertension and stroke rather than kidney damage, as measured using biomarkers in the earlier studies. The large population studies conducted so far did not provide clear evidence on differential toxicity of PM components.

Epidemiological studies on workers who were occupationally exposed to certain chemicals provided important evidence that IARC considered to classify a large number of carcinogenic compounds. In addition, occupational epidemiological studies on workers who were exposed to a range of pollutant levels for long periods in controlled quasi-experimental work environments that allowed periodic ambient, personal and biological monitoring and health surveillance provided key data to infer exposure–response relationships and thresholds for health effects for the general population.

To develop new WHO air quality guidelines requires methodological advances and systematic reviews of direct evidence from epidemiological studies in general populations exposed to low levels of these pollutants. Systematic reviews may benefit from updated causality determinations from US EPA or Health Canada (e.g. causal, likely causal, suggestive to be causal). However, the current WHO approach does not invalidate previous air quality guidelines that were developed using different approaches.

The expert consultation suggested formulating questions to help those intending to update health-based values and guidelines for the general population such as:

- Is there sufficient evidence for the update?

- Do we already have new well-designed values?

- Can we expect the new values to have an impact since they may still be orders of magnitude higher than the measured air concentrations?

- Which exposure pathways these values are based on – are they based on inhalation studies?

For some vulnerable groups that are still exposed to higher levels of pollutants compared with the general population (e.g. those living in the vicinity of smelters, gold mines, informal electric waste recycling plants), the following approach could be taken: (i) note the main sources of exposure in the general population for each of the pollutants, and (ii) note which specific groups are exposed to these higher levels and need further protection (e.g. with stricter industrial emission controls, indoor smoking bans, lead-based paint bans).

For carcinogenic pollutants and pollutants for which there may be no threshold, the target should be to reduce the concentrations as much as possible.

The impact of climate change on atmospheric levels of the six pollutants should be investigated. Changing weather conditions can affect emission sources, the composition of emissions, and the reactivity of the airborne mixture in the atmosphere. The vulnerability of populations to extreme weather conditions and their adaptability to changing climate should also be considered, as changes in lifestyle and daily routines could make populations less resilient to exposure to these pollutants.

9. Conclusion

The expert consultation was not intended to provide a new set of air quality guidelines levels for the six pollutants under discussion. Instead, it assessed whether sufficient new evidence exists to trigger the process of updating air quality guidelines.

During the consultation, the available evidence was critically reviewed by the group of experts.

The main findings of this review are that:

- **there is insufficient new evidence** to support a review of the current air quality guidelines for cadmium, mercury, nickel and metalloid arsenic;

- **lead exposure is associated with an increasing number of new health outcomes and warrants close follow-up** – however, the current evidence does not yet justify updating the guidelines for lead;

- although it may be appropriate to review the existing air quality guidelines for benzene, **the current air quality guidelines already state that there is no safe level;**

- **for the carcinogenic air pollutants** (benzene, arsenic, cadmium and nickel):

  - the lowest possible exposure should be the aim to minimize the risk of cancer development, given the lack of a no-effect threshold; and

  - a possible threshold effect in the dose–response relationship should be investigated, especially for arsenic, which is a non-genotoxic, non-stochastic[12] carcinogen; and

- **for the non-carcinogenic air pollutants** (lead and mercury), important health effects have been identified and guidelines are already in place and the available evidence does not support their review.

Based on the expert consultation, considerations for further research to derive health-based guidance values and guidelines are to:

- **explore non-carcinogenic health end-points** to provide a broader understanding of health outcomes, especially for (but not limited to) those affecting development and the cardiovascular and central nervous systems;

- **conduct epidemiological studies on:**

  - the low exposure levels of airborne pollutants that are experienced by the general population; and

  - susceptible populations who might be disproportionately impacted by exposures to these pollutants because of biological susceptibilities that increase the likelihood of health effects or of socioeconomic and lifestyle susceptibilities that increase exposure to these pollutants;

- **conduct toxicological studies** using environmentally realistic doses to identify the biological mechanisms underpinning the epidemiological observations, especially those related to development and the cardiovascular and central nervous systems;

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[12] Non-stochastic effects are those for which incidence and severity depends on dose, but there also is a threshold dose.

- **determine the shape of the dose-response function for each pollutant at the low concentrations** experienced by the general population to provide new evidence for defining or updating the existing air quality guidelines, and investigate possible threshold effects for carcinogenic compounds that are not genotoxic;

- **conduct exposure studies to:**

  - characterize exposure to the six pollutants in the general population, especially in vulnerable populations and under different exposure conditions;

  - characterize the physicochemical properties of individual and mixtures of pollutants and assess their bioavailability and possible synergistic effects (such as inflammatory responses to oxidative stress) that are more likely trigger the observed health outcomes;

  - determine the physicochemical profiles of ambient and indoor-generated PM and their relative contributions on health effects; and

  - improve the usefulness of biomarkers of exposure by assessing the relationship between airborne pollutant concentrations and those measured in different biological matrices, especially those previously used to derive air quality guidelines;

- **optimize monitoring programmes** to help to protect populations from benzene and metal or metalloid exposure by establishing high-resolution networks in hot spots, providing comprehensive temporal and spatial trends or high-resolution spatiotemporal modelling, and sustained human biomonitoring programmes; and

- **combine exposure, epidemiological and toxicological studies** to explore the impact of climate change on the atmospheric levels, distribution and toxicity of the pollutants, taking into account any potential changes in population vulnerability.

In addition, the consultation suggested formulating questions to help those intending to update health-based values or guidelines for the general population.

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Annex 1. Evidence overview on benzene

Contents

A1.1 Exposure risk assessment

A1.1.1 Characteristics, sources, and environmental occurrence

Benzene (chemical symbol, C_6H_6; relative molecular mass, 78.1 g/mol; density, 874 kg/m^3 at 25°C, Chemical Abstracts Service (CAS) Registry Number 71-43-2) is an aromatic compound with a single six-member unsaturated carbon ring. It is a highly flammable and volatile liquid that is clear and colourless with a characteristic odour *(1)*, low melting (5.5°C) and boiling (80.1°C) points and high vapour pressure (12.7 kPa at 25°C). Other properties are related to water solubility (1.78 g/L at 25°C), lipid and organic solvent partitioning (log $K_{octanol-water}$, 2.14; log $K_{soil\ organic\ carbon-water}$, 1.85 at 25°C) and Henry's Law constant (550 Pa.m^3/mol at 25°C) *(1)*.

Atmospheric benzene exists almost exclusively in the vapour phase. Benzene reacts with other compounds (primarily hydroxyl radicals) in the atmosphere, resulting in an atmospheric residence time of 2 h (higher hydroxyl radical concentrations) to 8 days (lower hydroxyl radical concentrations) *(2)*. The main benzene reactions are the substitution of hydrogen atoms and addition of methyl groups *(3)*. Since its double bonds can be cleaved by oxidizing reagents such as ozone, it can rapidly gain atoms such as bromine (Br) or chlorine (Cl) to form chlorobenzene (C_6H_5Cl) or bromobenzene (C_6H_5Br). Secondary compounds formed during this process may also be toxic to humans.

Benzene is a ubiquitous environmental pollutant. Natural sources include forest fires and volcanoes, but anthropogenic sources are the major environmental contributors to atmospheric concentrations. The latter include industrial emissions, coal and oil combustion, motor vehicle exhaust emissions, and fuel evaporation *(4)*. Benzene is primarily derived from petroleum and is used in the manufacture of chemical intermediates and organic chemicals *(4)* such as plastics, synthetic rubber, dyestuffs, resins, raw materials for detergents and plant protection agents; it is used extensively as a solvent *(5)*. Historically, benzene has been a major component in petrol, but the percentage benzene content in petrol has been declining due to regulatory pressure. The benzene concentration in petrol is now 1–2% by volume in the United States of America *(6)* and less than 1.0% by volume in the EU *(7)*.

There are also numerous sources of benzene emissions in indoor environments. Since benzene is a component of tobacco smoke *(4)*, smoking contributes to benzene levels in indoor air. Other indoor sources of benzene include personal and home care products, new furniture, carpets, paint and activities such as cooking *(8,9)*.

A1.1.2 Environmental levels

The benzene concentration in the atmosphere is a complex function of emission rates, meteorological and topographical conditions, and chemical removal. In the atmosphere, benzene is primarily removed by reacting with hydroxyl radicals *(2,10)*. Concentrations tend to be highest in cities, where wind speeds are lower *(11)*. Benzene concentrations can build up in mountainous terrain with a relatively stable air mass. Concentrations are higher in proximity to trafficked streets and petrol and diesel service stations than the urban background levels. Benzene and benzene homologues are important chemical precursors of ground-level ozone and of secondary organic aerosol in the atmosphere *(12)*.

Globally, there is a wide range of ambient air concentrations of benzene *(4)*. A European Environment Agency review of air quality data for 2019 reported benzene concentrations of above the limit value (5 μg/m^3) at only two stations (in two out of 31 reporting countries) *(13)*. At 93% of locations, annual mean concentrations were below the lower assessment threshold of 2 μg/m^3. In all, 11% of stations across 15 European countries reported concentrations above the estimated WHO reference level (1.7 μg/m^3). In 2011 very few (0.9%) monitoring stations in

Europe exceeded the annual limit value for benzene (5 µg/m^3) *(14)*. In 2013 the average benzene concentrations across 343 monitoring stations in the United States ranged from 0 µg/m^3 to 4.41 µg/m^3 *(15)*. China has among the highest reported levels, with benzene concentrations averaging 21.75 µg/m^3 between 1994 and 2014 and averages for cities ranging from 2.33 µg/m^3 to 65.39 µg/m^3 *(16)*. Extremely high average concentrations have also been reported from cities in Bangladesh (Dhaka), Egypt (Cairo), India (Delhi, Mumbai), Iran (Islamic Republic of; Tehran), Kazakhstan (five districts), Mexico (Nuevo Leon), Thailand (Bangkok) and Viet Nam (Hanoi) *(17)*. In Europe, background concentrations were 0.57–0.89 µg/m^3 in 2015–2017 *(18)*, whereas ambient benzene concentrations in urban areas were 1.5–12 µg/m^3 *(8,19,20)*. Concentrations are generally higher indoors than outdoors *(20,21)*

Ambient benzene concentrations in Europe significantly declined over the 2000–2019 period *(13)*, with a decline of > 70% between 2000 and 2014 *(22)*. In the United States there was a 66% decline between 1994 and 2009 *(23)*, and in China there was a a decline of 84% between 2001 and 2016 *(12)*. In addition, there is seasonal variability, with higher concentrations in winter and lower concentrations in summer *(24,25)*.

Industrial disasters may have short-term effects on air quality. For example, in the first 5 months after the Deepwater Horizon oil spill in the Gulf of Mexico in April 2010, mean benzene atmospheric concentrations in the vicinity of the spillage of 0.12–290 µg/m^3 were reported, whereas concentrations of 0.51–2.33 µg/m^3 were measured in urban areas of Louisiana over the same period *(26)*.

A1.1.3 Human exposure

Benzene exposure mainly occurs via inhalation, although skin absorption and exposure from ingestion of water and foods contaminated with benzene can also occur *(6)*. Benzene exposure via inhalation mainly occurs while undertaking activities near traffic (e.g. driving, walking), petrol stations (refuelling) or petrochemical facilities; using solvents; or smoking or inhaling second-hand smoke *(4)*.

In most studies that compared benzene concentrations in residential indoor air and ambient air, concentrations were higher in indoor air *(17,21)*. An analysis found that the average benzene level in residential indoor air was 4.7 µg/m^3 in Europe, 6.3 µg/m^3 in North America and 111 µg/m^3 in Asia, with an average of 50 µg/m^3 in India *(17)*.

A recent review suggests that ambient benzene has a significant, if not dominant, influence on indoor concentrations worldwide *(27)*. Although most benzene measured indoors originates from outdoor sources *(20)*, indoor sources also have a strong impact on personal exposures to benzene *(28)*. People living in homes with an attached or integral garage may have a higher exposure to benzene *(8,29,30)*. A United Kingdom study reported that personal exposures to benzene were higher for people living in houses with an integral garage (3.5 ± 3.0 µg/m^3) than for those living in houses without an integral garage (2.0 ± 2.3 µg/m^3) *(8)*. Personal exposure concentrations of benzene were also higher in people exposed to second-hand tobacco smoke (2.5 ± 3.0 µg/m^3) than in those not exposed to second-hand tobacco smoke (2.0 ± 2.1 µg/m^3) *(8)*. The highest levels of indoor benzene exposure were observed in homes with traditional biomass cooking stoves *(31)*.

A1.1.4 Absorption, distribution, metabolism and excretion

Benzene is well absorbed via inhalation (approximately 50%; range: 20–60%) as well as by oral and dermal exposure *(6)*. Benzene is then widely distributed throughout the body by blood circulation. Due to its lipophilic nature, benzene usually accumulates in fat-rich tissues such as fat and bone marrow. Benzene can cross the blood–brain barrier into the brain. It can also cross the placenta, and is found in equal or higher concentrations in umbilical cord blood than in maternal blood *(32,33)*.

Most absorbed benzene is excreted as water-soluble metabolites in the urine. Benzene metabolism starts with oxidation to benzene oxide by cytochrome P450, and is then transformed into several reactive electrophiles via multiple metabolic pathways in various tissues, including bone marrow. The main benzene metabolites detected in urine are catechol, hydroquinone, (*E,E*)-muconic acid, phenol and phenylmercapturic acid *(4)*. In addition, small amounts of unmetabolized benzene can be found in urine, although most unmetabolized benzene is excreted in exhaled breath *(34,35)*.

Although the mechanism of benzene toxicity is not fully elucidated, it requires metabolization. Some data suggest that benzene metabolism is increased at low exposure concentrations. In particular, a series of studies in workers in Tianjin (China) used air and urinary excretion data to investigate the dose-specific metabolism of benzene over a wide range of air concentrations (0.03–88.9 ppm) *(36–38)*. The highest dose-specific metabolism of benzene occurred at air concentrations of < 1 ppm. Several reports have reanalysed these data to assess whether the relationship between benzene metabolism against air concentration is nonlinear *(39–44)*. In 2018 the IARC Working Group noted that "overall, there are some data suggesting increased metabolism at low exposures, but the data are not definitive" *(4)*. Benzene oxide, benzoquinone and muconaldehyde are considered to be the key metabolites for cytotoxicity and the induction of leukaemia *(1,45–50)*.

A1.2 Toxicological studies

This section builds on the *Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* [French National Agency for Food, Environmental and Occupational Health Safety] (ANSES) review *(51)* and ongoing surveillance of benzene toxicity, IARC monograph 120 on benzene *(4)*,[1] WHO documents provided for the expert consultation, and references listed in the collected articles (i.e. snowballing).

A1.2.1 Laboratory animals: short-term effects

Acute exposure to high concentrations of benzene causes death in laboratory animals *(6)*. One study calculated a lethal concentration 50 value[2] of 13 700 ppm for rats exposed by inhalation for 4 h *(52)*. Another study reported that four out of six rats died after exposure to 16 000 ppm benzene for 4 h *(53)*. However, a study of male CD-1 mice exposed by inhalation to benzene concentrations up to 4862 ppm for 6 h/day for 5 days reported no deaths *(54)*. No deaths were reported in mice exposed to lower benzene doses (up to 400 ppm) for 2 weeks *(55)*. One study reported sudden death in monkeys and cats exposed to unknown concentrations of benzene *(56)*, attributed to ventricular fibrillation due to increased adrenaline release. In rabbits exposed to 45 000 ppm of benzene, involuntary reflexes were reduced and narcosis triggered within 30 min, followed by death for all animals *(57)*.

One study reported a 90% decrease in hind limb grip strength after a single exposure to 1000 ppm or 3000 ppm benzene in C57BL/6 mice (data not reported for 100 ppm), and tremors that persisted for 30 min after a single exposure to 3000 ppm benzene *(58)*. Benzene exposure induced the depression of evoked electrical activity in the brain impulses in male albino specific-pathogen free rats exposed for 4 h (dose not specified; 30% effect level: 929 ppm) and in female H strain mice exposed for 2 h (dose not specified; 30% effect level: 856 ppm) *(59)*. A 2019 study reported concentration-dependent anxiolytic effects, impaired learning and an analgesic effect in rats exposed for 30 min to 500, 1000, 2000, 4000 and 8000 ppm benzene *(60)*.

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[1]   This annex includes text reproduced from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans volume 120 *(4)*, reproduced with permission.

[2]   Concentration of a chemical in the air that will kill 50% of test animals via inhalation.

Short-term (< 2 weeks) repeated-dose studies have reported haematological effects in animals. In one study, male C57BL/6J mice (seven to eight mice per batch) were exposed for 6 h/day for 6 consecutive days to 0, 10.2, 31, 100 or 301 ppm benzene (0, 33, 101, 325 or 978 mg/m³) [61]. A significant decrease in erythrocyte number was observed in mice exposed to 100 ppm and 301 ppm benzene (325 mg/m³ and 978 mg/m³), and decreased circulating lymphocytes at the lowest dose. A lymphoblastic transformation test using liposaccharides or phytohemagglutinin was performed on medullary and splenic lymphocytes in vitro. At a concentration of 10.2 ppm benzene (33 mg/m³), there was a significant decrease in lipopolysaccharide-induced B-cell colonies (from spleen and bone marrow) without a significant decrease in total B-cell numbers. A decrease in phytohemagglutinin-induced spleen blasts was noted at 31 ppm (101 mg/m³), without a significant alteration in total T-cell counts.

Several tests have shown benzene to be a skin and eye irritant [53,62,63], including those conducted according to the Organisation for Economic Co-operation and Development's guideline, *Test no. 404: acute dermal irritation/corrosion* [64].

There is no evidence for sensitization induced by benzene in laboratory animals [6].

A1.2.2 Laboratory animals: long-term effects

A1.2.2.1 Haematological effects

There are numerous repeated dose toxicity studies on benzene. In mice, the haematopoietic system is the target organ for the effects of benzene, by whichever administration route. Dose–response studies have identified a no observed adverse effect concentration (NOAEC) and lowest adverse effects concentration (LOAEC) for benzene. Repeated inhalation exposure in mice induced haematological alterations starting from 10 ppm (32 mg/m³), including reduced counts of erythroid precursors, lymphocytes and red blood cells [6,51]. A 14-day exposure to 50 ppm benzene induced lymphocytopenia in a dose-dependent manner and leukopenia [65]. A lifetime exposure to 300 ppm benzene also induced macrocytic, hypochromic anaemia [66]. No effects on erythrocyte cells were observed in rats after oral or inhalation administration of benzene [51]. Reduced white blood cell counts correlated with increased leukocyte alkaline phosphatase activity in female rats (NOAEC: 50 ppm; LOAEC: 100 ppm). Leukocyte alkaline phosphatase activity has been suggested as a useful parameter for assessing chronic benzene poisoning in rats and humans.

A subchronic study examined the peripheral blood and bone marrow of male and female CD-1 mice and Sprague-Dawley rats exposed to 0, 1, 10, 30 or 300 ppm benzene (0, 3.2, 32, 96 or 958 mg/m³) for 6 h/day, 5 days/week for over 13 weeks [67]. Haematological effects were not observed in mice or rats exposed to 1–30 ppm benzene. Mice exposed to 300 ppm for 90 days had reduced haemoglobin concentration, red and white blood cell counts, platelet numbers, percentage lymphocytes and myeloid/erythroid lineage ratios. Many of these effects appeared as early as day 14 and persisted throughout the exposure but without increasing severity. Less severely affected rats had decreased white blood cells and femoral bone marrow cells at 300 ppm exposure [67]. The authors concluded that the haematological effects were similar to those in other studies. This study provided a NOAEC of 30 ppm and LOAEC of 300 ppm associated with peripheral blood abnormalities in mice and rats. The large number of animals used (50 rats/sex, 150 mice/sex) in this study and evaluation of several parameters related to haematotoxicity support the authors' conclusions. Another study reported a significantly delayed lymphocyte response in male mice exposed by inhalation to 10 ppm benzene (32.5 mg/m³), 6 h/day, 5 days/week for 20 days [68].

These long-term haematological effects are consistent with the decrease in lymphocytes and erythrocytes observed in the short-term (< 2 weeks) repeated-dose studies (section A1.2.1).

A1.2.2.2 Immunological effects

Benzene depresses cellular and humoral immunity in mice following exposures of 10 ppm (32 mg/m³) and higher for 6 h/day for 6 days *(6,51)*. No specific effect on the humoral immune response was seen in rats.

A1.2.2.3 Neurological effects

Behavioural activity was evaluated in two strains of mice (CD-1 and C57BL/6) exposed to 300 ppm or 900 ppm benzene for 6 h/day for 5 days and repeated after 2 weeks *(69)*. Increased behavioural activity was observed in both strains of mice, and was greater after exposure to 300 ppm than to 900 ppm, probably because of narcosis-like effects induced at the higher exposure level.

There was a significant increase in sweetened milk-licking in C57BL/6 mice after 1 week of exposure to 300 ppm benzene for 6 h/day *(58)*.

In male mice, benzene inhalation for 2 h/day, 6 days/week for 30 days at a concentration of 0.78, 3.13 or 12.52 ppm (2.53, 10 or 41 mg/m³) induced a significant increase in forelimb contraction at 0.78 ppm (2.53 mg/m³), with decreased effects at the higher concentrations *(70)*. The same study reported decreased brain acetylcholinesterase activity.

A1.2.2.4 Respiratory effects

Snyder and colleagues reported no effect of benzene on the lung tissue of Sprague-Dawley rats after a lifetime exposure to 0, 100 or 300 ppm for 6 h/day, 5 days/week *(71,72)*. In addition, no pulmonary effects were observed in AKR/J or C57BL/65 mice after a lifetime exposure to 300 ppm benzene *(66,71)*.

A1.2.2.5 Reproduction and developmental effects

Numerous studies have exposed animals to benzene during gestation *(73–77)*. None of the studies have demonstrated that benzene is teratogenic, even at concentrations that induce maternal and fetal toxicity. Altered haematopoiesis has been observed in the fetuses and offspring of mice exposed to low concentrations (≤ 20 ppm) of benzene in pregnancy *(78,79)*.

According to ATSDR, the results of inhalation studies in laboratory animals are consistent across species *(6)*. Benzene fetotoxicity in animals is suggested to relate to maternal toxicity, and the effects usually co-occur with reduced maternal weight *(80)*. However, the underlying mechanism has not been fully identified because of a lack of data on the effect of benzene on maternal food consumption and on the levels of benzene and its metabolites maternal and fetal blood. As noted in section A1.2.2.1, there is evidence for persistent haematopoietic abnormalities in animals exposed in utero to 20 ppm benzene *(78)*. Lower concentrations may also cause these effects, but this cannot be confirmed because of insufficient testing.

Effects on the reproductive system have also been observed in animal models. However, most studies used exposure concentrations much higher than occupational or ambient air concentrations *(6,81)*. In a 13-week study *(67,81)*, gonadal alterations were observed in mice exposed to 980 mg/m³ (307 ppm) benzene, with more severe effects in males.

A1.2.2.6 Carcinogenicity

IARC monograph 120 *(4)* reported that benzene (or its metabolites):

- induces oxidative stress and oxidative DNA damage in human and other mammalian cell lines and in various murine tissues in vivo, including bone marrow;

- is genotoxic, inducing DNA damage in human cells in vitro, and chromosomal changes, and DNA adducts in bone marrow and leukocytes in experimental animals;

- alters DNA repair or causes genomic instability by inhibiting topoisomerase II (which is involved in DNA replication) in human cell systems and in exposed mice;

- is immunosuppressive in assays for humoral and cell-mediated immune function and haematotoxic in experimental animals and exposed humans;

- induces apoptosis and alters nutrient supply, cell proliferation or cell death; and

- modulates receptor-mediated effects, primarily of the aryl hydrocarbon receptor.

Less evidence is available to evaluate whether benzene induces chronic inflammation, epigenetic alterations or immortalization.

A systematic literature search focusing on relevant end-points concluded that there is strong or moderate evidence, in both humans and experimental animals, that benzene shows eight out of the 10 key characteristics of carcinogenicity *(82)*.

Recent reviews concluded that benzene exposure may induce epigenetic effects and that several of the epigenomic changes in response to environmental exposures may be mechanistically associated with susceptibility to diseases *(83,84)*.

The European Chemicals Agency review on carcinogenicity and mode of action reported that some effects of benzene are likely to occur in humans at low exposure levels (≤ 1 ppm), in particular genotoxicity (clastogenicity and aneugenicity), oxidative damage, immunotoxicity, altered gene expression, and receptor-mediated effects *(85)*.

In a 2021 reanalysis of published data, Cox and colleagues underscored the potential importance of chronic inflammation as a metabolic pathway for benzene *(44)*.[3] They reported recent findings that "benzene induces inflammatory programmed cell death (pyroptosis) [*(86,87)*] and autophagy [*(88)*]".

IARC reported 17 studies on the effects of benzene inhalation in mice: nine reported positive associations, seven reported negative associations and one was considered inadequate for evaluation by the IARC Working Group *(4)*. Positive associations included an increased incidence of one or more types of neoplasms (including haematopoietic and lymphoid tumours) in mice exposed to 300 ppm benzene (100 ppm in one study). Three whole-body inhalation studies showed benzene-induced neoplasms and preneoplastic effects in genetically modified mouse models. In two of the studies, benzene induced cancer in different tissues (including haematopoietic and lymphoid tumours) in genetically modified mice exposed to 100 ppm or 300 ppm benzene. The other study had negative findings.

One inhalation study in Sprague-Dawley rats reported an increased incidence of neoplasms (including haematopoietic and lymphoid tumours) in pregnant rats (and their offspring) exposed to 200–300 ppm benzene. In one study of transplacental exposure followed by inhalation, exposure to 200 ppm or 300 ppm benzene significantly increased the incidence of Zymbal gland carcinoma in rat offspring (both male and female). In female offspring, there was increased squamous cell carcinoma of the oral cavity, carcinoma in situ of the forestomach,

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[3]   In the declaration of interest, the authors mentioned contractual support of the study by Concawe, a division of the European Petroleum Refiners Association, and financial support from ExxonMobil.

and hepatocellular carcinoma. Therefore, benzene is significantly associated with an increased incidence of haematopoietic and lymphoid tumours in female offspring.

Premature deaths have been observed in carcinogenicity studies in rats and mice exposed to 200 ppm or 300 ppm benzene *(32,33,89,90)*.

A1.3 Epidemiological studies

This chapter builds on the ANSES review *(51)* and the ongoing ANSES surveillance of benzene toxicity, published reviews collected through an exploratory PubMed search for this expert consultation,[4] IARC monograph 120 *(4)*,[5] WHO documents provided for the consultation, and references listed in the collected articles (i.e. snowballing).

A1.3.1 Short-term effects

A1.3.1.1 Mortality

As early as the beginning of the 20th century, studies in humans reported that massive inhalation exposure to benzene causes death, either suddenly or within hours of exposure *(91,92)*. The concentrations of benzene in such exposures are often not known.

Mortality associated with cerebrovascular ischaemia was associated with elevated benzene exposures of 20 000 ppm (64 980 mg/m³) for 5–10 min *(93,94)*. Death following benzene exposure is often attributed to asphyxiation, respiratory arrest or central nervous system depression. Cyanosis, haemolysis, and organ ischaemia or haemorrhage were observed in studies where postmortems could be performed *(92,95,96)*. Bronchitis, congestive gastritis, laryngitis and massive haemorrhage of the lungs were observed postmortem in an 18-year-old man after voluntarily exposure by inhalation to benzene *(97)*.

A1.3.1.2 Neurological effects

In mild forms of benzene intoxication, excitation followed by speech disorders, headaches, dizziness, insomnia, nausea, paraesthesia in the hands and feet, and fatigue are reported *(98)*. These symptoms are generally observed at concentrations between 300 ppm and 3000 ppm (975 mg/m³ and 9750 mg/m³) *(91,93,99)*.

Specifically, inhalation of 50–100 ppm (162–325 mg/m³) benzene for 30 min causes fatigue and headaches, and inhalation of 250–500 ppm (812–1625 mg/m³) benzene causes dizziness, headache, malaise and nausea *(45)*.

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[4] PubMed search on 22 March 2022: search terms were ("benzene"[Title/Abstract] AND "air pollut*"[Title/Abstract]) AND (meta-analysis[Filter] OR review[Filter] OR systematic review[Filter]).
[5] The chapter includes text, figure and table reproduced from the IARC monograph volume 120 with authorization from IARC *(4)*.

A1.3.1.3 Irritation and sensitization

In 15 male workers, occupational exposure to benzene vapours (> 60 ppm; > 195 mg/m^3) for 27 h (range: 3–150 h) caused irritation of the mucous membrane and skin, as well as dyspnoea (99). Skin irritation was due to direct contact of benzene vapours with the skin.

High benzene concentrations in air cause irritation of the mucous membranes of the eyes, nose and respiratory tract. Direct skin contact with liquid benzene may cause erythema. Skin irritation has been noted for occupational exposure to benzene at atmospheric levels of > 60 ppm for more than 3 weeks (6). In a study of 300 workers exposed for more than 1 year to 33 ppm benzene (10.15 mg/m^3; men) or 59 ppm (191.8 mg/m^3; women) both sexes complained of eye irritation (46).

There is no evidence for sensitization to benzene in humans (11).

A1.3.1.4 Haematological effects

A study found evidence of leukopenia, anaemia and thrombocytopenia in workers exposed for more than 2 days to benzene concentrations above 60 ppm (195 mg/m^3) (99).

A1.3.2 Long-term effects

A1.3.2.1 Haematological effects: studies in occupational populations

Numerous epidemiological studies of workers exposed to different benzene concentrations over subchronic or chronic exposure periods have demonstrated haematological effects. In several studies, there are uncertainties about historical exposures of workers, co-exposures and lack of an adequate control group. However, sufficient data are available to show that the haematopoietic system is a target of benzene in humans.

Blood effects such as aplastic anaemia, granulopenia, leukaemia, lymphopenia pancytopenia, and thrombocytopenia have been associated with benzene inhalation (47). Bone marrow damage is one of the first signs of chronic benzene toxicity, and aplastic anaemia is one of the most severe effects. Benzene impairs bone marrow function and prevents stem cells maturation. Aplastic anaemia may progress to myeloproliferative syndrome and then to leukaemia (47).

A significant decrease in the number of red blood cells, leukocytes and neutrophils was observed in occupationally exposed workers (chronic benzene exposure: 0.08–54.5 ppm; 0.26–177 mg/m^3) (48–50). An inverse dose–response relationship was reported, with reductions in red blood cells, leukocytes and neutrophils associated with higher exposures to benzene, as well as urinary metabolites and albumin adducts. Compared with control subjects, effects were observed even in the group with lower exposures ≤ 0.82 mg/m^3).

Other epidemiological studies have shown haematological effects (decreased leukocyte, platelet and red and white blood cell counts) at low benzene concentrations (> 1 ppm; > 3.25 mg/m^3) (96–106). Reduced haemoglobin concentration was also reported, but only for the group exposed to the highest benzene concentration (≥ 10 ppm). The authors of these studies compared the haematological effects in a group of workers exposed to benzene concentrations below 1 ppm for 1 year (the previous year) with those developed in a group of workers with a lifetime cumulative exposure to benzene of up to 40 ppm-years (130 mg/m^3-years). Decreased numbers of the same cell types were found in both groups, but with different percentage decreases.

A study of haematological parameters in 855 workers from five factories in China exposed to a wide range of benzene concentrations (controls: n = 73) (107). Individual benzene exposures

ranged from 0.07 mg/m³ to 872 mg/m³ (0.02–270 ppm; median: 7.4 mg/m³, 2.3 ppm). Anaemia and macrocytosis were observed in workers exposed to concentrations above 10 ppm. Regression analysis has shown that the most sensitive end-points are decreased neutrophils (7.77 ppm) and decreased mean platelet volume (8.24 ppm) (15,108).

One study analysed 8532 blood samples from workers in the Dow Chemical Company exposed to low levels of benzene and 12 173 samples from control workers not exposed to benzene (109). Benzene exposure concentrations (8-h averages) ranged from 0.06 ppm to 1.24 ppm. The study found no effect of benzene on haematological parameters in exposed workers.

A preliminary study of 215 police officers exposed to atmospheric benzene in an urban area found a significant inverse correlation between blood benzene levels and numbers of leukocytes, lymphocytes and neutrophils (110).

Several other studies have investigated the haematological effects of benzene exposure, but at concentrations well above 1 ppm (3.25 mg/m³).

A1.3.2.2 Immunological effects: studies in occupational populations

Benzene exposure also affects the humoral immune system. It was first shown that benzene alters this system by inducing changes in blood antibody levels. Painters occupationally exposed to benzene (3–7 ppm; 0.9–22.75 mg/m³), toluene and xylenes for 1–21 years showed increases in immunoglobulin M and decreases in immunoglobulin G and immunoglobulin A (111). This result suggests that some people exposed to benzene develop allergic dyscrasia. However, as the workers were exposed to a mixture of substances, the specific role of benzene is unclear.

Another study reported a significant decrease in immunoglobulin M and immunoglobulin A in 10 cargo tank maintenance workers exposed to crude oil residue compared with controls (n = 9) (112). Individual benzene concentrations in air ranged from 0.01 ppm to 0.62 ppm (mean: 0.15 ppm). However, no statistically significant effects were observed in exposed workers for immunoglobulin G or immunoglobulin E; total lymphocyte levels; levels of several cluster of differentiation (CD) proteins (CD3,[6] CD8,[7] CD19[8] or CD56[9]); or the CD4 : CD8 ratio.[10]

A1.3.2.3 Neurological effects: studies in occupational populations

Older studies found that chronic exposure to high benzene concentrations can induce neurological abnormalities.

A study into the effects of chronic exposure (2–9 years) to benzene and toluene in 121 workers found that between 1962 and 1965 the benzene concentration in the workplace ranged from 6 ppm to 15.6 ppm (20–50 mg/m³) whereas the concentration of toluene vapour did not exceed 5 mg/m³ (113). Of these workers, 74 complained of frequent headaches (often at the end of the working day), fatigue, sleep disturbance and memory loss. The limitations of this study are that the workers were exposed to both benzene and toluene and that the precise exposure concentrations of benzene and exposure times are unknown.

Another study reported a significant association (P < 0.05) between the prevalence of acquired dyschromatopsia of the left eye (but not the right eye) and increasing exposure to benzene

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[6]   A protein complex subunit and T-cell co-receptor involved in activating cytotoxic T cells and T helper cells.

[7]   A transmembrane glycoprotein that is a co-receptor for the T-cell receptor.

[8]   A transmembrane protein on B cells that in humans is encoded by the *CD19* gene.

[9]   A homophilic binding glycoprotein expressed on the surface of glia, neurons and skeletal muscle cells (also called Neural cell adhesion molecule 1).

[10]   The ratio of T helper cells to cytotoxic T cells, a measure of immune function.

(mean concentrations: 0.27–2.43 ppm-years) in 736 workers in a petrochemical industry (compared with 172 controls who were not exposed to benzene) *(114)*. The prevalence of dyschromatopsia correlated significantly with age and duration of employment.

A1.3.2.4 Neurological effects: studies in the general population

Changes in cognitive function and related brain regions were documented in a patient with chronic benzene intoxication *(115)*. A significant improvement in the patient's health was observed 3 months after hospitalization.

Recent meta-analyses found no association between benzene in ambient air and attention deficit hyperactivity disorder in children *(116)* or multiple sclerosis in adults *(117)*.

A1.3.2.5 Respiratory effects: studies in the general population

There have been very few studies on the respiratory effects of benzene exposure.

One study analysed the relationship between exposure to benzene via indoor and ambient air and respiratory health in 352 1-year-old children from the *Infancia y Medio Ambiente* (known as INMA) cohort in Valencia, Spain *(118)*. Benzene exposure levels were assessed both inside and outside the home by passive measurements over 15 days. Concentrations were significantly higher inside the home. Furthermore, 42% of indoor and 31% of ambient measurements exceeded the WHO guideline value of 1.7 $\mu g/m^3$. The respiratory health of children during the first year of life was assessed via a parent questionnaire (cough, respiratory infections, wheezing). No association between benzene exposure and the children's respiratory health was found after adjusting for the main confounding factors. These results are consistent with those of a previous study by the same team that found no significant association between maternal exposure to benzene and the occurrence of respiratory symptoms during the first year of life *(119)*.

A cross-sectional study assessed the association between air exposure to benzene and PM_{10} and clinical manifestations in 88 patients with systemic scleroderma *(120)*. The Spearman's correlation coefficient showed a direct correlation between benzene air concentrations and the skin involvement score ($R = 0.3$, $P \leq 0.05$) and an indirect correlation with the pulmonary diffusion capacity of carbon monoxide (used as an indicator of lung involvement; $R = -0.36$, $P = 0.04$). The authors reported that these results indicate a potential role for benzene exposure in the development of diffuse skin damage and its progression to pulmonary manifestations of systemic sclerosis.

Time series studies in the early 2000s identified positive associations between air exposure to benzene and the hospitalization rate for respiratory diseases *(121,122)*. More recently, a 2021 meta-analysis found an association between traffic-related exposure to benzene in air and the prevalence of childhood asthma *(123)*. The association was stronger for benzene (meta-analysis odds ratio (meta-OR): 1.21; 95% confidence interval (CI): 1.13–1.29) than for $PM_{2.5}$ (meta-OR: 1.07; 95% CI: 1.00–1.13) and NO_2 (meta-OR: 1.11; 95% CI: 1.06–1.17). However, the meta-analysis included only four cross-sectional studies, of which three were based on the same study but involved three different asthma metrics. The authors concluded that "subsequent research should focus on the association between organic pollutants in traffic-related air pollution and childhood asthma".

A1.3.2.6 Reproduction effects: studies in occupational populations

Occupational studies suggest that benzene exposure reduces fertility in women *(124,125)*. However, it is difficult to be sure because of uncertainties in exposure assessment and limitations in the data.

One study examined 30 women with symptoms of benzene poisoning *(125)*. The benzene concentrations in air were not specified, but the authors stated that they were well above 1 ppm (3.25 mg/m^3). Of the 30 women, 12 had menstrual cycle disorders and information on fertility was provided for 10 of them. Two of these women had spontaneous abortions and did not have any children during their working life, even though they were not using contraception. However, the authors did not investigate the relationship between childlessness and fertility. Gynaecological examinations showed that in five of the women disturbances in the menstrual cycle were caused by ovarian atrophy.

A study of 500 women aged 20–40 years (control group: 100 women) also found disturbances in the menstrual cycle in women occupationally exposed to aromatic hydrocarbons (benzene, toluene, xylenes) *(126)*. The levels of exposure to benzene and toluene were below 0.25 ppm (0.8 mg/m^3). In all, 21% of exposed women had irregular menstrual cycles compared with 12% in the control group. Short (up to 2 days), long (6–9 days) and prolonged (> 9 days) menstrual periods were observed in 26% of the exposed women compared with 13% of the control group. However, this study had several limitations: the women were exposed to a mixture of three substances, benzene concentrations were not well defined, and the exposure times and occupational activity of the control group were not reported.

The effects of benzene on male reproduction were studied in 823 men working in two chemical plants in France *(127)*. A total of 1739 pregnancies, among which spontaneous abortions occurred, were analysed. For each pregnancy, paternal exposure to benzene during the first 3 months after conception was reported, along with previous occupational exposure. Benzene exposure was divided into two levels: low exposure, < 5 ppm (< 16.25 mg/m^3); and moderate exposure, ≥ 5 ppm. Out of all pregnancies, spontaneous abortion occurred in 171 (rate: 9.8%). Of the 823 men, 270 were exposed just before conception and 145 were exposed in the first 3 months after conception. The frequency of spontaneous abortion was not significantly affected by benzene exposure to men, whether they were exposed before conception or during the first 3 months after conception.

Another study analysed the semen volume and quality in 160 benzene-exposed workers and 200 unexposed controls *(128)*. No significant differences in semen characteristics (appearance, liquefaction time, pH, viscosity, volume) were observed between exposed workers and controls. However, in exposed workers increasing exposure duration was related to a significant decrease in sperm count and motility ($P < 0.05$) and significant increases in the percentage of morphologically abnormal sperm and sperm comet tail length. The study did not assess reproductive success.

A1.3.2.7 Developmental effects: studies in general populations

Available data on the developmental effects of benzene exposure in humans are limited and inconclusive *(6)* due to a lack of information on exposure levels and/or exposure to multiple substances.

In humans, benzene crosses the placental barrier and is present in the umbilical cord. A case–cohort study assessed the association between maternal exposure to air pollutants, including benzene, and the risk of neural tube defects (spina bifida, anencephaly) *(129)*. Air concentrations of benzene were derived from US EPA modelling work, and five exposure levels were defined: low, 0.12–0.45 µg/m^3 (reference); medium–low, > 0.45–0.98 µg/m^3; medium, > 0.98–1.52 µg/m^3; medium–high, > 1.52–2.86 µg/m^3; and high, > 2.86–7.44 µg/m^3. No significant association between benzene exposure and the risk of anencephaly was reported, regardless of the exposure level. For the risk of spina bifida, significant associations were found for the medium–low, medium and high exposure levels, but not for the medium–high level, from which the authors reported the lack of a monotonic relationship between benzene exposure and these conditions *(129)*. A United States study reported a significant relationship between increased atmospheric concentrations of benzene and reduced birth weight, in which a unit increase in benzene exposure increased the odds of a low-birth-weight event by 7% *(130)*. Another study in Texas (United States) reported no significant association between atmospheric concentrations of benzene and the risk of oral clefts in children of women who were pregnant between 1999

and 2008 *(131)*. All three studies used annual ambient air data from US EPA modelling and not individual exposure measurements *(15)*.

Two other recent studies reported no association between environmental exposure to benzene in utero and birth defects *(132,133)*, cognitive effects or child psychomotor development at 15 months *(134)*.

Lastly, one study reported a significant association between maternal exposure to benzene and preterm birth at 5 days before term) *(135)*. The mean daily level of benzene exposure was 6.56 µg/m³ (standard deviation: 4.83). However, no association was found for the other exposure windows (10, 15, 60 or 90 days before term).

A1.3.2.8 Carcinogenicity: studies in occupational and general populations

DNA strand breaks and gene mutations have been reported in people occupationally exposed to benzene *(4)*.

In several studies in human haematopoietic cells, levels of benzene metabolites were positively associated with levels of benzene-derived DNA adducts. In addition, chromosomal aberrations and micronuclei upon benzene exposure were consistently reported. Specific cytogenetic changes have also been observed in exposed humans, including aneuploidy, translocations and various other structural chromosome changes *(4)*.

No data on effects on topoisomerase II activity (involved in DNA repair and genomic stability) were available in exposed humans *(4)*.

Benzene is immunosuppressive in exposed humans. Human studies that directly examined changes in immune function were not available. However, many studies have reported haematotoxicity in humans exposed to benzene, including decreased leukocyte counts at lower exposures and aplastic anaemia and pancytopenia at higher exposures. Specifically, many studies of benzene exposure in humans have reported a decrease in B-cell numbers and/or maturation of CD4-positive T-cells *(4)*.[11]

Several studies have also reported an association between benzene-induced haematotoxicity (various levels of severity) with a risk of developing a haematological malignancy or related disorder *(4)*.

No data on the aryl hydrocarbon receptor were available in exposed humans *(4)*.

Several human studies have reported benzene exposure–response gradients related to chromosomal aberrations, leukocyte counts and micronucleus formation *(4)*.

The European Chemicals Agency review on benzene carcinogenicity and mode of action noted that "it is challenging to connect the carcinogenicity of benzene to one specific mode of action. However, genotoxicity in the haematological system is likely to precede haematotoxicity and carcinogenicity" *(85)*. It considered the leading genotoxic effects to be clastogenicity and aneugenicity, and indicated that "benzene is only weakly effective in directly inducing DNA mutations and a significant role of adduct formation in benzene leukaemia is unlikely".

In 2021 Cox and colleagues underscored the potential importance of chronic inflammation as a mode of action of benzene *(44)*.[12] They reported that in "Chinese worker data, chronic inflammation followed by an immune-mediated inflammatory response, rather than cytogenetic

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[11] CD4 is a glycoprotein expressed on the surface of several immune cells that is a co-receptor for the T-cell receptor. CD4-positive T helper cells are essential white blood cells in the human immune system; their main role is to send signals to other immune cells in response to infection.

[12] In the declaration of interest, the authors mentioned contractual support of the study by Concawe, a division of the European Petroleum Refiners Association, and financial support from ExxonMobil *(44)*.

abnormalities per se, appears to drive initiation and progression of benzene-induced [myelodysplastic syndromes] and AML [(136)]".

To summarize, the mechanism(s) of benzene carcinogenicity are not yet fully understood but appear to be complex and multifactorial; several modes of action are possible and may act synergistically (85).

Benzene has been characterized as a genotoxic carcinogen for which fully protective, health-based limit values cannot be derived. Recent reviews argue that a threshold based on mode of action can be established for risk assessment of benzene-induced adverse health effects (44,85).[13] There is large interindividual variability in benzene metabolism, which suggests that a wide distribution of exposure concentration thresholds may exist in the population. If the mechanistic evidence suggests sublinearity (44),[13] then a linear non-threshold approach might overestimate the excess risks in the low-exposure range.

IARC found that benzene exposure is associated with an increased risk of AML and/or ANLL (4). It based this conclusion on several occupational cohort studies that showed an exposure–response trend between cumulative exposure to benzene and AML and/or ANLL.

Similarly, IARC has associated benzene exposure with AML, chronic lymphoid leukaemia, chronic myeloid leukaemia, multiple myeloma and non-Hodgkin lymphoma in children (4). It also associated benzene exposure with lung cancer (4), although a small minority of the IARC Working Group did not agree. There was some evidence that benzene exposure may be associated with non-Hodgkin lymphoma in the general population. This is consistent with a recent systematic review including a meta-analysis that suggests a causal link between human benzene exposure and non-Hodgkin lymphoma, especially diffuse large B-cell lymphoma (137).

The IARC Working Group investigated the shape and slope of the exposure–response function for AML in a meta-regression analysis of six published occupational cohort studies with suitable data. The relationship of benzene exposure with the log relative-risk was described by a linear model. The slope was moderately sensitive to whether a cohort study of rubber hydrochloride workers, which had the highest exposure estimates, was included in the model. The observed instability in deriving the meta-exposure–response association highlights a degree of uncertainty in these results.

A 2010 natural spline-based meta-regression including nine human observational studies indicated an increased risk of leukaemia (risk ratio (RR): 1.14; 95% CI: 1.04–1.26) at a benzene exposure level of 10 ppm-years (138).

More recently, a 2021 study estimated the exposure–response function for benzene and AML by fitting linear and spline-based Bayesian meta-regression models that included six human AML studies, three human leukaemia studies, 10 human biomarker studies and four experimental animal studies (139). A linear meta-regression model with an intercept term best predicted the AML risks after cross-validation, for both the full dataset and the AML studies only. The approach took into account the expected high heterogeneity in RRs between studies. It provided comparable risk estimates when using the full dataset and AML data only, but estimates were more precise in the low range (< 40 ppm-years) when using the full dataset. However, the approach of combining all studies (full dataset) relies on poorly verified assumptions about the link between AML and the other end-points included (animal–human extrapolation, chromosomal aberrations, micronucleus formation). Therefore, including AML studies only might be a more cautious approach for deriving a unit risk (or excess risk).

Case–control studies assessed childhood cancer, in particular leukaemia (the most common childhood cancer) and benzene exposure in ambient air. One study found no association (except in an analysis restricted to Hodgkin's lymphoma) (140). This result may be partly due to the aggregate outcome definitions combining all leukaemia subtypes that might bias the results towards null if benzene exposure differentially affects leukaemia subtypes. Another study of a

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[13]   In the declaration of interest, the authors mentioned contractual support of the study by Concawe, a division of the European Petroleum Refiners Association, and financial support from ExxonMobil (44).

small number of cases reported positive associations between benzene exposure and childhood leukaemia and a dose-dependent trend in exposure *(141)*. Another study found significant positive associations between benzene exposure and AML when the analysis was restricted to children aged 0–4 years *(142)*. One study observed associations with acute leukaemia *(143)*, whereas another observed non-significant positive associations with ALL and AML *(144,145)*. One study found an association with AML, with an exposure–response relationship over exposure quartiles *(146)*. However, three studies found no association between benzene exposure and ALL *(146–148)*. In an adult population, long-term exposure to traffic-related air pollution was associated with AML but not with other subtypes of leukaemia (chronic myeloid or lymphocytic leukaemia); however, benzene was not measured *(149)*.

One study found no association between benzene exposure and central nervous system tumours, *(140)*. However, an exploratory study identified a positive but non-significant association with neuroblastoma *(144)*. One study reported an association with primitive neuroectodermal tumours of the central nervous system and no association with medulloblastoma *(150)*, whereas another found a tendency towards a higher risk for medulloblastoma and lower risk for ependymoma in association with higher benzene exposure *(147)*.

Studies on other organ systems reported a significant association of benzene exposure with retinoblastoma *(151)* and no association with Wilms tumour *(152)*.

All of these case–control studies on ambient air pollution were limited by non-differential misclassification of exposure. However, because in all of these studies exposure was assessed similarly in cases and controls, most exposure misclassification probably biased the results towards finding no association.

Several recent meta-analyses of epidemiological studies appear to support a relationship between air pollution, particularly benzene emissions from motorized traffic, and the risk of childhood leukaemia *(153–157)*, although another found no association between traffic density (without benzene measurements) and childhood leukaemia *(158)*. The strongest associations were found for AML *(153,154)*, and heterogeneity was particularly low for studies on AML *(153,154)*. There was little evidence of any threshold of exposure *(154)*. These associations in children are similar to those already established for adults *(4)*, which supports their biological plausibility. Furthermore, summary relative risks were greater than 1.0 for several different potential metrics of benzene exposure, including maternal occupational exposure, household use of benzene-related products, and traffic-related air pollution *(153)*. Some studies found higher effect estimates when results were stratified by geographical region, more commonly in European than in United States; however, this could relate to the fact that residential mobility is more common in the United States than in Europe *(155)*. Therefore, residential mobility should be taken into account to avoid exposure misclassification, particularly in United States studies. Regional differences might also relate to differences in pollutant mixtures and/or genetic variation among study populations *(154)*. In all of the meta-analysis on ambient air pollution, funnel plots and related tests suggested publication bias, even if the occurrence and influence of such bias are difficult to assess[14]. Closer inspection of one meta-analysis suggested that funnel plot asymmetry might be caused by the largest study rather than publication bias *(153)*, which typically affects smaller studies.

One meta-analysis that included only three studies and estimates found a non-significant positive association between residential proximity to petrol stations or automobile repair facilities and childhood leukaemia (RR: 1.59; 95% CI: 0.70–3.62) *(153)*. Benzene levels were not measured and leukaemia was defined by selecting leukaemia subtypes in the following order: AML, all types combined and ALL. A reanalysis of all leukaemia subtypes combined that excluded automobile repair facilities and used a control group with non-leukaemia cancers found a stronger association (RR: 2.42; 95% CI: 1.51–3.89) *(159)*. This provides new evidence that

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[14] Note that funnel plots and associated measures can only test for positive forms of publication bias. As meta-analysis guidelines do not currently account for negative forms of publication bias (e.g. suppression of an article showing positive association), such measures should be interpreted with caution.

childhood leukaemia is associated with residential proximity to petrol stations, a known benzene source *(160)*.

One meta-analysis that included 16 epidemiological studies found that people living less than 5 km from a petrochemical facility (refinery or petrochemical manufacturer) had a 30% higher risk of developing leukaemia than those living in communities with no petrochemical activity, but benzene was not measured *(161)*. Nevertheless, the petrochemical industry is a known source of hazardous air pollution and is associated with the release of a range of carcinogens including benzene, as well as other volatile organic compounds (e.g. ethylbenzene, toluene, xylene), polycyclic aromatic hydrocarbons, polychlorinated biphenyls and polyvinyl chloride. Heterogeneity between the study risk estimates was moderate ($I^2 = 52.2\%$) and almost completely removed when controlling for differences in quality based on the participant selection process used by each study ($I^2 < 1\%$). No publication bias was found.

Only one systematic review has investigated the shape of the dose–response relationship between benzene exposure and childhood leukaemia risk derived from a meta-analysis of six studies *(154)*. It found little evidence for a threshold of benzene exposure, especially for AML. In contrast, analyses conducted for other air pollution metrics (such as traffic density and nitrogen dioxide level) using the same methodology found evidence of a threshold. The association with benzene exposure was markedly stronger for AML than for ALL. These results may be useful for deriving a unit risk (or excess risk) for benzene exposure in ambient air but are limited by potential bias in the included studies, which is difficult to avoid (non-differential misclassification of exposure, no or low control of other pollutants in ambient air that covary with benzene emissions), and by including only six studies.

A1.4 Information on causality and related evaluations

Table A1.1 summarizes the available information that links benzene exposure and health effects, such as carcinogenicity and haematological effects, as assessed by the European Commission, IARC, US EPA and WHO.

Table A1.1 Information on causality by inhalation exposure to benzene

Authoritative body	Causality	Notes
IARC (1987, 2012, 2018) *(4,162,163)*	Carcinogenic to humans (Group 1)	Sufficient evidence for: • carcinogenicity in humans – benzene exposure causes AML in adults • AML and/or ANLL in adults • carcinogenicity in experimental animals Limited evidence of acute myeloid leukaemia, ALL, chronic lymphocytic leukaemia, chronic myeloid leukaemia, lung cancer, non-Hodgkin lymphoma and multiple myeloma in children Strong evidence that benzene: • induces oxidative stress and associated oxidative DNA damage, including in human studies; • is genotoxic, inducing DNA damage and chromosomal changes, including in exposed humans; • alters DNA repair or causes genomic instability; • is immunosuppressive, including in exposed humans; • alters cell proliferation, cell death or nutrient supply, specifically with respect to induction of apoptosis; and • modulates receptor-mediated effects, specifically for AhR
WHO Regional Office for Europe (2000, 2010) *(1,164)*	Haematological effects	Aplastic anaemia, granulopenia, leukaemia, lymphopenia, pancytopenia and thrombocytopenia
	Carcinogenesis	AML demonstrated in occupational exposures
EC (2004) *(165)*	Known human carcinogen (Category 1A)	
US EPA (1998) *(166)*	Known human carcinogen (Category A)	

EC: European Commission.

A1.5 Health-based evaluations and regulatory numbers from authoritative bodies

Table A1.2 shows the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect populations from the adverse health effects of benzene exposure.

Table A1.2 Health-based evaluations and regulatory numbers for benzene from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value (annual mean, unless otherwise stated)
Worldwide	WHO Regional Office for Europe (1987) *(167)*	Increase in leukaemia mortality	URF: 4×10^{-6} (per 1 µg/m³)	No safe level for benzene exposure can be recommended
Worldwide	WHO Regional Office for Europe (2000, 2010) *(1,164)*	Increase in leukaemia mortality	URF: 6×10^{-6} (per 1 µg/m³) Increased lifetime cancer risk of no more than 1:10 000, 1:100 000 or 1:1 000 000 is associated with a lifetime exposure to concentrations of 17, 1.7 or 0.17 µg/m³, respectively	No safe level for benzene exposure can be recommended
Canada	Health Canada (1993) *(168)*	Increase in leukaemia mortality	URF: 2.9×10^{-5} (per 1 µg/m³)	–
United States	US EPA (2003) *(169)*	Decrease in lymphocyte count	Chronic TRV: 30 µg/m³	–
		Increase in leukaemia mortality	URF: 2.2×10^{-6} – 7.8×10^{-6} (per 1 µg/m³)	
United States	ATSDR (2007) *(6)*	Decrease in proliferative response of B-cells (mitogenic action induced by LPS) and circulating lymphocytes	Acute TRV: 29 µg/m³	–
		Delayed in vitro alloreactivity of lymphocytes	Subchronic TRV: 19 µg/m³	

Table A1.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value (annual mean, unless otherwise stated)
		Decrease in lymphocyte count	Chronic TRV: 9.7 µg/m³	
United States	NIOSH (1970) *(170)*	Increase in leukaemia mortality	Occupational exposure: • REL-TWA: 0.1 ppm (0.33 mg/m3) (up to 10-h TWA) • REL-STEL: 1 ppm (3.29 mg/m³)	–
United States	OSHA (1989) *(171)*	Increase in leukaemia mortality	Occupational exposure: • REL-A: 8.20 ppb (27 µg/m³) • REL-TWA: 0.91 ppb (3 µg/m³)	Occupational exposure: • PEL-TWA: 1 ppm (3.29 mg/m³) • PEL-STEL: 5 ppm (16.45 mg/m³)
United States	ACGIH (2012) *(172)*	Increase in leukaemia mortality	–	Occupational exposure: • TLV-TWA: 0.5 ppm (1.65 mg/m³) • TLV-STEL: 2.5 ppm (8.22 mg/m³)
United States (California)	OEHHA (2005, 2008) *(108,173)*	REL-A: fetal and neonatal haematotoxicity REL-TWA: decrease in lymphocyte count URF: increase in tumour incidence and mortality (breast, foreskin, leukaemia or lymphoma, Zymbal glands)	Occupational exposure: • REL-A: 27 µg/m³ (0.008 ppm) • REL-TWA: 3 µg/m³ (0.001 ppm) • URF: 2.9×10^{-5} (per 1 µg/m³) Assuming a linear dose–response, no safe level for benzene exposure can be recommended	Occupational exposure: • PEL-TWA: 1 ppm (3.29 mg/m³) • PEL-STEL: 5 ppm (16.45 mg/m³)
EU	European Parliament and Council (2008) *(174)*	–	–	Annual limit value for human health protection: 5 µg/m³ (1.5 ppb)

Table A1.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value (annual mean, unless otherwise stated)
EU	ECHA (2017) *(85)*	Chromosomal damage in bone marrow	–	OEL: 0.05 ppm (0.16 mg/m^3) Biological limit value: 0.7 µg benzene/L urine Biological limit value: 2 µg SPMA/g creatinine
Netherlands (Kingdom of the)	RIVM (2001) *(175)*	Increase in leukaemia mortality	URF: 5×10^{-6} (per 1 µg/m^3)	–
France	ANSES (2014) *(51)*	Increase in leukaemia mortality	URF: 2.6×10^{-5} (per 1 µg/m^3)	–
France	AFSSET (2008) *(176)*	Increase in leukaemia mortality	URF: 6×10^{-6} (per 1 µg/m^3)	–
United Kingdom	Government of the United Kingdom (2010) *(177)*	–	–	Annual air quality objective: 5 µg/m^3 (1.5 ppb; England and Wales) Annual air quality objective: 3.25 µg/m^3 (1 ppb; Northern Ireland and Scotland)
United Kingdom	HSE (2005) *(178)*	–	–	Occupational exposure: • 1 ppm (3.29 mg/m^3; long-term exposure limit, 8-h TWA reference period)

ACGIH: American Conference of Governmental Industrial Hygienists; AFSSET: *Agence française de sécurité sanitaire de l'environnmentale et du travail* [French Agency for Environmental and Occupational Health and Safety] (now ANSES); AhR: aryl hydrocarbon receptor; DEFRA: United Kingdom Department for Environment, Food and Rural Affairs; ECHA: European Chemicals Agency; LPS: lipopolysaccharide; NIOSH: National Institute for Occupational Safety and Health; OEL: occupational exposure limit; OSHA: Occupational Safety and Health Administration; PEL-STEL: permissible exposure limit expressed as short-term exposure limit; PEL-TWA: permissible exposure limit expressed as a time-weighted average; REL-STEL: REL expressed as a short-term exposure limit; REL-TWA: REL expressed as a time-weighted average; RIVM: *Rijksinstituut voor Volksgezondheid en Milieu* [Dutch National Institute for Public Health and the Environment]; SPMA: *S*-phenylmercapturic acid; TLV-TWA: threshold limit value, time-weighted average; TLV-STEL: threshold limit value expressed as a short-term exposure limit; TRV: toxicity reference value; TWA: time-weighted average.

Notes: Creatinine is a protein excreted in the urine in relation to the hydration level. Therefore, creatinine levels are used to normalize other urinary biomarkers to take into account the dilution factor from hydration *(179)*. PEL-TWA is defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h working day or 40-h working week *(180,181)*. TLV is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime, usually expressed as a time-weighted average *(172)*).

Source: Sekar et al. (*182*). Reproduced under CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

A1.6 Future research needs

There is a need to:

- conduct high-quality prospective studies on the relationship between benzene in ambient air and risk of leukaemia (in particular, childhood leukaemia and AML and/or ANLL leukaemia subtypes in both children and adults);

- determine the shape of the dose–response at low environmental benzene concentrations for leukaemia (in particular, childhood leukaemia and AML and/or ANLL leukaemia subtypes) and haematological end-points;

- investigate benzene metabolism and interactions with co-pollutants at exposure to low environmental concentrations; and

- monitor and model exposure to benzene and other air pollutants for people living close to petrochemical sites and petrol and diesel service stations, as well as indoor levels for the general population.

A1.7 Concluding remarks

- Benzene is a volatile and ubiquitous air pollutant. It is a constituent of crude oil and, therefore, is present in petroleum products and their vapours and combustion gases. Benzene and benzene homologues are important chemical precursors to the formation of ground-level ozone and secondary organic aerosol in the atmosphere.

- The main sources of benzene are anthropogenic, including combustion processes and evaporation of crude oil and petroleum products. It is a component of petrol, vehicle exhaust emissions, industrial emissions and tobacco smoke. Occupational benzene exposure may occur in several industries, including those related to the petroleum, chemical, coke-making and manufacturing industries. Benzene exposure mainly occurs via inhalation, but skin absorption is also possible.

- Benzene concentrations measured in ambient air are generally orders of magnitude lower than those reported in occupational environments. A significant decline in benzene ambient air concentrations has been observed over time in Europe and the United States (current annual average concentrations are < 5 µg/m^3). However, higher concentrations are present in urban environments in other regions of the world. Higher air concentrations are also observed in other microenvironments such as in the proximity of high-traffic roads, petrol service stations and petrochemical facilities and in households.

- In Europe in 2019, ambient concentrations were above the limit value for benzene (5 µg/m^3) at only two stations (in two out of 31 reporting countries). At 93% of locations, annual mean concentrations were below the lower assessment threshold (2 µg/m^3). In Europe, 11% of all stations reported concentrations that were above the WHO reference level (1.7 µg/m^3), distributed across 15 countries.

- Bone marrow damage is one of the first signs of chronic benzene toxicity. Most haematological effects have been associated with benzene inhalation exposures. Epidemiological studies have shown haematological effects (decreased leukocyte, platelet and red and white blood cell counts) at benzene levels lower than those reported in most occupational exposures (i.e. ≤ 0.82 mg/m^3) but still higher than in most urban environments.

- IARC had concluded that there is sufficient evidence that benzene causes cancer in humans: "benzene causes acute myeloid leukaemia in adults". This conclusion was supported by inhalation studies in humans (including several cohort studies on occupational exposure) and inhalation studies in laboratory animals.

- The mechanism(s) of benzene carcinogenicity are not yet fully understood but appear to be complex and multifactorial; several modes of action are possible, and may act synergistically. In the haematological system, DNA damage is likely to precede toxic effects and carcinogenesis. The European Chemicals Agency considers that the leading genotoxic effects are clastogenicity and aneugenicity: benzene is only weakly effective in directly inducing DNA mutations, and adduct formation is unlikely to have a significant role in benzene-induced leukaemia *(85)*. A recent review highlighted the potential importance of chronic inflammation as a mode of action.

- Benzene in ambient air is associated with higher risk for childhood leukaemia, with a much higher risk for AML than for ALL, consistent with evidence in adults. Recent epidemiological results support an etiological relation between ambient air pollution and childhood leukaemia risk, which appears to be mainly attributable to benzene; however, a contribution from other pollutants that covary with benzene emissions is plausible, either alone or in mixtures. There is little evidence of a threshold for benzene exposure, especially for AML.

- Benzene has been characterized as a genotoxic carcinogen for which fully protective, health-based limit values cannot be derived. Recent reviews suggest that a threshold based on mode of action could be established for risk assessment of benzene-induced adverse health effects. Large interindividual variability in benzene metabolism suggests a wide distribution of exposure concentration thresholds may exist in the population. If the mechanistic evidence is suggestive of sublinearity, the range of excess risks in the low exposure from a linear non-threshold approach might be an overestimate.

- Health-based guidance values for benzene inhalation have been reported. Of the three guidance values on chronic toxicity, the most recent is the OEHHA toxicological reference value, or chronic REL, of 3 $\mu g/m^3$, based on a decreased lymphocyte count observed in workers *(100)*, is below the current European air quality standard (5 $\mu g/m^3$). Since the excess unit risk for leukaemia was proposed in the 2000 WHO *Air quality guidelines for Europe* (4.4×10^{-6} – 7.5×10^{-6}, geometric mean: 6×10^{-6}) *(183)*, four new excess unit risk values have been identified, ranging from 2.2×10^{-6} to 2.9×10^{-5} *(51,169,173,175)*. Recently, two meta-regression analyses of occupational cohort studies *(4,139)* and one of case–control studies on benzene in ambient air *(154)* provided substantial information on the shape of the relationship between benzene air exposure and leukaemia risk (in particular, of AML). These analysis may be useful for deriving new excess unit risk values.

- Globally, annual air quality standards for benzene range from 2 $\mu g/m^3$ to 20 $\mu g/m^3$. In Europe, the annual limit value is 5 $\mu g/m^3$. No air quality standard for benzene was identified for North America, China or most other countries in Africa, Asia and South America, where benzene levels in ambient air are highest. The first pan-European analysis of benzene exposures from the petrochemical industry recommended extending the European annual standard for benzene to an hourly or daily limit *(184)*.

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Annex 2. Evidence overview on arsenic

Contents

A2.1 Exposure risk assessment

A2.1.1 Characteristics, sources and environmental occurrence

The substance name proposed by the European Commission and various EU countries is "arsenic and its compounds" *(1)*, which comprises *(2)*:

- elemental arsenic (chemical symbol, As; atomic number, 33; relative atomic mass, 74.92), CAS Registry Number 7440-38-2;

- inorganic arsenic (oxidation state +3) compounds:

    - As^{3+} or As(III) ion, CAS Registry Number 22541-54-4
    - arsenic trioxide (As$_2$O$_3$,), CAS Registry Number 1327-53-3
    - dimethylarsinic acid (DMA), CAS Registry Number 15132-04-4;

- inorganic arsenic (oxidation state +5) compounds:

    - As^{5+} or As(V) ion, CAS Registry Number 17428-41-0
    - arsenic pentoxide, CAS Registry Number 1303-28-2
    - monomethylarsonate, CAS Registry Number 124-58-3; and

- organic As(III) compounds and As(V) compounds, such as arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine *(3)*.

Arsenic can combine with non-carbon elements as sulfur and oxygen to form arsenides, arsenites and arsenates (oxidation states −3, +3 and +5, respectively), which are collectively known as inorganic arsenic compounds. Arsenic trioxide (a trivalent compound known as white arsenic) is a common natural form that is used commercially and can be released into the air. Arsenic can also combine with organic substances in the environment to form organic arsenic compounds such as arsenobetaine, arsenocholine, arsenosugars and trimethylarsine oxide. Arsine (AsH$_3$) is a reactive, gaseous hydride that is manufactured in small quantities for use in the manufacture of electronics and semiconductor components, organic synthesis, and lead-acid storage battery manufacturing. Arsenic toxicity depends strongly on the type of chemical species present in the body. Inorganic arsenic is generally recognized as more toxic than organic arsenic, with As(III) more toxic than As(V) *(1)*. Arsine is an extremely toxic gas to humans, but is not considered in this document because its use is much more limited compared with other inorganic compounds. US EPA has summarized relevant information on arsine *(4)*. Note that the text refers to both the metal and its compounds where relevant.

Arsenic is a ubiquitous, naturally occurring metalloid found as a contaminant of air, cigarettes, drinking water, food, industrial effluent, occupational environments and soil.

Natural and anthropogenic sources emit arsenic to the atmosphere, with natural sources accounting for nearly one third (7900 t/year) *(2)*. Volcanic emissions are the main natural source of arsenic, and others include volatilization at low temperatures, root exudates from plants, and wind-blown dusts. Anthropogenic sources account for approximately 24 000 t As/year *(2)*. The main anthropogenic sources are industrial processes involving high-temperature heating of arsenic-containing materials such as smelting metal ores (copper, lead, and other metals); fuel combustion (e.g. waste and low-grade brown coal), and use of arsenic-based pesticides *(2)*. Recently, informal recycling of electronic waste has become a significant source of arsenic to the environment, especially in developing countries *(5–7)*.

A2.1.2 Environmental levels

In air, arsenic mainly exists as a mixture of arsenite and arsenate (arsenic species are oxidized in air to pentavalent arsenic). It is usually absorbed onto PMs but it can also exist as a particulate in itself. Arsenic in the vapour phase is only released by high-temperature volatilization. Air concentrations of vapour-phase arsenic are low in general and may only be of concern in the vicinity of industrial processes that use arsenic compounds *(8)*. However, vapour-phase arsenic has not been detected in Europe *(8)*. Airborne organic species are negligible except in areas of arsenic-pesticide use or biotic activity *(9)*. Inorganic arsenic can be methylated in water and soil. Consequently, methylated species such as monomethylarsonic acid (MMA) and DMA can be detected in air, especially in coastal areas or near swamps *(10)*.

Arsenic compounds in the air are predominantly concentrated in $PM_{2.5}$ *(10)* and, therefore, can be transported over long distances *(11,12)* before being removed via wet or dry deposition. Plants can be contaminated by arsenic deposition onto leaves or absorption through the roots. In the vicinity of arsenic-emitting sites or where arsenic is present in the surface layers of soil, plant leaves may be significantly contaminated and may represent an important source of arsenic exposure through ingestion of leafy vegetables (and even of root vegetables and fruit if they are not peeled) *(12)*. Arsenic is also taken up from the soil by plant roots, but contamination levels are much lower than from external deposition and are mainly confined to the roots *(12)*.

Worldwide, the range of total arsenic concentrations in air is 0.02–4 ng/m³ in remote and rural areas and 3–200 ng/m³ in urban areas *(2)*. Considerably higher levels (> 1 µg/m³) are reported in the vicinity of industrial sources, such as arsenic-rich coal-fired power plants and non-ferrous metal smelters *(13,14)*. Recently, a simulation of worldwide distributions of atmospheric arsenic using the Goddard Earth Observing System-Chem model and data for 2015 showed large spatial variations *(15)*, with the highest atmospheric arsenic concentrations in Chile (mean: 8.68 ng/m³) and China, in particular, eastern China (mean: 4.38 ng/m³). In Chile, the mean arsenic concentration appeared relatively stable between 2005 and 2015, with only slight increases (by 4%). In eastern China, over the same period the mean arsenic concentrations reduced (by 22%), largely driven by efforts to control PM emissions from industrial sources such as coal-fired power plants and boilers, which reduced arsenic emissions. In India, the mean arsenic concentration strongly increased (by 65%) over the 2005–2015 period as a result of a dramatic increase in uncontrolled coal combustion.

In Europe, airborne arsenic pollution in PM_{10} is highly localized and usually associated with emissions from specific industries. Decreased arsenic in both $PM_{2.5}$ and PM_{10} was observed in industrialized areas after a period of economic crisis and implementation of the best available technologies *(16)*. Decreased arsenic levels were consistent with reductions in arsenic emissions *(17)*. Exceedances of the target value for arsenic in PM_{10} samples (annual mean concentration: 6 ng/m³) were observed at only seven out of 645 stations in 27 European countries in 2017 and in six out of 665 stations in 28 European countries in 2018 *(18,19)*. High levels are still recorded in specific locations. For example, in 2019 arsenic levels of up to 550 ng/m³ in PM_{10} were measured near a copper production facility in Bor (Serbia) *(20)*, one of the most polluted regions in southeastern Europe. The target value was exceeded at all measuring sites around the facility, with a maximum exceedance more than 90 times greater at a suburban site. Surprisingly, arsenic levels were notably higher after modernization of the flash smelting technology for copper production.

A2.1.3 Human exposure

Chronic arsenic exposure most commonly occurs from drinking water from wells contaminated with arsenic that is naturally present in the soil *(21)* and from ingestion of food crops grown in arsenic-contaminated soil and/or irrigated with arsenic-contaminated water *(1)*, including rice *(21)*, fruit, milk, vegetables and seafood *(12)*.

Atmospheric arsenic exposure appears to be the least significant contributor by far of the three pathways (air, drinking water and food) to total arsenic intake in both heavily *(22)* and lightly contaminated areas *(12)*. In general, the reported daily intake of total arsenic from food and

beverages was 20–300 µg/day, whereas daily intakes from inhalation for non-smokers were about 20–200 ng/day in rural areas, 400–600 ng/day in cities with low or negligible industrial emissions, approximately 1 µg/day in polluted areas compared with nearly 10 µg/day for smokers (3,13).

Inhalation can be an important exposure route for people living near polluting industries and, above all, for adults and children who are occupationally exposed through activities that involve mining or smelting metal ores, fuel combustion, manufacturing or using pesticides, wood preservatives, paint and pigment, manufacturing glass and ceramics, lead–arsenic alloys, and electronics and assembling batteries (2,23,24). The main route of occupational exposure is inhalation of arsenic-containing particulates, although ingestion and dermal exposure may be relevant in some settings.

Total arsenic exposure can be measured by biomonitoring, with blood and urine the most commonly used biological matrices. Urinary arsenic monitoring includes determining the sum of inorganic arsenic compounds and the methylated metabolites DMA and MMA (25). Therefore, arsenic urinary levels are considered a suitable biomarker of arsenic exposure. However, total urinary arsenic concentrations do not provide information related to particular arsenic species, which makes assigning toxicity and potential health risk to various arsenic species complicated (26).

Geometric means of total arsenic in urine reported in surveys in European countries corresponded to a range of 4–16 µg/g creatinine,[16] with highest reported values (90th percentile) reaching approximately 70 µg/g creatinine (26). The distribution of arsenic species in total arsenic urinary levels were on average 10–20% for MMA, 10–30% for inorganic arsenic and 60–70% for DMA in most environmentally exposed populations. However, there is large interindividual variation, possibly due to genetic polymorphisms that affect the methylation capacity of arsenic (26).

Environmental arsenic exposure may influence urinary arsenic levels even in high-income countries with relatively low levels of environmental exposure. A study of the general population in Italy found a significant correlation between urinary levels of inorganic arsenic plus methylated forms and occupational exposures and consumption of fruit, seafood, tap water, whole milk and vegetables (28). This was consistent with another study that found that non-occupational arsenic exposure of residents of an industrial area in Italy was associated with consumption of shellfish and/or seafood, and tap water (29). However, since other arsenic species can also be found in seafood (30), arsenic biomonitoring studies should include speciation analysis.

Biological matrices other than blood or urine could be useful because arsenic accumulates in keratin-rich tissues (31). Interestingly, a study of 524 adults (aged 20–80 years; mean: 66 years) found a clear association between arsenic in fingernails and distance from the home to a coal-fired power plant with high arsenic emissions in Slovakia ($P < 0.001$) (32). The association between distance from the power plant and total urinary arsenic ($n = 436$; no fish consumption during the last 3 days) was less pronounced ($P = 0.018$). Arsenic levels in fingernails were associated with urinary total arsenic and urinary levels of different arsenic species. Therefore, arsenic concentrations in fingernails reflected arsenic exposure to a similar extent as urinary total arsenic and urinary arsenic species.

A2.1.4 Absorption, distribution, metabolism and excretion

On average, arsenic inhalation represents less than 1% of the total dose of absorbed arsenic (10). Approximately 80–90% of soluble inorganic arsenic compounds are readily absorbed after oral exposure (with lower absorption for less-soluble arsenic compounds), with lower absorption rates after inhalation (which is higher for small particulates and soluble arsenicals)

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[16] Creatinine is a protein excreted in the urine in relation to the hydration level. Therefore, creatinine levels are used to normalize other urinary biomarkers to take into account the dilution factor from hydration (27).

and the lowest for dermal exposure *(33,34)*. The proportion deposited in lungs ranges from 30% to 60% *(17)*, with studies on workers exposed to arsenic trioxide in smelters suggesting that about half of inhaled arsenic is deposited in the lungs *(17)*. Large airborne arsenic-containing particulates deposited in the upper airways may be swallowed and eventually absorbed in the intestines *(2)*.

After absorption, inorganic arsenic is widely distributed within the body, including in cord blood and fetal organs in pregnant women, although data are limited on arsenic distribution after inhalation exposure. Arsenic accumulates in keratin-rich tissues such as skin, hair and nails *(13,35)*. Arsenate is reduced in the body to arsenite (oxidation state +3), though some reduction may occur in the gut prior to absorption. Arsenite is then oxidatively methylated to MMA and DMA, and subsequently excreted, primarily in the urine *(17)*. MMA and DMA are much less toxic than As(III) and As(V) *(36)*. Recent toxicokinetic studies reported that some organoarsenicals are bioaccessible and cytotoxic, with toxicity similar to As(III) *(30)*, although those findings need to be verified. Inorganic arsenic and its metabolites have elimination half-lives of approximately 2–4 days *(37,38)*. In tin miners in Yunnan (China), arsenic-containing particles accumulated in the lungs and had a half-life for pulmonary clearance of 6 years *(39)*.

A2.2 Toxicological studies

A2.2.1 Laboratory animals: short-term effects

From evidence published before 2009, OEHHA derived an acute REL of 0.2 µg/m³ for intermittent 1-h arsenic exposures *(40)* based on decreased fetal weight in CFLP pregnant mice exposed in a whole-body inhalation chamber for 4 h/day on gestation days 9, 10, 12 to an aerosol of arsenic trioxide (As_2O_3, 76% arsenic by weight) *(41)*. The critical effect aimed to protect against adverse effects on development (teratogenicity) and on the cardiovascular and nervous systems. The no observed adverse effect level (NOAEL) was 260 µg/m³ and the lowest adverse effects level (LOAEL) was 2900 µg/m³. The Texas Commission on Environmental Quality derived an acute reference value[17] of 9.9 µg/m³ and an acute effects screening level[18] of 3 µg/m³ for intermittent 1-h exposures *(42)* based on maternal respiratory distress (rales) in female Crl:CD(SD)BR rats exposed to aerosolised arsenic trioxide in a whole-body inhalation chamber for 6 h/day for 14 days prior to mating and throughout gestation until gestation day 19 *(43)*. The NOAEL was 3 mg/m³ and the LOAEL was 10 mg/m³, and no reproductive or developmental effects were reported *(43)*.

A2.2.2 Laboratory animals: long-term effects

No animal inhalation studies reporting cancer effects or other health effects or outcomes from inorganic arsenic exposure were identified.

The 2019 ANSES review investigated the weight of evidence on health effects related to ambient PM compounds, size and sources, including human and laboratory animal studies published after the 2013 REVIHAAP review up to February 2016 *(44,45)*. The animal studies did not report an association between (sub)acute or (sub)chronic arsenic exposure in ambient air particles and impaired health. A significant but weak negative correlation was reported between arsenic

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[17]   The acute reference value is only to be used to evaluate air monitoring data.

[18]   The acute effects screening level is only to be used for air permit reviews and not to evaluate ambient air monitoring data. If the predicted 1-h maximum ground level concentration is equal to or less than the acute effects screening level , then no acute health effects would be expected.

inhalation in rodents and an inflammatory response (by measuring cellularity in bronchoalveolar lavages), but with no control/adjustment for the effects of other compounds.

A2.2.3 Mechanisms of carcinogenicity

The Dutch Expert Committee on Occupational Safety considers that arsenic compounds are non-stochastic carcinogens (46). In vivo and in vitro studies conducted in humans and animal models reported clastogenic damage, but no point mutations (31). The biological mechanism associated with the genotoxic effects is under debate.

Arsenic compounds are assumed not to form DNA adducts or DNA–protein crosslinks and, therefore, not to directly affect DNA (31,46). Since arsenic exposure is not associated with point mutations, arsenic might act as a comutagen that enhances the mutagenicity of other agents.

Effects of arsenic on several biochemical processes suggest that arsenic genotoxicity occurs via a non-stochastic mechanism (31,46): reactivity of arsenicals with protein thiol-groups, inhibition of DNA repair enzymes, DNA hypermethylation (especially in promoter regions) and associated inactivation of tumour suppressor genes or genes involved in DNA repair, histone modification processes (e.g. acetylation, methylation and phosphorylation of histone tails), gene-specific alteration of miRNA expression, and oxidative stress. A 2022 comprehensive review discusses various mechanisms involved in arsenic-induced epigenetic alterations (47).

There is controversy about which approach should be used for arsenic risk assessments: a default linear approach, which assumes no safe level of arsenic oral exposure, or a nonlinear (or threshold) approach, which assumes that a threshold level exists below which arsenic exposure is safe (48,49).[19] This issue also concerns arsenic inhalation exposure for which dose–response relationships with lung cancer have been linearly extrapolated from studies on highly exposed workers to low levels of exposure. Currently, there is no clear evidence on the mode of action of inhaled arsenic toxicity (50)[19] and, therefore, no indication of whether a linear or nonlinear approach should be used. If the mode of action requires a threshold approach, but a linear dose–response relationship is used instead, the risk of cancer would be overestimated at exposure levels below the threshold effect.

Some evaluations provide an alternative approach based on the mode of action to assess the health-protective concentrations for oral arsenic exposure based on collective evidence from animal (in vitro and in vivo) and human studies rather than using a linear low-dose extrapolation approach. This alternative approach could also be applied to arsenic inhalation exposure. The proposed modes of action are a threshold process, requiring sufficient concentrations of trivalent arsenic to disrupt normal cellular function (48,51).[19] Cohen and colleagues presented evidence for a mode of action involving the formation of reactive trivalent metabolites that interact with critical cellular sulfhydryl groups, leading to cytotoxicity and regenerative cell proliferation (51). This mode of action suggests a nonlinear, threshold dose–response relationship for both non-cancer and cancer end-points.

As reported by the European Chemicals Agency (31), Lewis and colleagues explored the approach of using a nonlinear threshold model to conduct a quantitative risk analysis for the general population (50).[19] They suggested that a possible threshold for arsenic-induced lung cancer via inhalation could be proposed based on the available information from occupational studies, mechanistic data and the mode of action of ingested inorganic arsenic. Data on cumulative exposure and the reported standard mortality ratio from the Anaconda and Tacoma cohorts (52,53) was combined in a pooled analysis that calculated a NOAEC of 1.28 μg/m³ for the general population in the United States. A LOAEC of 0.1 mg/m³ for the general population was calculated based on dose–response data on concentrations of airborne arsenic and respiratory cancer mortality reported by Lubin and colleagues in 2008 (53). They argued that this represents a sufficient margin of safety considering that the general population is exposed to airborne concentrations in the range of 30 ng/m³. They concluded that to characterize the arsenic

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[19]   The authors of three studies received financial support from arsenic-related industries (48,50,51).

carcinogenic potential via inhalation there is a need to explore both the impact of exposure concentrations and a threshold model.

In 2017 the European Committee for Risk Assessment concluded that the carcinogenic mode of action for arsenic and inorganic arsenic compounds has not been established, but the available evidence suggests that it is not related to DNA reactive genotoxicity, which indicates that a threshold exposure level may exist. Despite this, evidence is insufficient to define exposure thresholds for key events in the mode of action. Exposure–response relationships were derived by linear extrapolation, which introduces uncertainties outside the observed concentration range. Evidence on the mechanistic pathways suggests that the exposure–response relationship is not linear. Therefore, the excess risk might be overestimated in the low exposure range *(31)*.

A2.3 Epidemiological studies

A2.3.1 Short-term effects

Workers who inhaled very high arsenic levels over a short period have experienced respiratory tract symptoms (cough, chest pain, dyspnoea, pulmonary oedema), gastrointestinal effects (abdominal pain, diarrhoea, nausea), and central and peripheral nervous system effects (frank encephalopathy, peripheral neuropathy) *(35,54,55)*. The existing data does not include any cases of death in people following acute inhalation exposure to inorganic arsenic, even at very high exposure levels *(31)*.

A2.3.2 Long-term effects

A2.3.2.1 Non-carcinogenic effects

Chronic inhalation exposure of humans to elevated levels of inorganic arsenic has been associated with effects on the cardiovascular system, including peripheral vascular effects such as acrocyanosis, blackfoot disease[20] and Raynaud disease[21]; on skin; on mucous membranes, including conjunctivitis, dermatitis, pharyngitis and rhinitis; and with nerve damage *(31,35,54–56)*.

The 2019 ANSES review investigated the weight of evidence on health effects related to ambient PM compounds and their size and sources, including human and laboratory animal studies published after the 2013 REVIHAAP review up to February 2016 *(44,45)*. All clinical and pathophysiological end-points (*n* = 83) were included. However, a weight-of-evidence assessment was not performed for arsenic and 27 other poorly documented elements.[22] The number of publications with statistically significant associations was reported for information purposes.

Regarding epidemiological research, two studies reported an association between short-term arsenic exposure and respiratory hospitalization. Arsenic was among the poorly documented

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[20] Manifested as tissue necrosis in the extremities.
[21] Manifested as episodes of ischaemia resulting from spasms in the blood vessels, usually in the arteries of the fingers.
[22] Aluminium (Al), antimony (Sb), barium (Ba), bromine (Br), cadmium (Cd), calcium (Ca), cerium (Ce), chlorine (Cl), copper (Cu), iron (Fe), lanthanum (La), lead (Pb), magnesium (Mg), manganese (Mn), molybdenum (Mo), neodymium (Nd), nickel (Ni), phosphorus (P), potassium (K), rubidium (Rb), selenium (Se), sodium (Na), strontium (Sr), tin (Sn), titanium (Ti), vanadium (V) and zinc (Zn).

pollutant for which most human studies observed associations with cardiovascular end-points. Short-term arsenic exposures were associated with impaired heart rate variability (three studies), impaired blood pressure (two studies), markers of systemic inflammation (one study) and markers of systemic oxidative stress (one study). Long-term arsenic exposure was associated with heart attack and/or coronary events (one study). However, the associations observed for the 28 elements, considered individually in this screening approach and derived from observational studies may reflect the health effect of common sources or of other pollutants in mixtures that covary with arsenic rather than the intrinsic toxicity of arsenic, and/or exposure through other routes than inhalation (drinking water, food).

Information on arsenic in ambient air might not be exhaustive because the review targeted studies that examined different compositions, sources or sizes (ultrafine or coarse) of ambient air particles; it stated that there were unexplored reserves in the literature on PM from industrial sources.

An investigation in Phoenix (United States) in 1995–1998 assessed the associations between daily ambient concentrations of particulate pollutants (including arsenic and mercury, among others), daily source contributions from coal-fired power plants and smelters (individually, combined and with interaction), and daily CVD mortality, using single and multipollutant models (57). A strong relationship was found with particulate mercury and no support for an independent effect of arsenic or selenium on CVD mortality (57). A review reported that none of five area-based studies of estimated arsenic concentrations in ambient air around pregnancy or infancy had identified a statistically significant relationship with autism spectrum disorder (58).

In summary, a few observational studies on arsenic in ambient air identified positive associations with health effects, mainly cardiovascular end-points: heart attack and/or coronary events, impaired heart rate variability, impaired blood pressure, systemic oxidative stress, and systemic inflammation. These results may reflect the health effects of common pollutant sources or of other pollutants in mixtures that covary with arsenic, rather than the intrinsic toxicity of the arsenic compound and/or exposure through other routes than inhalation (drinking water, food). A broad range of health adverse effects are consistently related to high arsenic environmental exposure; these mainly relate to cancer and CVD, with emerging evidence of neurodevelopmental impairment. Although the extent of the contribution of arsenic to ambient air is still unknown, reducing airborne arsenic levels may reduce arsenic levels in food and water, thereby reducing exposure to this harmful element. Several variables may modulate or confound the relationship between environmental arsenic exposure and adverse health effects, including exposure route; genetic susceptibility; ionizing radiation; levels of B vitamins, folate and selenium; malnourishment; sex; and smoking.

A2.3.2.2 Carcinogenic effects

The European Commission, IARC and US EPA have classified inorganic arsenic compounds as carcinogenic to humans.

Occupational studies have shown that inhalation exposure to inorganic arsenic increases the risk of lung cancer in humans (2,35,54,56). IARC monograph 100C on arsenic, metals, fibres, and dusts (2) considered the available evidence on airborne arsenic from several cohort studies and nested case–control studies (59–64). This included occupational studies with workers in metal smelters (copper (52,65,66), zinc–lead–cadmium (67)) and refineries, ore miners (gold (68), tin (69) and uranium (68,70)) and other workers exposed to arsenic (71–73). Case–control studies in the general population addressed occupational exposures more generally (74–76). Therefore, co-exposure to other potentially carcinogenic by-products of combustion (e.g. sulfur oxides with copper smelting (74), polycyclic aromatic hydrocarbons (76) and PM) were also considered in the latter analysis. IARC concluded that since most studies did not isolate the effects of airborne arsenic from other inhaled co-exposures, confounding or modifying effects of synergistic interactions could not be ruled out (2).

In 2013 the WHO REVIHAAP review investigated, among other questions, whether new evidence on the health effects of exposure to arsenic and arsenic compounds should be considered in

view of the current target values *(77)*. The review included three epidemiological studies on occupational exposures published between 2007 and 2009, and did not include either human or animal experimental studies on arsenic in ambient air. It concluded that the new evidence on the cancer risk of air emissions of arsenic was contradictory.

Supplemental reviews and studies collected from an exploratory search in PubMed did not provide evidence of adverse health effects in the general population that were specifically associated with exposure to arsenic in ambient air. Interestingly, an ecological study conducted during 1994–1996 generated a database of arsenic exposure and deaths due to cancer for the 1950–1996 period, covering each of the 335 Chilean municipalities *(22)*. For each municipality, the lifetime cumulative arsenic exposure (by air and water) was estimated for six age groups (cohorts) and related to mortality due to cancer in the 1985–1992 period. The study evaluated cases of bladder, kidney, liver, lung and skin cancer (compared with gastric cancer, which is not associated with arsenic). Arsenic exposure through drinking water was determined to be a highly significant risk factor (Poisson regression analysis) for all arsenic-associated cancers but showed no association with gastric cancer. Airborne arsenic could not explain the excess risk for any of the cancers.

Previous studies described in the WHO and International Programme on Chemical Safety Environmental Health Criteria review *(13)* and reported elsewhere *(17)* showed mixed evidence of a positive association between lung cancer and residential exposure to arsenic emissions or living in the vicinity of arsenic-emitting industry.

A2.4 Information on causality and related evaluations

Table A2.1 summarizes the information available linking exposure to arsenic and health effects by the European Commission, IARC, US EPA and WHO.

Table A2.1 Information on causality by inhalation exposure to benzene

Authoritative body	Air pollutant	Causality	Notes
IARC (2012) *(2)*	As compounds	Carcinogenic to humans (Group 1)	Sufficient evidence in experimental animals for carcinogenicity of inorganic As compounds.
			Sufficient evidence in humans for carcinogenicity of mixed exposure to inorganic As compounds, including arsenate, As_2O_3 and arsenite. Inorganic As compounds (including arsenate, As_2O_3 and arsenite) cause bladder, lung and skin cancer. Positive association between exposure to As and inorganic As compounds and kidney, liver and prostate cancer.
			Sufficient evidence in experimental animals for carcinogenicity of calcium arsenate, DMA and sodium arsenite.
			Limited evidence in experimental animals for carcinogenicity of As_2O_3, gallium arsenide, sodium arsenate and trimethylarsine oxide.
			Inadequate evidence in experimental animals for carcinogenicity of arsenic trisulfide and MMA.
			The evaluation considered the overall effect of As and inorganic As compounds rather than of individual compounds. The Working Group assessed the available evidence from epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism and modes of action of carcinogenicity.

Table A2.1 contd

Authoritative body	Air pollutant	Causality	Notes
IARC (2012) *(2)*	As compounds	Carcinogenic to humans (Group 1)	Elemental As and inorganic As species share the same metabolic pathway: arsenate → arsenite → methylarsonate → dimethylarsenite Therefore, different inorganic As species should be considered carcinogenic independently of the mechanism(s) of action of carcinogenicity and of which metabolite is the actual carcinogen: • carcinogenic to humans (Group 1): As and inorganic As compounds • possibly carcinogenic to humans (Group 2B): DMA and MMA • not classifiable as to carcinogenicity to humans (Group 3): arsenobetaine and other organic As compounds not metabolized in humans
WHO Regional Office for Europe (2000, 2010) *(3,78)*	Arsenic	Carcinogenesis	Lung cancer
WHO Regional Office for Europe (2000, 2010) *(3,78)*	Arsenic	Carcinogenesis	Lung cancer
European Chemicals Agency (2004) *(31)*	Arsenic acid, diarsenic pentoxide and As_2O_3	Known human carcinogen (Category 1A)	–
US EPA (2021) *(4)*	As compounds	Known human carcinogen (Category A)	–

EC: European Commission.

A2.5 Health-based evaluations and regulatory numbers from authoritative bodies

Table A2.2 presents the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect human health from arsenic exposure.

Table A2.2 Health-based evaluations and regulatory numbers for arsenic compounds from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
Worldwide	WHO Regional Office for Europe (2000) (3)	Geometric mean of the URFs for lung or respiratory cancer mortality on three URFs from three copper smelter cohorts	Inhalation URF: 1.5×10^{-3} (corresponding to an air concentration of 6.6 ng/m^3 and equivalent to an excess lifetime risk level of 1:100 000)	–
United States	US EPA (1984, 1991, 1994) (56,79,80)	Weighted geometric mean of the URFs for respiratory or lung cancer mortality in five studies on two copper smelter cohorts (Anaconda (81–85) and Tacoma (86))	Inhalation URF: 4.3×10^{-3}	–
United States	NIOSH (2005) (87)	Lung cancer	Occupational exposure: • REL for dust: 2 µg/m^3 (15 min) • IDLH: 2 µg/m^3	–

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/ limit value
United States	OSHA (2005) *(88–91)*	PEL: lung cancer	–	Occupational exposure to As dust: • PEL-TWA: 0.01 mg/m^3 (general industry for inorganic As compounds) • PEL-TWA: 5 mg/m^3 (general industry for organic As compounds) • PEL-TWA: 0.5 mg/m^3 (constructionindustry for organic As compounds) • PEL-TWA: 0.5 mg/m^3 (shipyard industry for organic As compounds)
United States	ACGIH (2004) *(92)*	Lung cancer	–	Occupational exposure: • TLV: 0.01 mg/m^3 for dust
United States (California)	OEHHA (2008) *(40)*	REL-A: development (teratogenicity), cardiovascular system; nervous system REL-TWA: development, cardiovascular system, lungs, nervous system, skin	As and inorganic As compounds (including arsine): • REL-A: 0.20 µg/m^3 • REL-TWA: 0.015 µg/m^3	–
United States (California)	OEHHA (2011) *(93)*	Similar starting data as US EPA, linear modelling with adjustment for smoking using the occupational mortality studies of smelter workers in Anaconda (unpublished)[a] *(94,95)* and Tacoma *(96)* The proposed URF is the upper limit of the 95% CI from one selected copper smelter cohort study	Inhalation URF: 3.3 × 10^{-3}	–
Geographical scope	**Authoritative body**	**Health end-point upon which recommendation is based**	**Guidelines and regulatory levels**	**Guideline/target/ limit value**

Table A2.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
United States (Texas)	TCEQ (2012) *(42)* (based on Erraguntla et al. (2012) *(97)*)	Lung or respiratory cancer mortality in three copper smelter cohorts (Anaconda (unpublished)a, Ronnskar and Tacoma) *(65,72)*. Weighted procedure utilizing the reciprocal of the URFs variance	Inhalation URF: 1.5×10^{-4}	–
Canada	Health Canada (1993) *(98)*	Lung or respiratory cancer mortality in three copper smelter cohorts (Anaconda (unpublished)[a], Ronnskar and Tacoma) *(65,72)*	Inhalation URF: • Anaconda – 6.4×10^{-3} • Ronnskar – 1.0×10^{-3} • Tacoma – 4.9×10^{-3}	–
EU	EC (2004) *(99)*	Non-cancer effects	–	Arsenic target value: 6 ng/m³ (for the total content in the PM_{10} fraction averaged over a calendar year)
EU	ECHA (2017) *(31)*	Extrapolated from the URF proposed for workers by DECOS *(46)* and a conversion to continuous lifetime exposure. Extrapolated from the URF of 1.4×10^{-4} µg/m³ derived by DECOS for an occupational exposure (8 h/day, 5 days/week, for 40 years) *(46)*, to a continuous lifetime exposure (24 h/day, 7 days/week, 70-year lifetime) for the general population. Lung cancer mortality in one copper smelter cohort study (Anaconda) *(53,66)*	Inhalation URF: 1.0×10^{-3}	–
Netherlands (Kingdom of the)	RIVM (2001) *(100)*	Lung cancer	Maximum permissible risk level: 1 µg/m³	–

ACGIH: American Conference of Governmental Industrial Hygienists; DECOS: Dutch Expert Committee on Occupational Safety; EC: European Commission; ECHA: European Chemicals Agency; IDLH: immediately dangerous to life or health; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PEL: permissible exposure limit; PEL-TWA: permissible exposure limit expressed as a time-weighted average; REL-A: acute REL; REL-TWA: REL expressed as a time-weighted average; REL expressed as a time-weighted average; RIVM: *Rijksinstituut voor Volksgezondheid en Milieu* [Dutch National Institute for Public Health and the Environment]; TCEQ: Texas Commission on Environmental Quality; TLV: threshold limit value.

[a] Unpublished report: Higgins ITT, Oh MS, Kryston KL, Burchfied CM, Wilkinson NM. Arsenic exposure and respiratory cancer in a cohort of 8044 Anaconda smelter workers. A 43-year follow-up study. Submitted to Chemical Manufacturers' Association and Smelters Environmental Research Association, 1985.

Notes: ILDH is defined as the concentration representing maximum level from which an individual could escape within 30 min without escape-impairing symptoms or irreversible health effects *(100)*. Maximum permissible risk is defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk *(101)*. PEL-TWA is defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h working day or 40-h working week *(102,103)*. TLV-TWA is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime, expressed as a time-weighted average *(104)*. URF is defined as the additional lifetime cancer risk in a hypothetical population after a lifetime exposure of 1 g/m^3 to arsenic compounds *(3)*.

A2.6 Future research needs

There is a need for studies to identify the:

- relationship between air pollution and biomarkers of arsenic exposure;

- factors determining the metabolism and kinetics of arsenic;

- genetic and epigenetic determinants of arsenic susceptibility and mode of action; and

- mode of action of arsenic that may produce disease from chronic low-level inhalation exposures.

A2.7 Concluding remarks

- Arsenic is a ubiquitous, naturally occurring metalloid found as a contaminant of air, cigarettes, drinking water, food, industrial effluent, occupational environments and soil. Of the various routes of arsenic exposure, drinking water is the largest source of arsenic poisoning in the general population worldwide. Arsenic exposure from ingested food usually comes from food crops grown in arsenic-contaminated soil and/or irrigated with arsenic-contaminated water, as well as milk and seafood.

- There is large variability in the arsenic concentrations found in air depending on the type of monitoring site. Worldwide, the mean total arsenic concentrations in air are 0.02–4 ng/m^3 in remote and rural areas and 3–200 ng/m^3 in urban areas. The concentrations measured near industrial sources, such as power plants that burn arsenic-rich coal and non-ferrous metal smelters are considerably higher (> 1000 ng/m^3).

- Arsenic in air is concentrated in $PM_{2.5}$. Worldwide simulations of mean atmospheric arsenic concentrations show large spatial variations, with the highest levels in Chile (the first copper producer) and China in 2015, and a strong increase in India between 2005 and 2015.

- In Europe, arsenic air pollution is highly localized and usually associated with emissions from specific industries. Exceedances of the target value (6 ng/m^3) defined for arsenic in PM_{10} samples were observed at only seven out of 645 stations in 27 European countries in 2017 and in six out of 665 stations in 28 European countries in 2018 *(18,19)*. High local levels are still recorded. For example, in 2019 arsenic levels in PM_{10} of up to 550 ng/m^3 were recorded near a copper production facility in Bor (Serbia), one of the most polluted regions in southeastern Europe.

- For the general population, atmospheric arsenic exposure appears to be the least significant contributor by far of the three exposure pathways (air, drinking water, food) to total arsenic intake, in both heavily and lightly contaminated areas.

- Most evidence on the health effects of arsenic exposure are based on ingestion as the main exposure pathway. It should be emphasized that health effects related to arsenic inhalation might not be the same as those triggered by ingestion. There is a need for further studies focused on inhalation as the main arsenic exposure pathway to help to derive air quality guidelines.

- Although inhalation is not the main exposure pathway, arsenic can remain in the lungs for years, and such chronic accumulation might result in lung cancer. However, there is currently insufficient evidence on arsenic bioaccumulation in the lungs, and evidence on risk from arsenic exposure in ambient air is insufficient to change guidelines compared with evidence on arsenic exposure from other routes.

- A few observational studies on arsenic in ambient air found positive associations, mainly with cardiovascular end-points: heart attack and/or coronary events, impaired heart rate variability, impaired blood pressure, systemic oxidative stress and systemic inflammation. These results may reflect the health effect of emissions from common sources or of other pollutants in mixtures that covary with arsenic rather than the intrinsic toxicity of the arsenic compound and/or exposure through other routes than inhalation (drinking water, food).

- A broad range of health adverse effects are consistently related to high arsenic environmental exposure; these mainly relate to CVD and cancer, but with emerging evidence of neurodevelopmental impairments. Although the contribution of arsenic in ambient air to these health effects is unknown, airborne arsenic levels may increase arsenic levels in food and water, thereby increasing arsenic exposure through this route. Several variables might modulate or confound the relationship between environmental arsenic exposure and adverse health effects, including exposure route; genetic susceptibility; ionizing radiation; levels of B vitamins, folate and selenium; malnourishment; sex; and smoking.

- IARC concluded that there is sufficient evidence that mixed exposure to inorganic arsenic compounds, including arsenate, arsenic trioxide and arsenite, cause cancer in humans *(2)*. Inorganic arsenic compounds, including arsenate, arsenic trioxide and arsenite, cause bladder, lung and skin cancer.

- In 2000 the WHO *Air quality* guidelines *for Europe* proposed a unit risk of 1.5×10^{-3} µg/m^3, based on linear extrapolations from the lung cancer risk related to cumulative exposure to arsenic in smelter cohorts *(3)*. Since then, studies have suggested that the true unit risk could be lower or higher.

- The European Committee for Risk Assessment concluded that the carcinogenic mode of action of arsenic and inorganic arsenic compounds has not been established but available evidence suggest that is does not relate to DNA-reactive genotoxicity and, therefore, that a threshold exposure level may exist. Despite this, insufficient evidence prevents exposure thresholds being defined for key events in the mode of action or pathway. Exposure–response relationships were derived by linear extrapolation, which introduces uncertainties outside the observed concentration range. Evidence on the mechanistic pathway(s) suggests

that the exposure–response relationship is not linear. Therefore, the excess risk might be overestimated in the low exposure range *(31)*.

- The values proposed by Health Canada *(98)* are rather old and may not be health based. This is consistent with the precautionary approach to assessing cancer taken by most of the jurisdictions, which had opted for a linear extrapolation by assuming the lack of a threshold rather than potentially underestimating the risk by taking a threshold approach.

- For population exposure caused by high background levels of geochemical arsenic or by soil pollution, the respiratory route might be a low or very low contributor. For chronic non-cancer effects, in the case of non-acute but abnormally high atmospheric concentrations (e.g. ≥ 30 ng/m^3), a pragmatic recommendation would be to calculate an equivalent dose by the oral route due to respiratory exposure. This dose should be added to the oral exposure dose and the sum compared to an oral toxicological reference value.

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Annex 3. Evidence overview on cadmium

Contents

A3.1 Exposure risk assessment

A3.1.1 Characteristics, sources and environmental occurrence

Cadmium (chemical symbol, Cd; atomic number, 48; relative atomic mass, 112.41; CAS Registry Number 7440-43-9) is a soft, silver-white metal that belongs to Group 12 of the periodic table. It is usually found in combination with other elements. In most compounds, the oxidation state of cadmium is +2, but in a few the oxidation state is +1 *(1,2)*. Cadmium and its compounds range in solubility in water from quite soluble (cadmium sulfate and cadmium chloride) to practically insoluble (elemental cadmium, cadmium oxide and cadmium sulfide) *(3)*. Atmospheric cadmium compounds in aerosols are mainly found in $PM_{2.5}$ *(4)*.

Cadmium has some industrial applications: it is used as a metal and as a component of Ni–Cd batteries, pigments, coatings and plating, stabilizers for plastics, semiconductors and photovoltaic devices, and in non-ferrous alloys. Cadmium is also present as an impurity in several metals and in fossil fuels, cement and fertilizers.

Cadmium occurs naturally in the earth's crust (average terrestrial abundance: 0.1–0.2 mg/kg) and in ocean water (at < 5 ng/L to 110 ng/L). Natural sources such as the erosion of cadmium-bearing rocks, volcanoes, forest fires and sea spray emit particulate cadmium to the atmosphere. Anthropogenic sources include the production of cement, non-ferrous and ferrous metals; fossil fuel combustion; and waste incineration *(5–7)*. In Europe, about 39% of cadmium emissions are from industrial production and 28% are from public electricity and residential combustion *(8)*. Cadmium emissions in 2020 had reduced by 61% compared with emissions in 2005 *(9)*. Informal recycling of electronic waste is becoming a significant localized source of cadmium to the environment, especially in developing countries *(10–12)*.

In the mid-1990s, approximately 3000 t cadmium were emitted globally by anthropogenic sources. Between 1990 and 2003, the anthropogenic emission rate declined by about half in Europe and by around two thirds in Canada *(6)*.

Cadmium does not break down in the environment, and so has a propensity to accumulate and enter food chains. Indeed, cadmium is highly ubiquitous in marine and terrestrial biota and ecosystems *(13–17)*. Atmospheric cadmium compounds can be transported in the atmosphere (sometimes for long distances) with minimal transformation *(5)*. Wet or dry deposition of cadmium from ambient air contributes about half of the cadmium input to surface soils, from where it can enter the food chain through foliar absorption and/or root uptake by crops. Numerous factors (e.g. soil pH, type of soil and plant, fertilizer use, meteorological conditions) determine the cadmium transfer rate from soil to plants. In France, the main source of cadmium in agricultural soils are phosphate fertilizers *(18)*. Reported concentrations in marine sediments range from 0.03 mg/kg to 1 mg/kg, whereas concentrations in river and lake sediments can be up to 5 mg/kg *(19)*. Soil concentrations higher than 1 mg/kg have been measured in the vicinity of smelters and other industrialized areas *(7)*.

European studies on the cadmium balance in topsoil indicated that the input rate exceeds the removal rate, which increases the risk of future exposure through food *(20,21)*.

To limit the temporal accumulation of cadmium in agricultural soils and decrease the cycle of environmental contamination linked to all types of cadmium inputs, an annual cadmium input flux limited to 2 g Cd/ha per year has been recommended regardless of the nature (e.g. fertilizer/soil amendment, organic/mineral origin) and the total quantity of fertilizing material(s) added to agricultural soil *(22,23)*.

A3.1.2 Environmental levels

Airborne cadmium can be found adsorbed onto or internally mixed within the core of PM. Its atmospheric residence time will be dependent on the size of the particles, meteorological conditions, and operating conditions of the industrial or combustion process responsible for its release *(24)*.

Concentrations measured in northern Europe during the 1980–1988 period were approximately 0.1 ng/m³ in remote areas, 0.1–0.5 ng/m³ in rural areas, 1–10 ng/m³ in urban areas and 1–20 ng/m³ in industrial areas *(7)*. Higher concentrations (approximately 100 ng/m³) have been measured in the proximity of emission sources *(7)*. The range of concentrations is consistent with those reported in the United States *(6)*.

In 2020 annual concentrations of cadmium were 0.01–0.2 ng/m³ over most of the EMEP region. The highest values were measured in central Europe, followed by western Europe. However, in western Europe a large variability in concentrations was observed. High cadmium levels of up to 0.5 ng/m³ were measured in some areas of the southwestern Germany, southern Poland, northern Serbia and southeastern Sicily. These peak values are mostly associated with high anthropogenic emissions in these regions *(8)*.

Cadmium concentrations measured in EMEP stations declined by 47% over the 2000–2020 period *(8)*.

A3.1.3 Human exposure

Food ingestion is the main route of cadmium exposure (> 90%) for non-smokers in the general population, representing a daily intake of approximately 10–30 µg *(20)*. The major contributors to dietary cadmium exposure are foods that are consumed in larger quantities such as cereals, potatoes and other vegetables *(25)*. Drinking water contains between 0.01 µg/L and 1 µg/L *(20)*.

Inhalation is a minor route for cadmium exposure. However, airborne cadmium concentrations are important for soil deposition and, therefore, for dietary intake. Assuming a daily inhalation volume of 20 m³ and based on the highest cadmium concentration found in rural, urban and industrialized areas, the average amount of cadmium inhaled daily does not exceed 0.04 µg, 0.2 µg and 0.4 µg, respectively.

A Canadian study reported median personal exposures of nickel in PM_{10} of 9 µg/g and was predominantly found in the coarse fraction *(26)*. A study conducted in Jinhua (Zhejiang Province, China), which has a large metal manufacturing industry, reported personal exposure concentrations of 9.3 ± 12 ng Cd/m³ (range: 0.75–47 ng/m³) *(27)*.

Cadmium naturally accumulates in tobacco leaves *(28)*. Therefore, smoking is a significant source of exposure for smokers and second-hand smokers. Smoking one cigarette is estimated to contribute approximately 1.7 µg cadmium, with approximately 10% being inhaled when smoked *(28)*. Smokers are estimated to have about twice as much cadmium in their bodies compared with non-smokers *(29)*.

The 2007 WHO report, *Health risks of heavy metals from long-range transboundary air pollution (20)*, stated that despite decreases in cadmium emissions, ambient air concentrations and deposition, the data fail to show a decrease in the cadmium body burden in non-smokers over the previous decade.

Occupational cadmium exposures are highest among people working in cadmium production and refining, Ni–Cd battery manufacturing, cadmium pigment manufacturing, alloy production and soldering, mechanical plating, zinc smelting and polyvinylchloride compounding *(1)*. Dust and fume inhalation is the main exposure route; however, incidental dust ingestion from contaminated hands and food may also occur *(5)*. The mean concentration of cadmium oxide dust measured in a battery manufacturing plant in China in 1986–1992 was 2.17 mg/m³ (range: 0.1–32.8 mg/m³) *(30)*. Occupational exposures vary greatly among the different industries,

but concentrations have reduced since the 1970s. For example, mean cadmium hydroxide concentrations in air from personal samples of Ni–Cd battery workers in the United Kingdom were 0.88–3.99 mg/m^3 in 1969–1973 versus 0.024–0.12 mg/m^3 in 1989–1992 *(31)*. Cumulative cadmium exposures among workers employed in cadmium alloy production in England and Wales (United Kingdom) declined from an estimated 600 µg/m^3 in 1926–1930 to approximately 56 µg/m^3 by the 1980s *(32)*.

A3.1.4 Absorption, distribution, metabolism and excretion

Cadmium exposure primarily occurs through ingestion of contaminated food and water and also, to a significant extent, through inhalation and cigarette smoking *(33)*. Animal studies have shown that following inhalation approximately 20% of cadmium may be retained in the lungs, especially after short-term exposures *(34)*. When ingested, little is absorbed into the gastrointestinal tract: reported cadmium absorption rates are 3–5% *(35)* or 6.5% *(36)*. Iron deficiency may increase gastrointestinal uptake of ingested cadmium (observed more often in women than in men) *(37)*.

When absorbed, cadmium forms a cadmium–metallothionein complex that is transferred primarily to the liver and the kidney via blood *(38)*. In the kidney, cadmium–metallothionein is readily filtered in the glomerulus and may be efficiently reabsorbed from the filtrate in the proximal tubules *(39,40)*. In the tubules, the protein component is rapidly degraded to release cadmium *(41)*. Cadmium accumulates in kidney tubules.

Once absorbed, cadmium is efficiently retained in the human body, where it accumulates throughout the lifetime *(33)*. Absorbed cadmium is excreted very slowly: in humans, half-life estimates are in the range of 7–30 years *(33,42,43)*.

A3.2 Toxicological studies

A3.2.1 Laboratory animals: short-term effects

The US EPA fact sheet on cadmium compounds *(44)* stated that "cadmium is considered to have high acute toxicity, based on short-term tests in rats [*(45)*]".

A3.2.2 Laboratory animals: long-term effects

The US EPA fact sheet on cadmium compounds *(44)* states that "chronic inhalation or oral exposure of animals to cadmium results in effects on the kidney, liver, lung, bone, immune system, blood, and nervous system [*(45,46)*]".

Animal studies included in an ANSES review did not support an association between (sub)acute or (sub)chronic exposures to cadmium in ambient air particles and indicators of impairment to human health *(47)*.

A3.2.2.1 Bone damage

The report, *Health risks of heavy metals from long-range transboundary air pollution (20)*, cited a study on rats indicating that relatively low exposure to cadmium in drinking water during the first few months of life (a period of intensive skeletal development) disturbs the accumulation

of bone mass, leading to osteopenia or more serious disorders of bone-mineral status, depending on exposure level *(48)*. The effect was intensified when exposure was continued until skeletal maturity.

A3.2.2.2 Reproductive and developmental effects

The US EPA fact sheet on cadmium compounds *(44)* described an association between inhalation and oral cadmium exposure with developmental effects, such as low fetal weight, skeletal malformations, interference with fetal metabolism, and impaired neurological development *(29,45,46)*. Oral exposures were also associated with decreased reproduction and testicular damage *(29)*.

A3.2.2.3 Carcinogenicity

IARC Monograph 100C on arsenic, metals, fibres, and dusts reported that inhalation of various cadmium compounds is associated with lung tumours in rats *(1)*.[24] Similarly, lung tumours were induced in rats following intratracheal administration of cadmium chloride and cadmium sulfide. A study found that subcutaneous injection of cadmium chloride caused lung tumours in mice *(49)*. Local sarcomas have been associated with exposure to various cadmium compounds and metallic cadmium in rats or mice. Testicular tumours were reported in rats following administration of various cadmium salts. Subcutaneous or oral administration of cadmium chloride induced prostatic proliferative lesions and testicular tumours in rats.

A3.2.3 In vitro systems

IARC Monograph 100C described cadmium compounds as weakly mutagenic to mammalian cells *(1)*, whereas no mutagenicity was reported in most bacterial assays *(50,51)*. Genotoxicity assays of soluble and insoluble cadmium compounds, tested in parallel, generally provide comparable results.

Cadmium induces oxidative stress despite not undergoing redox reactions under physiological conditions *(1)*. For example, cadmium sulfide induces the formation of hydrogen peroxide in human polymorphonuclear leukocytes, and cadmium chloride enhances superoxide production in human and rat phagocytes *(52)*.

Antioxidants and antioxidative enzymes suppress the formation of cadmium-induced DNA strand breaks and chromosomal aberrations in mammalian cells *(53–55)*.

IARC Monograph 100C *(1)* proposed that cadmium-induced generation of reactive oxygen species and oxidative cellular damage may be caused by cadmium-dependent inhibition of antioxidant enzymes *(54,55)*, as well as of DNA repair systems *(1)*.

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[24] This annex includes text reproduced from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans volume 100C *(1)*, reproduced with permission.

A3.3 Controlled human exposure studies

The REVIHAAP review *(21)* found an inverse association approaching significance between the cadmium content of inhaled concentrated ambient particles (CAP) and a decrease in brachial artery diameter in 24 healthy adults exposed to CAP plus ozone *(56)*. The findings were significant for organic and elemental cadmium concentrations.

A3.4 Epidemiological studies

A3.4.1 Short-term effects

A3.4.1.1 Respiratory effects: studies in occupational populations

The US EPA fact sheet on cadmium compounds *(44)* reported effects on the lung, including bronchial and pulmonary irritation following a single acute inhalation exposure to high cadmium levels that can result in long-lasting impairment of lung function *(29,45,46)*.

A3.4.2 Long-term effects

A3.4.2.1 Respiratory effects: studies in occupational populations

The US EPA fact sheet on cadmium compounds *(44)* reported that chronic exposure of humans to cadmium in air is associated with effects on the lung, including bronchiolitis and emphysema *(29,45,46)*.

A3.4.2.2 Kidney and bone damage: studies in occupational and general populations

The best-known health effects of cadmium following chronic inhalation and oral exposure are kidney damage (proteinuria resulting from proximal tubular cell damage) and toxic effects on bone tissue (osteomalacia and osteoporosis).

This toxicity profile has been clearly demonstrated in itai-itai disease (the Japanese *itai* means "ouch" or "painful"). The disease is characterized by osteomalacia and marked decalcification with severe bone pain and is associated with renal tubular dysfunction. An epidemiological survey conducted between 1967 and 1968 found that the largest epidemic of cadmium pollution-induced itai-itai disease in the world affected people living around the Jinzu River in Toyama (Japan) – cadmium-contaminated water from the river was used to irrigate rice fields *(57,58)*. The findings were that:

- cadmium concentrations in blood and urine were significantly higher in itai-itai disease patients, suspected patients and inhabitants in cadmium-polluted areas;

- urinary cadmium concentrations were mainly related to the body burden and did not decrease for several years following cessation of exposure; and

- there was a close association between urinary excretion of cadmium and beta-2-microglobulin.

The currently prevailing health risk assessment is based on the relationship between tubular proteinuria and urinary cadmium concentration *(7)*.

Cadmium-induced kidney damage is characterized by increased urinary excretion of enzymes (e.g. *N*-acetyl-β-ᴅ-glucosaminidase) and other proteins (e.g. beta-2-microglobulin). These proteins have been used as markers for the renal cadmium burden and possible adverse renal effects *(4,20)*.

Studies in industrial workers and the general population have shown that airborne cadmium exposure may affect calcium and phosphorus metabolism. Chronic exposure to cadmium in food has been associated with bone disorders, including osteoporosis and osteomalacia in humans. The latter affects most often women with several risk factors such as multiparity and poor nutrition *(59)*.

The 2000 WHO *Air quality guidelines for Europe* summarized pooled data from seven studies that examined the occurrence of tubular proteinuria with cumulative cadmium exposure *(7,60)*. The data showed a sharp increase in the prevalence of tubular dysfunction (background level: 2.4%) at a cumulative exposure of more than 500 µg/m³-years (to 8% at 400 µg/m³-years, 50% at 1000 µg/m³-years and > 80% at more than 4500 µg/m³-years). The Guidelines cited a kinetic model that predicted that after 10 years of exposure, 10% of workers exposed to 50 µg/m³ and 1% of workers exposed to 16 µg/m³ will reach a critical concentration of 200 mg/kg in the renal cortex *(61)*.

Several studies reported that childhood exposure to cadmium can affect renal function *(62)* and is associated with decreased glomerular filtration rate *(63,64)*.

The Joint WHO/Convention Task Force on the Health Aspects of Air Pollution *(20)* proposed a LOAEL of 2 µg/g creatinine[25] was based on evidence from several European studies conducted in the late 1990s and early 2000s that reported an association between urinary cadmium levels as low as 0.5–2.0 µg/g creatinine from environmental exposure and effects on bone and/or kidney.

The REVIHAPP review stated that some studies suggest that cadmium toxicity might not relate to the observed associations between low-level exposure to cadmium and excretion of low-molecular-weight proteins *(21)*. Instead, a more likely explanation is that the co-excretion of cadmium and proteins such as albumin, alpha-1-microglobulin, retinol-binding protein and beta-2-microglobulin is likely to relate to physiological factors, such as varying reabsorption of cadmium and proteins in renal proximal tubules *(66,67)*.

The REVIHAAP review *(21)* also identified studies that reported effects of low-level exposure to environmental cadmium on bone *(68–74)*, but acknowledged that not all studies found positive associations *(75,76)*.

The 2015 WHO Expert Consultation *(77)* highlighted the importance of a review on the health effects of cadmium exposure that challenges the basis of the existing health risk assessment for cadmium (i.e. the relationship between urinary cadmium concentrations and tubular proteinuria) *(78)*. The review found that exposure to low cadmium concentrations is associated with effects on bone, including an increased risk of osteoporosis and fractures, and that these and other health effects (in particular, cancer) are considered critical effects in the health risk assessment for cadmium.

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[25] Creatinine is a protein excreted in the urine in relation to the hydration level. Therefore, creatinine levels are used to normalize other urinary biomarkers to take into account the dilution factor from hydration *(65)*.

A3.4.2.3 CVD mortality: studies in the general population

The 2015 WHO Expert Consultation *(77)* highlighted the following reviews.

- A 2013 systematic review and meta-analysis evaluated the association between cadmium exposure (using concentrations in the urine) and CVD *(79)*. The findings supported an association with CVD (especially coronary heart disease) in general populations exposed to low–moderate levels of cadmium exposure. The review cited experimental evidence *(80)* that cadmium induces endothelial dysfunction in vitro and accelerates atherosclerotic plaque formation in vivo.

- A 2016 systematic review and meta-analysis examined the association between urinary cadmium concentration and mortality from all causes, cancer and CVD in the general population *(81)*. The evaluation concluded that even at low exposure levels, cadmium appears to be associated with increased mortality.

Since the 2015 WHO Expert Consultation *(77)*, further studies suggest that low levels of cadmium exposure may increase the CVD risk for the general population (examples are summarized below).

- A 2016 population-based study of Swedish men and women (whose cadmium levels were similar to those of most European and United States populations) examined the association between blood cadmium and cardiovascular events *(82)*. Blood cadmium levels in the highest quartile were associated with incident CVD and mortality. Notably (since smoking is a strong confounder), results were similar among never smokers. The findings suggest that measures to reduce cadmium exposures are warranted, even in populations without unusual sources of exposure.

- A 2017 prospective study estimated the potential contribution of reduced lead and cadmium exposure to decreasing cardiovascular mortality trends in the United States between 1988–1994 and 1999–2004 *(83)*. Over this period, there was a 31% decrease in urine cadmium concentrations. The cardiovascular mortality rate ratio associated with a doubling of metal levels was 1.20 (95% CI: 1.09–1.32) for urinary cadmium. The absolute reduction in cardiovascular deaths from 1988–1994 to 1999–2004 was 230.7 deaths per 100 000 person-years. Among these avoided deaths, 19.4 deaths per 100 000 person-years (95% CI: 4.3–36.4) were attributable to changes in cadmium. Given that cadmium remains associated with CVD at relatively low exposure levels, the authors discussed a potential need for prevention strategies to further minimize exposure.

- A 2018 systematic review and meta-analysis investigated the association of cadmium with CVD *(84)*: three studies reported cadmium levels in urine, four reported levels in blood and one reported levels in toenails. Pooled relative risks for cadmium were 1.33 (95% CI: 1.09–1.64) for CVD (six studies, 50 674 participants), 1.29 (95% CI: 0.98–1.71) for coronary heart disease (five studies, 32 070 participants) and 1.72 (95% CI: 1.29–2.28) for stroke (three studies, 9123 participants). The observed associations were approximately linear.

- A 2020 population-based cross-sectional study (Korea National Health and Nutrition Examination Survey) evaluated the association of blood cadmium levels with CVD *(85)*. The findings suggest that high cadmium levels in blood may be associated with prevalent stroke and hypertension in the population of the Republic of Korea aged under 60 years.

- A 2018 population-based prospective cohort study of randomly recruited women aged over 70 years in Perth (Australia). Baseline concentrations of urinary cadmium were available. Information on atherosclerotic vascular disease hospitalizations or death during the 14.5 years of follow-up was retrieved through the hospital database and mortality register data linkage *(86)*. Urinary cadmium was associated with an increased risk of heart failure (hazard ratio: 1.17; 95% CI: 1.01–1.35) and death from a cardiovascular event (hazard ratio: 1.36; 95% CI: 1.11–1.67).

- A 2022 systematic review and meta-analysis re-evaluated evidence on the relationship between cadmium exposure (blood, hair, urine and toenail samples) and blood pressure or

hypertension in general populations, and investigated whether the significance or magnitude of any association between cadmium and hypertension is sex or dose dependent *(87)*. The findings indicate that cadmium exposure is a risk factor for hypertension, but additional studies are needed to confirm these findings.

- A 2019 ANSES review investigated the weight of evidence on health effects related to ambient PM according to the components, sources and particle size, including human and laboratory animal studies published after the 2013 REVIHAAP review *(21)* up to February 2016 *(47,88)*. All clinical and pathophysiological end-points (*n* = 83) were included. However, a weight-of-evidence assessment was not performed for cadmium and 27 other poorly documented elements[26]. The number of publications with statistically significant associations was reported for information purposes. Of these pollutants, cadmium was the one for which the greatest number of human studies showed associations with cardiovascular end-points. Short-term cadmium exposures were associated with cardiovascular hospitalizations (one study), impaired heart rate variability (one study) and impaired blood pressure (three studies). None of the included studies reported an association between cardiovascular end-points and long-term exposure to cadmium in ambient air. However, the possibility cannot be excluded that the associations reported for each element (considered individually in the screening approach) reflect the effects of a common source or of a mixture of highly correlated compounds and/or exposure through routes other than inhalation (e.g. food). This is especially the case in observational studies, where exposure is not controlled. The ANSES review did not provide exhaustive information but targeted studies examining the different compositions of ambient air particles. It stated that there were unexplored reserves in the scientific literature on PM from industrial sources.

A3.4.2.4 Reproductive and developmental effects: studies in the general population

The US EPA fact sheet on cadmium compounds *(44)* found that there is (i) limited evidence for effects on a reduction in sperm number and viability in humans following cadmium inhalation of and (ii) some evidence to suggest that maternal cadmium exposure may result in decreased birth weights, despite a limited number of studies focused on human developmental effects *(29)*. More recent studies in 2012 and 2018 reported that prenatal exposure to cadmium is associated with restricted fetal growth *(89,90)*. Similarly, early life exposure is associated with slower growth trajectories in children aged between 9 months and 4 years *(91)*.

Prenatal cadmium exposure was associated with learning disabilities and lower cognitive performance in children from China *(92,93)*, Greece *(94)* and Republic of Korea *(95)*. Similarly, cadmium exposure in childhood was associated with adverse neurodevelopmental outcomes in children in China *(92)*, Spain *(96)* and the United States *(97)*. A 2022 systematic review evaluated the association between exposure to heavy metals and neurodevelopment in children in low and middle-income countries *(98)*. Limited data on cadmium exposure (blood or urine levels) included three prospective cohort studies (one in Bangladesh, two in China) examining children aged from 12 months to 10 years. Two of the three studies showed a negative association between prenatal cadmium levels and at least one neurodevelopmental domain. The only study to measure the effects of postnatal cadmium levels on neurodevelopment showed a negative association between cadmium exposure and Full-Scale Intelligence quotient (IQ) scores; in addition, urinary cadmium levels were negatively associated with prosocial behaviour and positively associated with hyperactivity in girls.

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[26]   Aluminium (Al), antimony (Sb), arsenic (As), barium (Ba), bromine (Br), calcium (Ca), cerium (Ce), chlorine (Cl), copper (Cu), iron (Fe), lanthanum (La), lead (Pb), magnesium (Mg), manganese (Mn), molybdenum (Mo), neodymium (Nd), nickel (Ni), phosphorus (P), potassium (K), rubidium (Rb), selenium (Se), sodium (Na), strontium (Sr), tin (Sn), titanium (Ti), vanadium (V) and zinc (Zn).

A3.4.2.5 Cognitive decline: studies in the general population

A 2023 review examined the available evidence on the effects of cadmium exposure on cognitive function in elderly populations *(99)*. Studies in China *(100–102)* and the United States *(103,104)* found that cadmium exposure is associated with detrimental effects on cognitive function in elderly adults.

A3.4.2.6 Carcinogenicity: studies in occupational, environmentally polluted and general populations

IARC Monograph 100C on cancer in humans *(1)* can be summarized as follows.

- Several limitations affect the assessment of cancer risks in occupational cohorts exposed to cadmium: the limited number of studies reporting long-term exposures, the very high concentrations to which workers are generally exposed, and the lack of historical data on cadmium exposure. In addition, co-exposure to other substances, mainly arsenic and nickel, might confound the observed effects. It has not been possible to define (and examine) a gradient of cumulative exposure across the available studies. However, analyses of workers exposed to low cadmium levels still report an increased lung cancer risk associated with cadmium exposure.

- A 2006 Belgium prospective population-based study in environmentally polluted areas provides additional support for lung cancer risks following airborne cadmium exposure *(105)*.

- A wide range of studies suggest an association between cadmium exposure and prostate cancer risk, including occupational cohorts exposed to cadmium, studies of residents in cadmium-contaminated areas, case–control studies of individuals with prostate cancer, but the results are inconsistent.

- Case–control studies suggest that dietary or respiratory cadmium exposure might be associated with increased risks of cancer of the bladder, breast, endometrium and kidney.

A 2014 review concluded that some (but not all) recent data suggest an association with certain cancer types (bladder, breast, endometrial, lung, kidney), even at the low dietary cadmium exposures experienced by the general population *(78)*. The association is independent of smoking status. The review highlights the important risk of lung and estrogen-dependent cancers.

Supportive evidence for cadmium exposure as a lung cancer risk factor comes from a 2022 longitudinal cohort study that assessed cadmium urinary levels in both the general population and cancer patients *(106)*. The geographical area included townships of Yunlin County (Taiwan, China) that were either 0–30 km or > 30 km from a petrochemical complex. Participants residing near the petrochemical industrial area with higher air cadmium concentration had higher urinary cadmium levels. After adjusting for sociodemographic and behavioural factors, tobacco smoking and air pollution remained potential sources of cadmium exposure. An increased prevalence of lung cancer was found in the highly polluted zone (cadmium concentration: 0.0117 ± 0.0060 µg/m^3). Participants with higher urinary cadmium had a higher risk of lung cancer incidence, and lung cancer patients with higher urinary cadmium levels had a significantly lower survival rate.

A3.5 Information on causality and related evaluations

Table A3.1 summarizes the available information linking cadmium exposure to health effects, such as carcinogenicity and damage to the bones and kidneys, as assessed by the European Commission, IARC, US EPA and WHO.

Table A3.1 Information on causality by inhalation exposure to cadmium

Authoritative body	Air pollutant	Causality	Notes
IARC (1993 (original evaluation), 2012 (most recent evaluation)) *(1,107)*	Cd and Cd compounds	Carcinogenic to humans (Group 1)	Sufficient evidence in humans for carcinogenicity of Cd and Cd compounds Cd and Cd compounds cause lung cancer Positive associations have been observed between exposure to Cd and Cd compounds and cancer of the kidney and prostate Sufficient evidence in experimental animal for the carcinogenicity of Cd compounds Limited evidence in experimental animals for the carcinogenicity of Cd metal
WHO Regional Office for Europe (2000, 2007, 2013) *(7,20,21)*	Cd	Concomitant exposure to arsenic complicated the classification of Cd as carcinogenic	–
		Kidney damage	–
		Damage to bone tissue (osteomalacia and osteoporosis)	–
US EPA (1999) *(108)*	Cd and Cd compounds	Probable human carcinogen with limited human evidence (Classification B1)	–
EC (2001) *(4)*	Cadmium chloride, oxide and sulfate	Should be regarded as carcinogenic to humans (Classification 2)	The importance of Cd as a carcinogen at environmental concentrations is not generally accepted. The concomitant exposure of arsenic with Cd in the induction of lung cancer is one of the reasons for disagreement

Authoritative body	Air pollutant	Causality	Notes
	Cadmium sulfide	Possible carcinogenic effects may lead to a cause of concern for humans, but available information precludes making a satisfactory assessment (Classification 3)	

EC: European Commission.

A3.6 Health-based evaluations and regulatory numbers from authoritative bodies

Table A3.2 presents the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect human health from cadmium exposure.

Table A3.2 Health-based evaluations and regulatory numbers for total airborne cadmium from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/ limit value
Worldwide	WHO Regional Office for Europe (2000) (7)	Carcinogenicity (lung)	–	Guideline value is based on effects other than cancer: 5 ng/m³ (annual mean). The guideline value aims to prevent increased deposition of airborne Cd in agricultural soils, which is likely to increase dietary intake for future generations
Worldwide	JECFA (2011) (109)	Effects on β2-M excretion level	Point estimate for the break point for elevated β2-M: 5.2 µg/g creatinine for urinary Cd concentrations This was transformed to a dietary intake of 0.8 µg/kg/day	–

Table A3.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
United States	US EPA (1985) [110]	NIOSH study assessed by Thun et al. [111]	Inhalation URF: 1.8×10^{-3} Increased lifetime cancer risks by no more than 1:10 000, 1:100 000 and 1:1 000 000 were estimated to be related to lifetime exposures to airborne Cd of 60 ng/m³, 6 ng/m³ and 0.6 ng/m³, respectively	–
United States	NIOSH (1997) [112]	–	–	Occupational exposure: • IDLH for dust or fume: 9 mg/m³
United States	OSHA (2004) [113]	–	–	Occupational exposure: • PEL-TWA: 5 µg/m³
United States	ACGIH (1999) [114]	–	–	Occupational exposure (8-h average) • TLV-TWA: 0.01 mg/m³ for dusts • TLV-TWA: 2 µg/m³ for respirable dusts
United States	ATSDR (2012) [115,116]	Effects on β2-M excretion level	MRL: 10 ng/m³	–
United States (California)	OEHHA (1997, 2000) [117,118]	Based on kidney and respiratory effects in humans	Occupational exposure: • chronic REL: 10 ng Cd/m³	–
United States (Texas)	TCEQ (2016) [119] (based on Hannay [120])	Excess lung cancer mortality in a key epidemiological study of Cd smelter workers ([121] – an update of the [111] cohort that was previously used by US EPA to derive a URF [110])	Inhalation URF: 4.9×10^{-4} per µg Cd/m³ Corresponding lifetime air concentration at the 1 in 100 000 no significant excess risk level is 20 ng Cd/m³	–

Table A3.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
EU	EC (2001) *(4)*	–	–	Concentration limit value: 5 ng/m^3 for the total Cd content in airborne dust (value is calculated to prevent renal damage and limit the excess lifetime cancer risk to not more than 1 in 1 million) Deposition limit value: 2.5–5 µg/m^2/day for Cd deposition in urban and industrialized areas
EU	EU (2005) *(122)*	–	–	Target value: 5 ng/m^3 (annual mean)
EU	EFSA (2009) *(123)*	Effects on the β2-M excretion level Effects on bone	Critical Cd concentration in urine: • 1 µg Cd/g creatinine • 0.5 µg Cd/g creatinine	–
France	ANSES (2017) (124)	Risk of osteoporosis or bone fractures (68,69)	TDI: 0.35 µg Cd/kg body weight/day TWI: 2.45 µg Cd/kg body weight/week TDI (or TWI) compatible with a urinary Cd concentration not exceeding 0.5 µg Cd/g creatinine in a 60-year-old adult, assuming that ingestion is the only source of Cd exposure (PBPK modelling)	–

β2-M: beta-2 microglobulin; ACGIH: American Conference of Governmental Industrial Hygienists; bw: body weight; EC: European Commission; EFSA: European Food Safety Authority; IDLH: immediately dangerous to life or health; JECFA: Joint Food and Agriculture Organization of the United Nations/WHO Expert Committee on Food Additives; MRL: minimal risk level; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PBPK: physiologically based pharmacokinetic; PEL-TWA: permissible exposure limit expressed as a time-weighted average; TCEQ: Texas Commission on Environmental Quality; TDI: tolerable daily intake; TLV-TWA: threshold limit value expressed as a time-weighted average; TWI: tolerable weekly intake.

Notes: MRL is defined as an estimate of daily human exposure to a substance that is likely to be without appreciable risk of adverse effects (other than cancer) over a specified duration of exposure *(125)*. PEL-TWA is defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h working day or 40-h working week *(126,127)*. TLV-TWA is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime, expressed as a time-weighted average *(114)*. URF is defined as the additional lifetime cancer risk in a hypothetical population after a lifetime exposure to Cd compounds of 1 µg/m^3 *(7)*.

A3.7 Future research needs

The following research needs have been identified upon reviewing the available scientific evidence.

- Recent studies suggesting that low levels of cadmium exposure may increase the risk of atherosclerosis and CVD (including mortality from CVD) in the general population call for further epidemiological studies. These should appropriately account for confounding by smoking and include a greater focus on never smokers. Further studies should also investigate developmental effects including prenatal outcomes and neurocognitive developmental effects.

- Epidemiological work should be supported by experimental studies to place the associations observed into causal pathways relevant to disease etiology, progression or exacerbation.

- Health risk assessment of cadmium should consider non-renal effects (e.g. on bone, cancer, CVD) rather than increased urinary protein excretion, given that the former are more important for public health.

A3.8 Concluding remarks

The following points should be considered in decision-making on whether current WHO air quality guidelines for cadmium should be updated.

- Cadmium is a highly ubiquitous trace metal that, owing to its toxicity (nephropathy, bone diseases, reproductive disorders and an increased risk of cancer), persistence in the environment and bioaccumulation in organisms, is considered of great concern to human health.

- The 2000 WHO *Air quality guidelines for Europe* limiting cadmium levels in air aims to reduce airborne cadmium deposition onto soil to prevent a further increase in dietary intake – the dominant exposure route *(7)*.

- This rationale is supported by the fact that average cadmium concentrations in the renal cortex in the general population in Europe (15–40 mg/kg) are similar to those observed for renal effects. Although inhalation is a minor component of total exposure, levels in ambient air contribute to cadmium deposition in soil and, therefore, affect dietary intake.

- The need to reduce cadmium airborne emissions to limit of cadmium input into soil has been reiterated since the 2000 WHO *Air quality guidelines for Europe (7)* were set in view of the narrow margin of safety for adverse effects on kidneys and bone *(20,21)*.

- Furthermore, the cadmium input into agricultural soils in Europe is larger than the output, which had prompted suggestions that cadmium intake will not decrease *(20)* and that current air concentrations of cadmium are too high to reach equilibrium in soil (i.e. the present AQG level for cadmium is not sufficient to reduce cadmium deposition) *(21,77)*.

- The most up-to-date evidence on the possible public health impact of long-term cadmium exposure in the general population goes beyond effects on bones and kidneys, and now includes cancer (especially hormone-related) and CVD.

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Annex 4. Evidence overview on lead

Contents

A4.1 Exposure risk assessment

A4.1.1 Characteristics, sources and environmental occurrence

Lead (chemical symbol, Pb; atomic number, 82; relative atomic mass, 207.20; CAS Registry Number 7439-92-1) is a bluish-grey, lustrous, highly malleable, dense and ductile metal in Group 14 of the periodic table. In nature, lead mainly occurs as a compound in oxidation states +2 and +4, and only very rarely in its pure metallic form. Lead has four stable isotopes: lead-204, lead-206, lead-207 and lead-208. Three of these are stable decay products of three naturally radioactive elements: lead-206 from uranium, lead-207 from actinium and lead-208 from thorium *(1)*.

Lead has a number of distinct properties that make it useful for a wide range of applications *(2)* such as in storage batteries (e.g. for solar power, motor vehicles and uninterrupted power supplies). Lead is also used in ammunition, ionizing radiation shielding systems, and tank and pipe linings *(3)*. Metallic lead is found in many alloys, including brass, bronze, solder, speciality steel and type metal. Enamel, glass, glazes, paint, pigment, plastic and rubber compounds all contain inorganic lead salts *(3)*. Lead has also been used in cosmetics and traditional medicines *(4)*.

Lead is a toxic metal that occurs naturally in the earth's crust *(5)*. It is also found in trace amounts in all biological materials, including animals, plants, soil and water *(6)*. The lead concentration is 24 000 ppmw[28] in lead and zinc ores, 11 000 ppmw in copper ores, 20 ppmw in wood, 6.60 ppmw in gold ores, 3–111 ppmw in bituminous coal, 0.31 ppmw crude oil and 1 ppmw in No. 6 fuel oil *(7)*.

Approximately 98% of lead that enters the environment and atmosphere is caused by anthropogenic activities such as mining and smelting, recycling and disposal of waste materials, fossil fuel combustion, and land application of fertilizer *(8,9)*. In the United States, lead emissions estimates have predominantly been associated with piston engine aircraft (590 tons[29]/year), followed by fuel combustion (224 tons/year), metal working and mining (149 tons/year) and other sources such as industry (totalling 244 tons/year) *(10)*. The main contributor in the 1970s was vehicle emissions owing to the use of lead as an antiknock agent in petrol, which has now been banned thanks to public health regulations. Lead emissions from metal processing industries have reduced 10-fold since the 1970s owing to implementation of the best-available technologies in the industry *(10)*. In Europe, about 57% of lead emissions are released by the industry production sector, with each of the other sectors contributing a maximum of about 14%. Road transport (leaded petrol) only contributes 14% *(11)*. There has been a 51% reduction in lead emissions in 2020 compared with 2005 *(12)*. Informal recycling of electronic waste has recently become a significant localized source of lead to the environment, especially in developing countries *(13–16)*.

Environmental lead can also come from dry deposition of airborne lead, as well as from the peeling of lead-based paint from buildings and other structures *(17)*. The DustSafe project (also known as the 360 Dust Analysis *(18)*) is the first international study to apply a standardized method to dust collection, analysis, source identification and health risk calculation across 35 countries. Lead in dust can also be found in wind-blown soil *(19)*.

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[28]   Parts per million by weight.
[29]   United States ton, or short ton, equivalent to 0.907 metric tonnes (t).

A4.1.2 Environmental levels

Lead in air is adsorbed onto the surface of or internally mixed within the core of $PM_{2.5}$. These particles can be transported in the atmosphere by wind and air currents until they are removed by wet or dry deposition. The atmospheric residence time of lead-rich particulates depends on the particle size, meteorological conditions and the operating conditions of the industrial process responsible for its release [20].

Lead concentrations in the atmosphere vary greatly, and decrease with the vertical and horizontal distance from emission sources. Indoor concentrations are approximately 0.3–0.8 times (mean ratio: 0.5) lower than ambient concentrations. Lead levels in the Antarctic atmosphere range from 5–60 pg/m³ in remote areas [21] to 800 pg/m³ in remote islands [22]. In urban areas in China, concentrations were 137 ng/m³ (measured in $PM_{2.5}$) [23], and in the United States were from 11–32 ng/m³ (measured in total suspended PM) in urban areas [10] and 30 ng/m³ (measured in total suspended PM) near stationary sources such as a large steelwork site near a motorway [24].

The lead level in the air has decreased significantly in the last few decades due to reductions in lead emissions from vehicles (leaded petrol is now banned in most countries) [25]. According to the US EPA National Air Quality Monitoring Program, by 2002 the mean atmospheric lead concentration (< 0.05 µg/m³) was approximately 94% lower than in the early 1980s [26].

In 2021 the mean airborne lead concentration in the United States was 30 ng/m³ [27]. In Europe, lead concentrations in air have decreased since the mid-1970s, from levels as high as 3000 ng/m³ (measured in Brussels) in 1976 to as low as 10 ng/m³ in 2007 [28]. Since 2000, airborne lead concentrations measured in EMEP stations have decreased by 76% [11]. In 2020 the mean annual lead concentrations ranged from 0.3 ng/m³ to over 20 ng/m³. The lowest levels were measured in the northern part of the EMEP region (Iceland, northern Russian Federation, Scandinavian peninsula), whereas central Europe is characterized by the highest spatial mean concentrations (about 4.5 ng/m³), followed by western Europe [11]. In Asia, the concentration range is 14–854 ng/m³ [29]. A study conducted in Egypt showed declining concentrations since the late 1990s, from as high as 26 µg/m³ to 0.3 µg/m³ (300 ng/m³) in 2007 [30].

Lead concentrations measured in blood have also declined over time, although not at the same rate as those measured in air [31].

A4.1.3 Human exposure

Inhalation and ingestion are the two most common routes of lead exposure in humans, with lead exposure through dermal contact reported infrequently [5,32]. Lead particles are also inhaled when lead-containing materials are burned, such as in smelting and recycling, stripping leaded paint, and using leaded aviation fuel [5]. Inhalation of lead as particles or fumes is a common occupational route of exposure. Inhalation may also occur in the home if there is lead-contaminated airborne dust, such as when old paint is being stripped [33].

Personal exposure in the general population was measured in several French cities: exposure levels of 15 ± 24 ng Pb/m³ were measured in PM_{10} [34]. Another study conducted in Windsor (Canada) found a median personal exposure level of 138 µg Pb/g PM_{10} [35]. It also compared the lead content of $PM_{2.5}$ versus PM_{10} and found that most lead was present in $PM_{2.5}$. A Swiss study reported personal exposures of lead in $PM_{2.5}$ of 23 ± 11 ng/m³ (range: 5–60 ng/m³) [36]. A study conducted in Jinhua (Zhejiang Province, China), whose main economic activity is the production of metal products and medicine, reported personal exposure concentrations of 28 ± 18 ng Pb/m³ (range: 2.9–103 ng Pb/m³) [37].

Children are especially vulnerable to lead exposure through eating lead-contaminated dust or soil, whereas the most common sources of lead exposure in adults are reported to be occupational (38–40). Lead inhalation may occur at high levels in industries that involve lead smelting, welding, soldering and cutting; refining industries; battery, rubber and plastic manufacturing plants; printing industries; firing ranges; and radiator repair shops (32,41,42). Lead inhalation may affect workers in the construction and demolition industries, painters, and municipal waste incinerators, as well as in pottery and ceramics industries that use lead solder (32).

Since lead is a component of tobacco, smokers frequently have higher lead blood levels than non-smokers (43). Tobacco smoking was found to correlate with lead exposure levels (44).

Elevated lead levels were measured in hair of children living near electronic waste facilities compared with children living in non-exposed areas (0.155 ± 0.187 mg Pb/g hair vs 0.0729 ± 0.08 mg Pb/g hair), suggesting that informal recycling of electronic waste is a source of chronic exposure to lead (14).

A4.1.4 Absorption, distribution, metabolism and excretion

Absorption of lead particles and fumes by inhalation is affected by particle size and concentration and by ventilation rate (45). Children are at a higher risk of lead exposure and subsequent absorption in the body for a combination of reasons, including increased hand-to-mouth activities and poor hygiene, and because they eat and drink more per unit body weight compared with adults. Nutritional differences between children and adults such as iron and vitamin D deficiencies in children, as well as a less developed blood–brain barrier in children, increases lead absorption in children. In addition, children breathe in more air per unit of body weight than adults, which increases their susceptibility to lead absorption (5).

Smaller lead particles (< 1 μm in diameter) are deposited in the lower respiratory tract, where they are almost entirely absorbed, whereas larger particles (1–10 μm in diameter) are likely to be deposited in the upper airways, from where they are transferred by the mucociliary system to the oesophagus and then swallowed (45).

Lead first binds to erythrocytes in the blood before being distributed to soft tissues and bones: the active pool is found in blood and soft tissues, whereas the storage pool is found in bones (41). In adults, the soft tissues with the highest lead concentrations are the liver and kidney cortex (46). In adults, the bones absorb approximately 94% of the total body burden of lead, whereas bones in children absorb approximately 73%. However, pregnancy, lactation, menopause and osteoporosis increase bone resorption and, consequently, lead levels in the blood (47). Fetal lead exposure is associated with vertical transmission from the mother (48), and there is evidence of lead transmission from mother to infant via breast milk (49).

Inorganic lead is not metabolized. Instead it can be found in plasma in four states: bound reversibly to proteins, such as albumin; complexed to amino acids, carboxylic acids and sulfhydryl compounds, such as cysteine, homocysteine; tightly bound to metalloproteins; and in free form as Pb(II) (32,50). Organic lead compounds metabolize to inorganic lead. Cytochrome P-450 oxidatively dealkylate alkyllead compounds such as tetraethyllead and tetramethyllead to form highly neurotoxic triethyllead and trimethyllead compounds (32,41).

Regardless of the exposure route, lead is primarily excreted in urine and faeces. Minor excretory pathways involve keratin-rich tissues such as hair and nails, as well as breast milk, saliva and seminal fluid, sweat. Lead elimination is multiphasic, reflecting the varying retention times of lead pools in the body. The apparent elimination half-time in blood varies with age and exposure history from 1 week to 2 years. Lead elimination from bones occurs over a period of one to two decades (51).

A4.2 Toxicological studies

A4.2.1 Laboratory animals: short-term effects

In rats, lead exposure has short-term effects on the male reproductive system via dose-dependent changes in the activity of alkaline phosphatase and Na (+)–K (+)-ATPase *(52)*. Higher lead doses result in a complete halt of spermatogenesis, a significant decrease in the germ cell layer, and disrupted histoarchitecture of the caput and corpus regions in the testes. However, lead poisoning of Sprague-Dawley rats via respiratory routes indicated a nonlinear relationship between the lead concentration and lead isotope ratios in blood *(53)*.

A4.2.2 Laboratory animals: long-term effects

A4.2.2.1 Reproductive system

Lead has a direct effect on fetal development *(54,55)*. Monkeys exposed to lead had lower levels of plasma luteinizing hormone after stimulation with gonadotropin-releasing hormone and a reduced inhibin : follicle-stimulating hormone ratio compared with controls *(56)*.

A4.2.2.2 Endocrine system

Rats treated with a lead dose of 30 mg/kg body weight had significantly lower serum levels of thyroid hormones (triiodothyronine, thyroxine and thyroid-stimulating hormone) compared with controls, and histopathological findings revealed enlarged thyroid follicles with flattened epithelium *(57)*.

A4.2.2.3 Haematopoietic system

Lead toxicity reduced total haemoglobin, red blood cell count, and plasma triiodothyronine and thyroxine levels without significantly affecting the white blood cell count *(58)*. Another study in female rats found that oral administration of lead acetate (10 mg/kg body weight) significantly reduced the haemoglobin concentration, mean corpuscular haemoglobin concentration, red blood cell count and packed cell volume, while increasing the percentage of monocytes, mean corpuscular volume, total protein level and white blood cell count *(59)*.

A4.2.2.4 Cardiovascular system

Lead ingestion induced hypertension in young Sprague-Dawley rats associated with decreased levels of nitric oxide *(60)*, which (i) downregulates soluble guanylate cyclase (which synthesizes cyclic guanosine monophosphate, a vasodilator), (ii) regulates blood pressure and (iii) modulates the adrenergic system (i.e. by increasing plasma norepinephrine levels, reducing vascular β-adrenergic receptor density, and increasing central sympathetic nervous system activity) *(32)*.

In rats, lead acetate ingestion (15 mg/kg body weight) increased the activity of serum glutamate oxaloacetate transaminase and lactate dehydrogenase, with evidence of heart damage *(60)*.

A4.2.2.5 Renal system and liver

In female rats, increased urea and creatinine concentrations were observed after lead acetate administration compared with other experimental groups *(61)*. Increased lipid peroxidation in the kidneys of lead-exposed animals has also been reported *(61,62)*.

In rats, lipid peroxidation is the most important pathway for lead-induced oxidative stress in the liver *(63)*. Lipid peroxidation alters plasma membrane integrity and fatty acid composition and is associated with elevated malondialdehyde concentrations in the liver tissue. Lead-induced oxidative stress correlates with mitogen-activated protein kinase activity and apoptosis levels in rat hepatocytes *(62)*.

Evidence suggests that renal lipid peroxidation might increase following intraperitoneal injection of 20 mg lead-acetate/kg body weight per day for 5 days or of 5 mg/kg body weight per day for 30 days *(64)*. Prolonged lead exposure was associated with free radical generation and lipid peroxidation in the kidney, followed by loss of membrane integrity and inactivation of tubular cell constituents.

A4.2.2.6 Neurological system

Negative neurological effects reported in rats after lead acetate administration include reduced vitality, muscle mass (leading to muscle weakness), tremors, lack of stability and equilibrium, and abnormal gait *(65)*. Lead exposure is associated with increased expression of glial fibrillary acidic protein, a critical event in astrocyte differentiation *(66,67)*. After administration, lead acetate can be detected in the cerebellum, where it causes physiological alterations, along with neurotoxicity, cellular deterioration and, possibly, cell death *(68)*.

A4.2.3 Oxidative stress damage

Lead at low to high doses induces oxidative stress affecting various target sites, including sperm *(69)*. Rat sperm exposed to reactive oxygen species (ROS) in vitro underwent an early acrosome reaction and had a reduced penetration rate for zona-intact ova *(69)*.

Organic lead accumulation in the liver was associated with oxidative imbalance and protein impairment, resulting in endoplasmic reticulum stress and liver injury *(70)*. Lead exposure is associated with suppression of osteoblastogenesis and altered progenitor cell differentiation, which promoted osteoclastogenesis and increased adipogenesis. Similarly, lead and non-esterified fatty acids levels were associated with increased peroxisome proliferator-activated receptor gamma (PPAR-γ) activity and β-catenin inhibition in a mouse MC3T3 cell model *(71)*.

A4.3 Epidemiological studies

Humans are mainly exposed to lead through the inhalation of lead in air and ingestion of lead in foods and beverages *(39)*. The reduction in the lead content of petrol from 0.7–0.8 g/L to < 0.15 g/L, as well as the use of lead-free petrol required by cars with catalytic converters between 1975 and 1985, has significantly reduced the distribution of lead in ambient air *(72)*. In the United Kingdom, levels of lead in the air decreased by 97% between 1980 and 2010 *(73)*. In the United States, lead levels decreased by 88% between 2010 and 2022 *(27)*. Lead concentrations declined by 99% in northwestern Europe, from 3 µg/m³ in the 1970s to 0.01 µg/m³ in recent years *(28)*, with a similar decline in most cities in China between 2011 and 2019 *(74)*.

Regulatory standards take into account associations between lead levels in ambient air and in blood. For example, US EPA standards are based on the assumption that a blood lead level of 0.15 g/mL (mean value for children) can be achieved at a level of 1.5 g Pb/m³ ambient air *(75)*.

A4.3.1 Short-term effects

Health complications can develop after acute exposure to high lead levels. Modes of action in humans include protein binding, oxidative stress, inflammation, endocrine disruption, cell death and genotoxicity *(3)*. In the short term, high lead levels can cause anaemia, muscle weakness, and kidney and brain damage. Excessive lead exposure can be fatal *(76)*.

A4.3.2 Long-term effects

Most epidemiological research has focused on the effects of lead on various organ systems, in particular on haematological, cardiovascular, renal and neural toxicities. However, the effects are reported to be widespread.

A4.3.2.1 Respiratory system

Epidemiological studies have shown an association between lead exposure and asthma *(77)*. A study on kindergarten children showed a positive association between lead exposure and both blood immunoglobulin E levels and asthma in boys *(3)*. A review of observational and experimental studies suggested that lead might be a factor in asthma development through inducing oxidative stress levels and altering immune and inflammatory responses *(78)*.

Lead exposure is reported to be associated with an increased frequency of respiratory symptoms and higher serum and urinary lead concentration, but lower pulmonary function test findings in lead-exposed workers compared with controls *(79)*. A study on blood lead levels and other clinical variables associated with COPD did not find an independent association between blood lead and COPD after controlling for age, male sex, smoking, occupation and education level *(80)*. This might be explained by lead ingestion through tobacco smoking, which is a strong predictor of COPD.

A4.3.2.2 Cardiovascular system

Studies have linked lead exposure to an increased risk of CVD and cardiovascular conditions such as hypertension, ischaemic heart disease and stroke *(45,81,82)*. Since these conditions have a long latency period, they are likely to be influenced by lead exposure in early years *(45)*. A systematic review concluded that there is sufficient evidence to infer a causal relationship between lead exposure and hypertension *(83)*. It also found that current occupational safety standards for blood lead levels must be reduced and a criterion established for screening elevated lead exposure in adults.

US EPA reported that lead exposure is also linked to changes in cardiac conduction, including increased intraventricular and atrioventricular conduction defects and QRS and QT intervals *(45)*.

A4.3.2.3 Central nervous system

The brain is one of the most sensitive organs to lead exposure *(84)*. Lead exposure affects both the peripheral and central nervous systems. In children, the central nervous system is affected most, whereas in adults it is the peripheral nervous system *(85)*.

Neuronal myelin sheath loss, decreased neuron number, interference with neurotransmission and reduced neuronal growth have been associated with lead poisoning *(86)*. Magnetic resonance imaging showed a reduced brain volume in adults who were exposed to high lead levels as children, particularly in the prefrontal cortex *(84)*.

Neuropsychiatric disorders such as attention deficit hyperactivity disorder and antisocial behaviour have been observed in children with higher lead exposure levels *(39)*. Moreover, prenatal and early childhood lead exposure correlate with committing violent crimes in adulthood *(87)*.

A large-cohort study of former organolead manufacturing workers (*n* = 535; mean period after workplace exposure: 16 years) supported a causal association between lead and dementia *(88)*. The study found elevated lead levels in bone and dose-related deficits in verbal and visual memory, executive ability and manual dexterity. A greater rate of decline in cognitive function (measured annually) was found in tetraethyllead workers compared with controls.

Lead exposure is also associated with permanent brain damage and even death at higher exposure levels *(5)*.

A general decline in lead pollution has enabled recent studies to include more cohorts with blood lead levels of < 100 µg/L. The evidence derived from these studies reinforces previous findings of a critical effect these lead exposure levels, particularly in utero and during early childhood, on the central nervous system, including on concentration, cognitive function, behaviour, attentiveness and IQ *(31,84)*.

The blood lead level at age 7 years (but not the peak level at age 2 years) had a direct effect on behavioural symptoms, externalizing behaviour and school problems at age 7 years *(89)*. Similarly, children aged 5.5 years and with greater lead exposure, as indicated by blood lead level (mean: 7.2 µg/dL; range: 0–20 µg/dL), performed more poorly on tests of executive processes *(90)*. An Italian study found a significant inverse association between blood lead concentration and IQ, with an extrapolated decline of 1.29 IQ points per µg/dL increase in lead blood concentration in a population of children (13–16 years old) with a mean blood lead concentration of below 10 µg/dL *(91)*. Similar results were reported for a group of children aged 6 months–6 years. Lifetime average blood lead concentration (mean: 7.2 µg/dL) was inversely associated with full-scale IQ and performance IQ, with a decline of 4.9 points in full-scale IQ in children with blood levels of 5–9.9 µg/dL *(92)*. An international pool analysis of children participating in population-based longitudinal cohort studies found that in children followed from infancy up to 5–10 years of age an IQ point decrement of 6.9 (95% CI: 4.2–9.4) was associated with an increase in concurrent blood lead levels from 2.4 µg/dL to 30 µg/dL *(93)*.

Prenatal lead exposure (at gestation week 28) was also related to reduced intellectual development in a cohort of children from Mexico City *(94)*. IQ at 6–10 years decreased significantly with increasing maternal blood lead concentrations (natural log) in the third trimester (β: −3.90; 95% CI: −6.45 to −1.36). Further studies on the same cohort show that a twofold increase in cord blood lead (e.g. from 5 µg/dL to 10 µg/dL) was associated with a 3.1-point decrement in the mental development score *(95)*. Similar results were found for maternal plasma lead concentrations in the same cohort *(96)*.

Lead blood levels were also associated with attention deficit hyperactivity disorder and conduct disorders in the United States National Health and Nutrition Examination Survey (NHANES) 2001–2004 *(97)* and in Romania *(98)*.

Lead concentration in hair (marker of chronic exposure) was also associated with poorer scores for attention, executive function, mental flexibility and cognitive efficiency in a cohort of adults (34 ± 15 years old) in the Middle East *(99)*.

A4.3.2.4 Haematological system

Lead may directly affect the haematopoietic system by inhibiting haemoglobin synthesis, as well as several key enzymes in the heme synthesis pathway *(4)*. In addition, lead exposure could shorten the life of circulating erythrocytes by increasing cell membrane fragility. Interaction of these two processes could result in anaemia *(100)*. This effect is commonly seen in children, with iron deficiency as an additional risk factor *(4)*.

A4.3.2.5 Reproductive system and development

Pregnant women with elevated blood lead levels are at a risk of giving birth prematurely or delivering babies with a low birth weight. Detrimental effects in the fetus may occur at blood lead concentrations well below 25µg/dL *(101)*. In blood collected from the neonate and mother at the same time, lead levels were higher in the baby *(102)*.

Lead affects both the male and female reproductive systems *(39,103)*. In men, blood lead levels exceeding 40 g/dL reduce the sperm count, induce changes in sperm volume, and affect sperm motility and morphology *(104)*. In pregnant women, toxic levels of lead can cause miscarriage, premature birth, low birth weight, and developmental problems in their children *(84)*.

An epidemiological study on male reproduction found a link between lead levels in seminal plasma and ROS levels in spermatozoa *(105)*. Increased superoxide dismutase activity was measured in people with prolonged lead exposure, suggesting a mechanism for increased ROS production caused by lead exposure *(43)*. Elevated ROS levels could result in oxidative damage to reproductive tissues.

Delayed menarche and pubic hair development, but not breast development, was associated with higher blood lead levels in the third NHANES (1988–1994). The odds ratios for delayed menarche fell from 1 to 0.42 to 0.19 with blood levels of 7–20 µg/L, 21–49 µg/L and 50–217 µg/L, respectively. The influence on pubic hair development was similar *(106)*. Blood lead levels of 3 µg/L influenced height and were also associated with delayed breast development (by 2.1–5.8 months), pubic hair development (by 2.2–6.0 months) and menarche (by 3.6 months) in the same cohort when adjusting for ethnic background *(107)*. Similar results were reported in Russian boys: in boys with blood lead levels of ≥ 5 µg/dL, the odds of having entered puberty were reduced by 43% compared with those with lower levels (odds ratio: 0.57; 95% CI: 0.34–0.95; $P = 0.03$) *(108)*.

A4.3.2.6 Renal system

Low environmental lead levels are associated with accelerated deterioration in renal function in people with chronic renal insufficiency. Exposure to high (> 60 µg/dL) or even low (~10 µg/dL) lead levels may cause renal dysfunction *(109)*. A 1975 study reported that excessive occupational lead exposure was associated with renal dysfunction *(110)*, as indicated by biopsy assessment of tubular dysfunction. Consequently, the study suggested that lead nephropathy may be an important occupational hazard.

Urate excretion was also reported after lead poisoning, suggesting that it causes gout, a condition in which urate builds up in the body *(111)*. Chronic lead nephropathy can develop after chronic lead exposure, as indicated by moderate focal atrophy, loss of proximal tubules and interstitial fibrosis in renal biopsy samples *(112)*.

A4.3.2.7 Musculoskeletal system

Bones are the primary site of lead storage in the human body. In adults, bones store approximately 85–95% of the lead, whereas in children, approximately 70% of lead is concentrated in soft tissues. Lead mobilization and storage in bones depends on lead exposure levels, age and ethnicity. During pregnancy, the gestation stage and dose of lead exposure are also important factors. Studies found that in adults bones are a reservoir for approximately 40–70% of the lead that is eventually discharged in the blood *(113)*.

In exposed rats, lead acetate caused moderate hyperplasia of hemopoietic tissue with megakaryocyte proliferation and the presence of thin trabeculae of calcified cartilage covered by a thin layer of bone *(58)*. In addition, mineralized cartilage bars caused by impaired osteoclast resorption were wider and projected further into the metaphyseal marrow cavity compared with normal healthy bones.

A study on data on adults older than 60 years from the third United States NHANES (1988–1994) reported a dose–response relationship between exposures to lead with frailty *(114)*.

A4.3.2.8 Immunological system

US EPA reported that prenatal and childhood lead exposure may be linked to an increased risk of allergic conditions such as asthma *(45)*. However, there is little evidence for these claims because there have not been many studies on the topic in either humans or animals.

A4.3.2.9 Carcinogenicity

IARC has classified lead as a Group 2A carcinogen (probably carcinogenic to humans) *(115)*. This classification is based on an evaluation of five occupational cohort studies of highly exposed workers from battery plants in the United States and the United Kingdom, as well as primary smelter workers in Italy, Sweden and the United States *(115)*.

Although data linking lead to human cancers is limited, many positive epidemiological studies have found an association between lead exposure and specific cancers. For example, occupational lead exposure was associated with brain. kidney and lung cancer *(116)*. Occupational exposure to inorganic lead in the printing industry is also associated with kidney and pancreatic cancer mortality *(117)*. Lead exposure was also associated with an increased incidence of breast cancer in Nigeria *(118)*.

Recent epidemiological studies have continued to investigate the association between lead exposure and specific types of cancer. Analyses of cancer incidence in two separate cohorts from Finland and the United Kingdom reported strong positive incidence trends for brain, lung, and rectal cancer with increasing blood lead level *(119)*.

A 2022 Finnish study examined whether occupational lead exposure increases the risk of lung cancer *(120)*. The study population worked in the lead battery industry, lead smelting, metal foundries, railroad machine shops and chemical manufacturing. In these workers, blood lead concentrations were monitored during 1973–1983. Among those who worked in these industries for over 60 months, the hazard ratio was 1.72 (95%CI: 1.28–2.31) in those with a mean blood lead level of 1.0–1.9 µmol/L and 2.63 (95% CI: 1.71–4.05) in those with a mean blood lead level of ≥ 2.0 µmol/L compared with the reference level of < 0.5 µmol/L.

A4.4 Information on causality and related evaluations

Table A4.1 summarizes the information available linking exposure to lead and health effects by the European Commission, IARC, US EPA and WHO.

Table A4.1 Information on causality by inhalation exposure to lead compounds

Authoritative body	Causality	Notes
IARC (2006) *(115)*	Pb and inorganic Pb compounds are possibly carcinogenic to humans (Group 2B)	Sufficient evidence that inorganic Pb compounds cause cancer in experimental animals Inadequate evidence in epidemiological studies for the carcinogenicity of inorganic Pb compounds
WHO Regional Office for Europe (2000) *(121)*	Effects on the auditory, endocrine, haematological and nervous systems	Impaired hearing and disturbed vitamin D metabolism in children Elevated free erythrocyte protoporphyrin in adults and cognitive deficits in adults and children
US EPA (2013) *(45)*	Nervous system effects in children and adults In adults: • cardiovascular system effects • immune system effects • haematological effect • reproductive and developmental effects • cancer	Causal relationship: • cognitive function decrements in children • externalizing behaviours – attention, impulsivity and hyperactivity in children • coronary heart disease • decreased red blood cell number and function • altered heme synthesis • development • male reproductive function Likely causal relationship: • externalizing behaviours – conduct disorders in children and young adults • internalizing behaviours in children • auditory function decrements in children • motor function decrements in children • cognitive function decrements in adults • psychopathological effects in adults • atopic and inflammatory responses • decreased host resistancea • cancer
German Research Foundation (2007) *(122)*	Classified as category 2 (to be regarded a human carcinogen)	–

a The ability of the host to hinder or arrest the growth and/or development of the pathogen *(123)*.

A4.5 Health-based evaluations and regulatory numbers from authoritative bodies

Table A4.2 presents the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect human health from lead exposure.

Table A4.2 Health-based evaluations and regulatory numbers for lead compounds from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
Worldwide	WHO Regional Office for Europe (2000) (121)	Critical effects include elevated free erythrocyte protoporphyrin in adults and cognitive deficit, disturbed vitamin D metabolism and impaired hearing in children	–	0.5 µg/m^3 (annual)
United States	US EPA (1990) (124)	–	–	0.15 µg/m^3 (3-month average)
United States	NIOSH (2005) (125)	–	Occupational exposure: • REL-TWA: 0.05 mg/m^3 (8-h)	–
United States	OSHA (2016) (126)	–	–	Occupational exposure to metallic Pb, all inorganic Pb compounds (Pb oxides and Pb salts) and a class of organic compounds called soaps: • PEL-TWA: 0.05 mg/m^3
United States	ACGIH (2017) (127)	Confirmed animal carcinogen with unknown relevance to humans	–	Occupational exposure: • TLV-TWA: 0.05 mg/m^3

Table A4.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
United States (California)	OEHHA (2014, 2019) *(128,129)*	REL-A: development (teratogenicity), cardiovascular and nervous systems REL-TWA: development, cardiovascular system, lungs, nervous system, skin	Occupational exposure to Pb (metallic) and inorganic compounds, dust and fume, as Pb: • REL-A: 0.20 µg/m³ • REL-TWA: 0.015 µg/m³	Occupational exposure to Pb (metallic) and inorganic compounds, dust and fume, as Pb: • PEL-TWA: 0.05 mg/m³
EU	EC (2008) *(130)*	Non-cancer effects	–	Limit value: 0.5 µg/m³
United Kingdom	DEFRA (2010) *(131)*	–	–	Air quality objective: 0.25 µg/m³ (annual mean)

ACGIH: American Conference of Governmental Industrial Hygienists; DEFRA: United Kingdom Department for Environment, Food and Rural Affairs; EC: European Commission; NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PEL-TWA: permissible exposure limit expressed as a time-weighted average; REL-A: acute REL; REL-TWA: REL expressed as a time-weighted average; TLV-TWA: threshold limit value expressed as a time-weighted average.

Notes: PEL-TWA is defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h working day or 40-h working week *(132,133)*. TLV-TWA is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime, expressed as a time-weighted average *(134)*.

A4.6 Future research needs

The current global burden of diseases caused by lead exposure is higher than calculated in the cited reports, indicating a knowledge gap. Consequently, more research is needed to determine the global burden of disease caused by lead exposure.

Furthermore, research is needed into the acceptability, feasibility and impact of any intervention to reduce lead poisoning as regards equity and human rights. Programmes are needed to help with policy development and implementation to eliminate lead exposure.

Previous studies have shown an association between lead exposure and CVD effects (i.e. hypertension, ischaemic heart disease and stroke). However, the specific level, timing, frequency and duration of lead exposure associated with CVD effects are not known, which calls for further research.

Most lead studies, whether in animals or humans, have focused on ingestion as the exposure route, with very few on lead inhalation. Consequently, research gaps relate to the contribution of lead inhalation to total lead exposure. More questions remain about links between lead in air, lead biomarkers in the blood, and effects on human health.

A4.7 Concluding remarks

Most health effects of lead in both children and adults occur at blood lead levels significantly lower (as low as 5 g/L) than the recommended levels for an exposed population (100 g/L). In addition, the earliest effects of lead, particularly in children, occur at blood levels of < 100 g/L.

Most human toxicity and epidemiological studies have focused on the effects of lead on the haematological, immune, nervous, renal and reproductive systems. However, a recent review of toxicity and epidemiological studies in humans and animals suggests that lead toxicity may affect even more organ systems.

Regulatory and public health interventions must be developed and implemented to prevent and reduce occupational exposure to lead in the air. Lead inhalation at potentially high levels has been reported in workers in industries such as battery manufacturing; construction; lead smelting, refining and welding; printing; and rubber and plastic manufacturing.

All of these factors, as well as additional research into the timing, frequency and duration of lead exposure in air, should be considered when updating the WHO air guidelines.

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Annex 5. Evidence overview on mercury

Contents

A5.1 Exposure risk assessment

A5.1.1 Characteristics, sources and environmental occurrence

Mercury (chemical symbol, Hg; atomic number, 80; relative atomic mass, 200.59; CAS Registry Number 7439-97-6) is a heavy metal *(1–3)*. It occurs naturally in the environment and exists in a large number of forms, with three possible oxidation states (0, +1 and +2). The properties and behaviour of mercury depend on the oxidation state. Its pure form is known as elemental mercury, which has a valence state of 0 (expressed as Hg^0 or Hg(0)). Mercury is rarely found in nature as a pure, liquid metal but instead within compounds and inorganic salts. Mercury compounds (inorganic and organic) can exist in two oxidation states: mercurous (Hg^+ or Hg(I)) and mercuric (Hg^{2+}, or Hg(II)).[31] Divalent Hg can form both inorganic Hg salts and organomercury compounds, in which the Hg atom is covalently linked to at least one carbon atom. However, the distinction between the three major forms of mercury present in the environment (elemental, inorganic and organic) is generally more important than the oxidation state in determining toxicity. Therefore, this expert consultation classifies mercury into elemental, inorganic and organic mercury.

Elemental mercury (Hg(0)) is usually referred to as mercury vapour when airborne and as metallic mercury when in liquid form. The vapour pressure of Hg(0) metal strongly depends on temperature – it will readily vaporize under ambient conditions *(4)*. The volatility of Hg(0) is without parallel among metals. Saturated air at 20°C contains 14 mg/m³ Hg vapour *(2)*. Mercury vapour exists in the monoatomic state and is both odourless and colourless. It is relatively insoluble in water but is lipophilic and readily dissolves in fatty compartments *(5)*.

Inorganic mercury occurs as monovalent (mercurous) and divalent (mercuric) salts. However, only the divalent form is considered here because mercurous mercury is unstable under environmental and physiological conditions and rapidly dissociates to one molecule of elemental mercury and one ion of mercuric mercury *(4,6)*. The mercuric cation is more stable and is generally associated with inorganic elements, such as chlorine (mercuric chloride), oxygen and sulfur (in the mineral cinnabar), and with hydroxyl ions. Many Hg(II) salts are readily soluble in water, including mercuric acetate and mercuric chloride. In addition, some mercury salts (such as $HgCl_2$) are sufficiently volatile that they can exist as an atmospheric gas *(7)*. In the environment, inorganic mercury is transformed by methylation into organic forms; these are more bioavailable, can bioaccumulate and are more toxic than the inorganic forms *(8)*.

Divalent mercury also forms organomercury compounds (or organomercurials), in which the mercury atom is covalently linked to one or two carbon atoms to form compounds of the type R-Hg-X and R-Hg-R', where R and R' represent an organic moiety and X represents a halogen. The carbon–mercury bond is chemically stable because of the low affinity of mercury for oxygen *(7)* and changes the toxic properties of mercury, especially in monomethylmercury and dimethylmercury *(9)*. A large number of organic mercury (R-Hg) compounds potentially exists (e.g. dimethylmercury, ethylmercury and methylmercury); however, methylmercury is the most common organic mercury compound in the environment. Note that in longer-chain organomercury compounds (e.g. aryl and alkoxyalkylmercury), the carbon–mercury bond is less stable, resulting in Hg(II) release. Short-chain mercury compounds (e.g. methylmercury and dimethylmercury), as well as alkylmercuric halogen salts, are volatile and lipid soluble *(5,7)*.

Mercury has increasingly been mobilized and released into the biosphere since the start of the industrial age. Once released, mercury persists in the environment, where it circulates between air, water, sediments, soil and biota in various forms. Current emissions add to the global pool, in which mercury undergoes a continuous cycle of mobilization, deposition on land and

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[31]   Nomenclature for the three ionization states of mercury: (i) elemental mercury, Hg(0), Hg^0;
       (ii) mercurous mercury, Hg(I), Hg^+; and mercuric mercury, Hg(II), Hg^{2+} *(3)*.

water, and remobilization. Most mercury in the atmosphere exists in the form of elemental mercury vapor. The atmospheric lifetime of elemental mercury is estimated to be approximately 12 months *(4)*, although more recent investigations suggest that it may be significantly shorter due to unaccounted-for chemical reactions in the atmosphere *(10)*. In any case, the atmospheric lifetime is sufficient to allow mercury to be distributed thousands of miles from the likely emission sources *(10)*. Most of the mercury in water, soil, sediments, or plants and animals is in the form of inorganic mercury salts and organic forms of mercury (e.g. methylmercury). Inorganic mercury, either bound to airborne particles or in gaseous form, can be removed from the atmosphere by precipitation (wet deposition) and dry deposition. Wet deposition is the main mechanism that transports mercury from the atmosphere to surface waters and land. After it is deposited, mercury is commonly emitted back to the atmosphere either as a gas or associated with particles, and re-deposited elsewhere. Note that the deposited form of mercury can be converted into methylmercury (mainly via microbial metabolism), which can bioaccumulate in organisms and bioconcentrate within the food chain, especially in aquatic species (fish and marine mammals) *(4)*.

Mercury is a trace element that is released into the environment; it has toxic effects on the environmental and human health, and plays an important role in the chemistry of the atmosphere, soil and water compartments *(11)*. Mercury is a global pollutant with no environmental boundaries; it is released into the environment from both natural and anthropogenic sources and distributed over long distances in the atmosphere and oceans. Consequently, regions with minimal mercury emissions and/or areas far from dense human activity may be adversely affected. For example, high mercury exposures have been reported in the Arctic, far from any significant source of emissions *(12)*. The current natural releases of mercury from soil and water surfaces are significantly influenced by previous mercury depositions from anthropogenic sources. Consequently, the total global anthropogenic and natural release of mercury is not known with precision and is difficult to measure. Based on the available information, natural sources are thought to account for less than 50% of the total release *(10)*.

The main natural processes that release Hg to the atmosphere are volatilization from marine and aquatic environments, volatilization from vegetation, volcanic emissions, degassing of geological materials, and wind-blown dust *(13,14)*. Mercury release to the atmosphere from wind-blown dust, weathering of mercury-containing rocks and abandoned mercury mines may be an important source of environmental mercury. Cinnabar has been known as the principal mercury-containing ore for the last 3000 years. The world's most abundant deposits are in Almadén (Spain), Idrjia (Slovenia) and Monte Amiata (Italy), which have been mined since ancient times for use in extracting gold and silver from ore in Europe and North America *(11)*.

Attempts have been made to predict mercury emissions to the atmosphere from natural sources, but there is considerable uncertainty in the data required to predict total atmospheric emissions due to spatiotemporal variations and incomplete knowledge of the sources, characteristics, spatial extent and temporal variability of emissions *(15)*.

Mercury has had a wide variety of uses based on its unique physicochemical properties (i.e. high specific gravity, low electrical resistance, constant volume of expansion). Consequently, environmental levels of mercury mobilized and released to the atmosphere have increased since pre-industrial times. Anthropogenic sources are the major contributors to mercury releases to the atmosphere. Annual global mercury emissions to air from anthropogenic sources is estimated at approximately 2220 t/year: the main source is artisanal and small-scale mining (> 800 t), followed by stationary combustion of coal (approximately 500 t), non-ferrous metal production (> 300 t), cement production (> 200 t) and waste from mercury-containing products (150 t) *(10)*. Other anthropogenic activities that contribute to environmental mercury levels are vinyl chlorine monomer production, biomass burning, ferrous metal production, chlor-alkali production, waste incineration, oil refining, and stationary combustion of oil and gas, with each contributing between 0.01 t and 0.5 t globally in 2015 *(10)*. These estimates represent emissions from major anthropogenic sectors and include mercury that is re-emitted. Some of these emission sources are more common in specific countries and regions. For example, artisanal small-scale gold mining is a very important mercury source in low-and middle-income countries, but emissions from crematoria and exposure of dental staff to mercury-containing amalgam are of particular concern in Europe and North America. Note that additional emissions in the

order of tens to hundreds of tonnes per year may arise from (generally smaller) anthropogenic sources that are not currently detailed in global inventories, bringing the total estimate up to approximately 2500 t/year *(10)*.

In Europe, the industry production sector is responsible for 47% of total mercury emissions, followed by energy generation industries (35%), mainly coal-fired power plants *(16)*. In the EU, mercury emissions in 2020 were 49% lower than in 2005 *(17)*. Atmospheric mercury concentrations measured in EMEP monitoring stations are consistently declining, with a total reduction of 59% between 2000 and 2020 *(16)*. However, in the EMEP East area, mercury concentrations have been steadily increasing since 2017, attributed to high emissions in Armenia, Kazakhstan and Ukraine *(16)*.

In recent years, informal recycling of electronic waste in small industries or at home has become a significant localized source of mercury to the environment, especially in developing countries *(18,19)*. Artisanal gold mining is another source of airborne mercury, which is emitted in restricted geographical areas *(20)*.

Emissions of mercury and mercury compounds declined by 64% from 2011 to 2020 in the United States *(21)*. The trend mainly relates to changes in the electricity generation sector, where there has been an 88% reduction. The decrease was driven by a shift from coal to other fuel sources (e.g. natural gas) and by installation of pollution control technologies at coal-fired power plants. A similar trend was observed in the EU, where emissions decreased by approximately 70% between 1990 and 2016 *(22)*.

A5.1.2 Environmental levels

Mercury can exist in several physical states and chemical forms. Based on its propensity for biological interactions, mercury generally undergoes complex and difficult-to-predict changes in concentration and chemical forms *(23)*. Following release to the atmosphere, and depending on its physical or chemical form, mercury can be either deposited in the vicinity of an emission source or undergo long-range atmospheric transport via air masses. Site-specific deposition of mercury is variable, and is affected by meteorological conditions and emission characteristics (e.g. source, stack height) *(24)*.

Mercury in the air exists as exists as three main species: (i) elemental mercury vapour (Hg(0) or GEM), (ii) gaseous divalent mercury (Hg(II)), also called reactive gaseous mercury (RGM), gaseous oxidized inorganic mercury or gaseous oxidized mercury; and (iii) particulate phase mercury (Hg(p)), also called total particulate mercury or particulate-bound mercury (PBM) *(23)*. In some cases, sampling and analysis of atmospheric mercury involves total gaseous mercury, which predominantly comprises GEM, but also includes RGM species *(23)*.

GEM is typically unreactive and is not efficiently removed by precipitation because of its relatively low solubility. Therefore, Hg(0) has a relatively long atmospheric residence time (0.5–2 years) and is thought to be transported significant distances in the troposphere *(23,25,26)*. It represents approximately 95% of the mercury compounds in ambient air. However, gaseous Hg(0) can be converted in the atmosphere to gaseous divalent mercury (Hg(II)), which is more likely to be deposited *(26)*. RGM species, are not well characterized chemically but are thought to comprise gaseous Hg(II) molecules, predominantly inorganic (e.g. $HgCl_2$) forms possibly also including organic (monomethylmercury or dimethylmercury) species *(23,25,26)*. Notably, RGM species are quickly deposited from the atmosphere to the earth's surface, and thus have short residence times (days to weeks) *(25,26)*. They are also highly reactive and represent less than 1% of the mercury in ambient air. Particulate phase mercury (Hg(p)) is divalent mercury adsorbed onto other PM *(25)*. It tends to be deposited near to the emission source. Similar to RGM, Hg(p) has a relatively short residence time in the atmosphere (days to weeks) *(26)*. It is also very reactive and represents less than 1% of the mercury compounds in air.

Mercury species in air principally comprise the gaseous (GEM and RGM) rather than the particulate forms. However, mercury concentration levels in air vary greatly in different

environmental settings (e.g. pristine regions, as well as rural and urban locations) and may be considerably higher in environments with strong local and regional sources *(23)*.

Several air Hg monitoring networks operate at the local, national and regional scales. The major global and regional mercury monitoring networks are:

- Arctic Monitoring and Assessment Programme (AMAP) *(27)*

- Asia-Pacific Mercury Monitoring Network (APMMN) *(28)*

- EMEP *(29)*

- European Union Network *(30)*

- GMOS *(31)*

- United States National Atmospheric Deposition Program (NADP) *(32)*.

Current data are insufficient to assess the global temporal trend in atmospheric Hg concentration and deposition, partly because of gaps in the geographical coverage of monitoring locations (e.g. Africa, Latin America and the Caribbean, the Russian Federation). However, data from Canada, Europe and United States show a general decline in atmospheric Hg concentrations *(10)*. In addition, data from the existing networks show a clear gradient in Hg concentration between the northern and southern hemispheres; with lower mean concentrations measured at sites in the southern hemisphere (GEM range: 0.76 ± 0.24 ng/m^3 to 1.07 ± 0.10 ng/m^3; PBM range: 1.45 ± 1.81 ng/m^3 to 5.04 ± 0.13 ng/m^3) than in the northern hemisphere (GEM range: 1.14 ± 0.17 ng/m^3 to 1.44 ± 0.27 ng/m^3; PBM range: 1.77 ± 2.46 ng/m^3 to 4.44 ± 5.87 ng/m^3) *(10)*. Consistent with this, annual atmospheric Hg(0) concentrations in the surface layer range from 1.2 ng/m^3 to 2 ng/m^3 over the EMEP region in 2020 (mean: 1.4 ng/m^3) *(16)*.

GMOS, which was launched in 2016 to support the Minamata Convention on Mercury *(33)* and is coordinated by UNEP, is expected to inform some of the current data gaps *(31)*.

In the EU, the range of mercury concentrations in air is 0.001–6 ng/m^3 in remote areas, 0.1–5 ng/m^3 in urban areas and 0.5–20 ng/m^3 in industrial areas *(34)*. Measurements by stations in the EMEP network in 2020 show concentrations in Europe of 1.18–1.64 ng/m^3 *(16)*.

A5.1.3 Human exposure

Mercury and its compounds are ubiquitous, and persist in the environment in air, sediments, soil and water. Once released into the environment, mercury follows a series of complex chemical and physical transformations as it cycles between the atmosphere, land and water. Although this report focuses on mercury in the atmosphere, it acknowledges that humans are routinely exposed to and accumulate mercury through multiple exposure routes from both environmental and non-environmental sources. Such sources include (but are not limited to) eating fish, use of mercury in occupational and household settings, and dental amalgam *(35,36)*.

Artisanal and small-scale mining is a main source of mercury exposures in humans. A study on a Ghanaian artisanal gold mining community reported concentrations higher than the US EPA reference dose (300 ng/m^3) in 91% of sampled households where the mercury–gold amalgam was heated; in other households, ambient air concentrations were still high, with over 64% exceeding the reference dose *(37)*. The 97.5th percentile concentration was estimated to exceed 800 µg/m^3 in fireplaces where the amalgam was heated.

Mercury levels in various body tissues (such as blood (whole and umbilical cord), breast milk, hair, nails, umbilical cord and urine) are a sensitive index of exposure *(38,39)*. They provide a measure of the internal dose, which can be used to evaluate the likelihood of adverse health

effects and improve clinical diagnoses. Blood, hair and urine are the most commonly used biomarkers of mercury exposure.

Inorganic mercury levels in blood or plasma and inorganic or total mercury levels in urine correlate highly with exposure to inorganic mercury (36). The best measure of methylmercury exposure is the concentration in whole blood or the total mercury concentration in red blood cells or hair because these tissues are the main reservoirs of methylmercury (36). Total mercury levels measured in blood and urine indicates the total exposure to all forms of mercury rather than the level of methylmercury, inorganic mercury compounds or elemental mercury exposure (36).

A5.1.4 Absorption, distribution, metabolism and excretion

The toxicokinetics (i.e. absorption, distribution, metabolism and excretion) of mercury is highly dependent on the species of mercury to which a person has been exposed (36,40).

Elemental mercury (Hg(0)): approximately 80% of inhaled dose of Hg(0) vapor is readily absorbed through the lungs. Possible absorption to the brain via olfactory nerves in the nasal passages is another possible route of uptake. There is limited absorption from the gastrointestinal tract (< 0.01% in rats, 0.04% in humans) and into the skin from air (2–2.6%). Once absorbed, mercury is rapidly distributed throughout the body; it can cross the blood–brain and placental barriers. The main organs of accumulation are the brain and kidneys. It can be transferred from the mother to the fetus and also from the mother to infant via breast milk. Most Hg in the blood has a half-life of 3.8 days, but it takes up to 45 days (the half-life) to remove the mercury that has absorbed onto other organs (e.g. kidney). Longer half-lives were reported for individuals exposed to higher cumulative doses of mercury. (41). Hg(0) is metabolized in tissues and is oxidized by catalase in blood to form Hg(II) and hydrogen peroxide (H_2O_2). H_2O_2 production is the rate-limiting step in Hg(0) metabolism. Hg(0) is excreted in exhaled air, sweat and saliva (minor) and Hg(II) is excreted in urine and faeces (major). The elimination half-life of Hg(0) is 30–90 days.

Mercuric mercury (Hg(II)): absorption of inhaled inorganic mercury aerosols depends on the particle size. Uptake by the olfactory pathway is currently not considered a mechanism of brain entry. Oral intake is a minimal pathway, with 1–16% of the ingested $HgCl_2$ dose absorbed from the gastrointestinal tract in humans. The absorption rate is proportional to the degree of water solubility of the mercuric salt. In guinea pigs, only 2–3% of the applied dose was absorbed through the skin. Hg(II) is distributed throughout the body, and the main organ of accumulation is the kidneys (≤ 90% of the total body burden). Neonates have increased distribution (i.e. less elimination) in the body. It can be transferred from mother to fetus through the placenta and also from mother to infant via breast milk. The half-life of Hg(II) in blood is 19.7–65.6 days: 24 days for the first phase and 15–30 days for the second. Hg(II) is metabolized by binding to sulfur-containing thiols (e.g. glutathione) and bisulfides, as well as selenium-containing selenols and selenides. Hg(II) may also be reduced to Hg(0). Hg(II) is not methylated in body tissues, but microorganisms in the gastrointestinal tract can convert it to methylmercury. It is excreted in urine and faeces (major), and also in bile, breast milk, exhaled air, saliva and sweat (minor).

Organic mercury (R-Hg): approximately 80–100% of methylmercury and dimethylmercury vapours are absorbed by inhalation in most populations; diet and dermal absorption are minor contributors. In countries with a high consumption of marine food (e.g. Japan, Republic of Korea, Arctic countries, Mediterranean countries and some South American countries), diet is the main source of methylmercury exposure (42–45). Absorption of alkylmercury salt aerosols depends on particle size and deposition rate in the respiratory tract. The oral route is also very efficient, with approximately 95% of ingested methylmercury absorbed in the gastrointestinal tract. In guinea pigs, only 3–5% of the applied methylmercury dose was absorbed through the skin. Dimethylmercury is readily absorbed by inhalation or dermal contact (7). The pattern of distribution of organic mercury in the body depends on the particular form (e.g. long chain vs short chain alkylmercury compounds). Methylmercury is distributed throughout the body and can cross the blood–brain and placental barriers.

Transport into cells and tissues is mediated by cysteine and neutral amino acid carrier proteins. The half-life in blood is 50 days, with 50% of the dose accumulating in the liver and only 10% in the brain. Long-chain alkylmercurials undergo rapid dealkylation of phenyl or methoxyalkyl groups, whereas short chain alkylmercurials have a slow dealkylation rate. Methylmercury is slowly demethylated to Hg(II) by tissue macrophages in tissues (brain, intestines and fetal liver) and by gut microorganisms in the intestines *(40)*. The demethylation rate is approximately 1%/day. The major excretory routes are bile and faeces (with some enterohepatic cycling); lactation increases methylmercury clearance from the blood. The elimination half-life is 70–80 days (whole body), depending on sex, animal strain, and the mercury species and dose.

A5.2 Toxicological studies

Health effects in laboratory animals for elemental mercury, mercuric mercury and organic mercury are based on information extracted from the 2022 draft ATSDR report *(36)*, as follows:

- neurological (including neurodevelopmental) effects:

  – elemental mercury – evidence of neurodevelopmental effects, including altered learning, behaviour and motor activity, and impaired habituation; some evidence of impaired motor function and damage to the central nervous system in adult animals;

  – organic mercury – consistent evidence for dose-dependent neurological effects, including sensorimotor dysfunction, vision and hearing deficits, and impaired learning and memory; exposure is associated with clear signs of neurotoxicity such as ataxia, clumsiness, hindlimb crossing, lethargy, partial paralysis, poor motor coordination (gross and fine) and tremor; and developing animals are more sensitive than adult animals to methylmercury-induced neurotoxic effects;

- renal effects:

  – elemental, mercuric and organic mercury – exposure is associated with increased nephrotoxicity severity in a dose (concentration and exposure time) dependent manner; effects include damage to the proximal and distal tubules and glomerular membrane, loss of brush border membranes and necrosis;

cardiovascular effects:

  – organic mercury – exposure is associated with increased blood pressure, positive inotropism[32] and decreased baroreflex sensitivity[33];

- immunological effects:

  – mercuric and organic mercury – exposure is associated with immunostimulation and immune complex disease in genetically susceptible strains of mice;

  – organic mercury – some evidence of immunosuppression in non-susceptible animals;

- reproductive effects:

  – organic mercury – consistent evidence for fertility impairment;

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[32] Positive inotropes make the heart muscle contractions stronger, thereby increasing cardiac output to a normal level and increasing the amount of blood pumped by the heart.

[33] Refers to autonomic control of the cardiovascular system.

- developmental effects (other than neurodevelopmental):

  – organic mercury – consistent evidence for reduced survival of offspring; increased fetal malformations such as cleft palate, skeletal malformations (ribs, sternebrae) and hydronephrosis; and decreased fetal weight in a dose (concentration and exposure time) dependent manner;

  – mercuric mercury – some evidence of carcinogenicity (forestomach and thyroid tumours) in male rats; and

- carcinogenicity:

  – mercuric mercury – some evidence of carcinogenicity (forestomach and thyroid tumours) in male rats.

A5.2.1 Mechanism of action

Although mercury poisoning has been recognized for centuries, the biochemical mechanism of action is likely to be complex, with many theories currently being investigated. Mercury is generally described as a potent, nonspecific enzyme toxicant *(6,46)*. Once it has entered the nervous system, mercury induces a broad range of damage and dysfunction through interactions with many cellular components *(36,47)*. The best current hypothesis is that binding to sulfur and sulfhydryl groups is the general mechanistic basis for mercury toxicity. Other possible mechanisms of action include induction of apoptosis and oxidative stress; enzyme inactivation; genotoxicity; immunotoxicity; molecular mimicry; disruption of calcium homeostasis, cell membranes and lipid peroxidation, DNA replication and DNA polymerase activity, microtubule formation, protein synthesis; and impairment to synaptic transmission and the immune response. It is important to emphasize that these mechanisms are interrelated and may be acting singly or in combination *(36,47)*.

Genetic polymorphisms that alter toxicokinetics or toxicodynamics have been associated with susceptibility to mercury. The best-studied polymorphisms are in genes associated with the glutathione pathway and with mercury transport and elimination.

Expression levels of catalase, which catalyses the oxidation of mercury vapour to divalent mercuric ion, vary across populations. In many individuals, catalase activity may be significantly reduced or completely lacking *(34)*. This could result in a wider distribution of mercury within the body, but the toxicological significance of low or absent catalase activity has not been reported. The effects of inorganic mercury and phenylmercury on the kidney are likely to manifest first in genetically susceptible individuals. However, there is no information on what proportion of the population may be genetically susceptible to mercury poisoning. The available data also suggest roles for genes encoding proteins involved in mercury uptake (amino acid transporters and organic anion transporters), biotransformation (glutathione-related enzymes), distribution (metallothioneins) and elimination (ABC transporters) *(48)*. Preliminary data from in vitro studies and animal models have shown that variants of these candidate genes can influence mercury toxicokinetics. Moreover, mercury exposure can alter expression levels of these genes and/or activity of the encoded proteins. Although functional genomics is a rapidly developing field, there are still many knowledge gaps regarding the functional relevance of candidate gene polymorphisms on susceptibility to mercury toxicity in the general population.

A5.3 Epidemiological studies

The health effects of elemental mercury, mercuric mercury and organic mercury described below are based on the 2022 ATSDR report *(36)*.

- Neurological (including neurodevelopmental) effects:

  - elemental mercury – consistent evidence for an association with neurological effects in adults, including tremor and effects on motor function (coordination and speed), nerve conduction and vision; consistent evidence for effects on cognitive performance (memory, integrative function) and physiological effects such as increased nervousness, irritability, loss of confidence, mood swings and timidity;

  - organic mercury – in utero exposure to methylmercury is associated with cognitive, neuromotor and neurosensory effects in children; in adults, evidence of decreased fine motor function (coordination and speed), reduced muscle strength and tactile sensation, and detrimental effects on cognitive performance (memory and learning), colour vision and visual contrast sensitivity;

- renal effects:

  - elemental mercury – some evidence that exposure is associated with decrements in glomerular function and tubular injury;

- cardiovascular effects:

  - mercuric mercury – evidence of increased blood pressure, altered cardiac function, positive inotropic effects and altered baroreceptor reflex sensitivity;

  - organic mercury – inconsistent evidence for small increases in blood pressure, clinical hypertension and altered cardiac function;

- immunological effects:

  - organic mercury – suggestive evidence that exposure to organic mercury is associated with alterations in some immune markers, such as serum cytokine levels, immune cell counts and immunoglobulin levels; however, evidence is unclear on immune system effects;

- reproductive effects:

  - mercuric mercury – evidence that exposure reduces fertility, and sperm motility and number in a dose-dependent manner; and

- developmental effects (other than neurodevelopmental):

  - organic mercury – evidence from the Minamata poisoning episode for congenital effects.

A5.3.1 Susceptible populations

Populations in distinct developmental stages are highly sensitive to mercury, in particular the fetus. Children are also at higher risk for the adverse effects of mercury because their behavioural and physiological characteristics can influence the exposure levels, distribution and, thus, toxicity. Although the mechanisms are not well understood, data also suggest that gender and genetic factors may also influence mercury toxicity. These susceptible populations are discussed in further detail below.

Both mercury vapour and methylmercury can readily cross the placental and blood–brain barriers. In contrast, inorganic Hg has limited potential to cross these barriers. However, the developing fetus and neonates, the incomplete blood–brain barrier can allow mercury to pass into the immature brain. Therefore, the developing fetus can be exposed to mercury from the mother through the placenta, and infants may be exposed to mercury from breast milk *(49)*. However, much more Hg is transferred via the placenta than via breast milk. In addition, neonates have less ability to excrete Hg compared with 2-year-olds *(50)*.

In general, the younger the brain, the greater the potential for adverse effects of mercury. Mercury exposure in utero and during childhood could cause neurodevelopmental and neurobehavioral alterations, including agitation, apathy, loss of language skills, loss of motor abilities, loss of social skills, personality change and withdrawn mood (35,51). In addition, the effects of mercury on the developing brain in utero may differ both qualitatively and quantitatively from those on the mature nervous system.

- **Qualitative differences:** diffuse damage affecting the cytoarchitecture of most brain areas occurs following prenatal exposure; in contrast, focal lesions are primarily observed in exposed adults. In general, the activity of antioxidant enzymes (including catalase, glutathione peroxidise and superoxide dismutase) are low in embryos. Activity of these enzymes increases at different rates during postnatal development and may modulate oxidative stress-mediated mercury toxicity (52).

- **Quantitative differences:** congenital effects of mercury exposure may be up 10 times lower than the earliest effects in non-pregnant adults (11,53). For example, effects on the central nervous system in children have been reported at Hg vapour concentrations of 10 μg/m³ (54). The risk of damage to the developing brain may depend more on the pattern of mercury exposure in developing nervous tissue. Dietary studies of high mercury meals have shown that infrequent episodic exposures may be more damaging than frequent low-level exposures, even though the average body burdens may be similar (6).

A5.4 Information on causality and related evaluations

Table A5.1 summarizes the information available linking exposure to mercury and health effects assessed by IARC, US EPA and WHO.

Table A5.1 Information on causality by inhalation exposure to elemental mercury and mercury compounds

Authoritative body	Air pollutant	Causality
IARC (1993) *(55)*	Hg and Hg compounds	Methylmercury compounds: possibly carcinogenic to humans (Group 2B) Elemental Hg and inorganic Hg compounds: not classifiable as to their carcinogenicity to humans (Group 3)
WHO Regional Office for Europe (2000) *(34)*	Elemental Hg	Not mutagenic, not carcinogenic, toxic to the central and peripheral nervous systems
US EPA (1997) *(4)*	Hg and Hg compounds	Elemental Hg is a neurotoxin Inorganic Hg and methylmercury are not likely to cause cancer in humans

A5.5 Health-based evaluations and regulatory numbers from authoritative bodies

Table A5.2 presents the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect human health from cadmium exposure.

These values reflect the selected epidemiological and toxicological studies, points of departure and uncertainty factors applied. Since the overwhelming majority of available toxicological data focus on exposures to Hg(0), the resulting health-based guidance values, guidelines and/or standards developed by the jurisdictions listed are based on Hg(0) dose–response data. However, some jurisdictions may have chosen to also apply the resulting value to other forms of mercury (e.g. inorganic mercury compounds) in policy decision-making.

Table A5.2 Health-based evaluations and regulatory numbers for mercury compounds from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/ limit value
Worldwide	WHO Regional Office for Europe (2000) *(34)*	Nonspecific symptoms following occupational exposure	–	Hg(0) vapor: 1.0 µg/m³ (annual)
United States	US EPA (1995) *(15)*	Neurobehavioral impairments in exposed workers, predominantly from chlor-alkali plants *(56–61)*	–	Hg(0) vapor: 0.3 µg/m³ (annual)
United States	OSHA (2005) *(62–64)*	Neurobehavioral impairments in exposed workers, predominantly from chlor-alkali plants *(56–61)*	–	Occupational exposure to organic (alkyl) Hg • PEL-C: 0.04 mg/m³ (construction and maritime only) • PEL-TWA: 0.01 mg/m³ (construction and maritime only) Occupational exposure to Hg(0) vapor • PEL-C: 0.1 mg/m³ (general industry) • PEL-TWA: 0.1 mg/m³ (general industry)

Table A5.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value
United States	ACGIH (2004) (65)	Neurobehavioral impairments in exposed workers, predominantly from chlor-alkali plants (56–61)	–	Occupational exposure: • TLV Hg(0) vapor: 0.025 mg/m^3
United States	ATSDR (2022) (36)	Tremors reported in occupational exposure studies (37,61,66–72)	–	Hg(0) vapor: 0.3 µg/m^3 (chronic)
United States (California)	OEHHA (2008) (73,74)	Neurobehavioral impairments in exposed workers, predominantly from chlor-alkali plants (56–61)	Occupational exposure to Hg and inorganic Hg compounds • REL-A: 0.6 µg/m^3 • REL-C: 0.03 µg/m^3 • REL-TWA: 0.06 µg/m^3	Occupational exposure to Hg, elemental and inorganic compounds as Hg • PEL-C: 0.1 mg/m^3 • PEL-TWA: 0.025 mg/m^3 Occupational exposure to alkylmercurials, as Hg • PEL-C: 0.04 mg/m^3 • PEL-TWA: 0.01 mg/m^3 • PEL-STEL: 0.03 mg/m^3 Occupational exposure to aryl Hg compounds as Hg • PEL-TWA: 0.01 mg/m^3

ACGIH: American Conference of Governmental Industrial Hygienists; OSHA: Occupational Safety and Health Administration; PEL-C: permissible exposure limit representing the concentration that shall not be exceeded even instantaneously; PEL-C: PEL-STEL: permissible exposure limit expressed as a short-term exposure limit; PEL-TWA: permissible exposure limit expressed as a time-weighted average; REL-A: acute REL; REL-TWA: REL expressed as a time-weighted average; REL-C: chronic REL; TLV: threshold limit value.

Notes: PEL-C is defined as the concentration that shall not be exceeded even instantaneously exceeded during any part of the working day. If instantaneous monitoring is not feasible, then the ceiling should be assessed as a 15-min time-weighted average exposure that shall not be exceeded at any time over a working day (75–77). PEL-TWA is defined as the concentration of a substance to which most workers can be exposed without adverse effect averaged over a normal 8-h working day or 40-h working week (78,79). TLV is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime (80).

A5.6 Future research needs

- Uncertainties about exposure levels and health effects associated with exposure in the general population, including vulnerable groups need to be better understood. Gaps in the geographical coverage of monitoring sites (i.e. in Africa, Latin America and the Caribbean, the Russian Federation) prevent a good understanding of potential exposures and health risks in some countries and regions. This might be especially important for countries with larger emissions to air from significant sources (e.g. artisanal gold mining, coal combustion).

- In general, it is important to ascertain the mechanisms of action, existence of threshold levels, best biomarkers, best estimation techniques, and point of departure for calculating health-based mercury levels.

A5.7 Concluding remarks

Epidemiological and/or animal studies have consistently reported neurological and renal effects from both inhalation and oral routes of exposure for all forms of mercury. In addition, many of these effects have been observed across exposure durations (from acute to chronic).

Mercury is an established developmental, neurological and reproductive toxicant.

The available health-based guidance values, guidelines and standards for elemental mercury (the main species in ambient air) range from 0.03 µg/m^3 to 1.0 µg/m^3. Similar values do not exist for other mercury species (inorganic and organic) owing to a lack of toxicological data combined with a general understanding that inhalation exposure is not likely to be a significant exposure route.

The 2022 ATSDR review of toxicological data identified new occupational data (focused on tremors in a larger worker population, with exposure extrapolated from urinary Hg levels) *(36)*. The resulting (draft) chronic health-based value is similar to the chronic health-based value developed by US EPA *(15)* but lower than the chronic value developed by the OEHHA *(73,74)* owing to the use of different uncertainty factors. For effects related to acute exposures, the only corresponding health-based value is from the OEHHA *(73,74)*.

However, the 2022 draft ATSDR protocol for arriving at the chronic health-based value for mercury has been questioned. ATSDR applied a steady-state mass balance model to convert urinary mercury concentrations to exposure concentrations. It also considered that the mercury body burden is more accurately reflected by urinary mercury concentrations than by air concentrations measured in rooms or the breathing zone, which are likely to be highly intermittent and variable. It also acknowledged that non-occupational sources, such as diet and mercury dental amalgams, might have contributed to the urinary mercury levels reported in the occupational studies used to derive the health-based guidelines. Despite this, it recognized that occupational exposures are probably still the main source of urinary mercury in these studies. One study noted that urine mercury alone is probably not a good biomarker of the contribution of GEM to the total body burden of mercury for some population groups *(81)*. Hair mercury levels can be used as a non-invasive matrix to distinguish the body burdens associate with atmospheric mercury inhalation and diet.

Based on 2019 UNEP data *(10)*, mean annual GEM concentrations are 1.3–1.6 ng/m^3 in northern hemisphere sites and approximately 1.0 ng/m^3 in southern hemisphere sites.

The available measured concentrations (as annually averaged values) are well below the available chronic health-based values. However, caution is recommended when interpreting annually averaged concentrations as surrogates of exposure because these values may not

reflect shorter-term peak concentrations. This is especially important given the ability of mercury to induce adverse effects on development within shorter timescales (such as in utero).

In addition, current gaps in the geographical coverage of monitoring sites prevent a good understanding of the effects of potential exposures and health risks in some locations.

GMOS (coordinated by UNEP) has been operating since 2016 *(31)*. A network for long-term mercury monitoring was set up in Europe and the northern hemisphere in response to the Heavy Metals Protocol to the CLRTAP *(82)*. Mercury concentrations measured by these two systems are likely to contribute to filling the existing gaps. This may be especially important for developing countries with larger emissions to air from significant sources (e.g. artisanal gold mining, coal combustion). In Europe, crematoriums are important sources of atmospheric mercury. Dental amalgam workers are a vulnerable group, and the EU is discussing changing legislation to protect these workers as part of a package of mercury regulations *(83)*.

Taken together, further consideration may be needed to not only understand the health risks associated with short-term mercury exposures but also address gaps in the toxicological database that currently limit the development of acute and intermediate health-based values (which are required to assess these health risks).

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Annex 6. Evidence overview on nickel

Contents

A6.1 Exposure risk assessment

A6.1.1 Characteristics, sources and environmental occurrence

Nickel (chemical symbol Ni; atomic number, 28; relative atomic mass, 58.69; CAS Registry Number 7440-02-0) is a silvery-white, lustrous, hard metal. The main oxidation state is +2, but nickel can also be found in oxidation states +3 and +4. Nickel is classified as a transition metal.

Nickel has several chemical properties that make it a suitable component of alloys, the main one being stainless steel. Nickel can also be used in jewellery, as a corrosion-free plating agent, in welding rods, in coin and battery manufacturing and in chemical catalysts.

Nickel occurs naturally in air, water and soil. The principal ores are nickel sulfide and oxide-silicate. Nickel salts can be water soluble (nitrate, sulfate, chloride) or insoluble (oxides, sulfides).

Natural sources such as wind-blown dust, vegetation and volcanoes release nickel into atmosphere: the estimated annual rate is 30 000 t/year (as nickel) *(1,2)*. However, anthropogenic sources release approximately 1.5 times more nickel than natural sources *(3)*.

Nickel is an essential trace element for animals. Based on extrapolation from animal data, the estimated daily nickel requirement for a 70 kg person is 50 µg Ni/kg diet *(4)*. Although nickel deficiency may affect reproduction in rodents *(5)*, this has not been reported in humans, probably owing to its universal occurrence in food *(6)*.

The main anthropogenic sources of nickel emissions to the atmosphere have been mining, combustion and production processes *(7)*. The main contributor of nickel to the atmosphere is fossil fuel combustion, which was responsible for estimated 62% of atmospheric nickel in the 1980s. Other contributors are nickel smelting and refining processes (17%), municipal waste incineration (12%), production of steel and other Ni-containing alloys (5%), and coal combustion (2%) *(4)*. Depending on the emission source, nickel can be found as different chemical species in aerosol. Ni emissions from coal and oil combustion are predominantly in the form of nickel sulfate, with a smaller percentage as nickel oxide and nickel combined with other metals in complex oxides. Industrial processes may also emit metallic nickel, nickel alloys and nickel sulfide. Informal recycling of electronic waste in small industries or at home has recently become a localized source of nickel in developing countries *(8–10)*.

Data on the size distribution of nickel particulates suggest mass median diameters of 0.83–1.67 µm in urban air *(11,12)*. Nickel emissions from coal-fired power plants are concentrated in the smallest aerosol fractions *(13)*.

A6.1.2 Environmental levels

Nickel can be adsorbed onto the surface or internally mixed within the core of $PM_{2.5}$. The atmospheric residence time depends on the particle size, meteorological conditions and emission factors related to the industrial processes responsible for the release. Wet and dry deposition are the main mechanisms of removing nickel from the atmosphere *(14)*.

Typically, nickel concentrations in air are 0.3–2 ng/m³ in rural areas, 1–13 ng/m³ in urban locations and up to 50 ng/m³ near to industrial sites *(6,15,16)*. In heavily industrialized areas and larger cities, nickel concentrations can be higher, in the range of 110–180 ng/m³. In urban background and rural locations, nickel is predominantly present as soluble salts (e.g. chlorides, nitrates and sulfate) and insoluble nickel oxides, with smaller proportion of nickel sulfides, metallic and nickel carbonyl *(15)*.

A6.1.3 Human exposure

Food is the main source of human exposure to nickel (approximate daily exposure: 70–300 µg/day *(4)*), followed by drinking water (8 µg/day) and air (0.4 µg/day) *(15,17)*. Smoking also contributes 0.04–0.58 µg Ni/cigarette) *(6)*, which can increase exposure to airborne nickel by up to 6 µg/day (for an estimated consumption of 20 cigarettes/day and a 50% absorption rate). In the proximity of significant nickel industrial sources (e.g. refineries, smelters), nickel exposure from local grown food, water and air may increase. Individuals are also exposed to nickel through skin contact with products made from nickel alloys and nickel-plated items (e.g. jewellery, stainless steel cooking and eating utensils) *(18)*. Although absorption via skin is a minor source of nickel exposure, it might be relevant for sensitized individuals. Another potential source of exposure is the leaching and corrosion of nickel in prosthetic devices.

Occupational exposures to nickel are highest for workers in industries that manufacture (mining and refining) and use nickel. In Ni mining and refining industries, historical exposures of up to 100 mg/m³ have been recorded; however, current estimates are 1–5 mg/m³. Although the nickel species present in workplace atmospheres can be difficult to evaluate, they are thought to comprise less-soluble compounds that might be retained for long periods in the lungs, resulting in an increased total body burden. The nickel concentration in lung tissue biopsies was considerably higher in ex-nickel refinery workers (50 ± 150 µg/g dry weight) than in non-occupationally exposed individuals (0.74 ± 0.44 µg/g dry weight) *(19)*.

A study of the general population in several French cities reported that subjects were exposed to 3 ± 4 ng Ni/m³ measured in PM_{10} *(20)*. A Canadian study reported that subjects were exposed to a median of 69 µg Ni/g PM_{10} collected during personal exposure sampling. In comparing the fine and coarse fractions, it found that most nickel was in the coarse fraction *(21)*. A Chinese study reported personal exposure concentrations of 17 ± 23 ng/m³ (range: 5.7–145 ng/m³) *(22)*.

A6.1.4 Absorption, distribution, metabolism and excretion

Inhaled particles containing nickel are deposited in the lungs according to their size *(6)*. Soluble nickel compounds are rapidly removed from the lung *(23)*, but approximately 40% of deposited nickel particles are retained in the deep lung, where clearance times are longer *(6)*. Studies in rats and hamsters reported that nickel chloride (soluble) was quickly removed from the lungs *(24)*. In contrast, approximately 50% of nickel oxide (much less soluble) was still present 45 days after exposure and only 10% of nickel sulfide (intermediate solubility) was retained after 35 days *(25)*.

The biological half-life of nickel depends on the compound and, therefore, its solubility. Nickel is transported in the blood bound to proteins (e.g. albumin, alpha-2-macroglobulin). Bound nickel can exchange with free histidine to form low-molecular-weight nickel-ʟ-histidine complexes that can cross biological membranes. Nickel is metabolized in tissues via oxidation–reduction reactions that generate Ni(III).

Most soluble forms of inhaled nickel are excreted in urine, with small amounts excreted in sweat and saliva. Therefore, high concentrations of (insoluble) nickel oxide in air give rise to relatively low Ni concentrations in plasma and urine and higher concentrations in the nasal mucosa and lungs *(26,27)*.

A6.2 Toxicological studies

A6.2.1 Laboratory animals: short-term effects

The US EPA fact sheet on nickel compounds *(17)*, citing ATSDR data *(4)*, summarized studies in rats that showed a wide range of acute toxicity values (from low to high) for nickel compounds. Soluble compounds, such as nickel acetate, were the most toxic and insoluble forms, such as nickel powder, were the least.

Individual studies by Campen et al. *(28)*, Muggenburg et al. *(29)* and Lippmann et al. *(30)* have been included in several reports *(15,31,32)*.

- Campen et al. (2001) reported that rats exposed to nickel sulfate aerosol concentrations of > 1.2 mg/m³ for 6 h/day for 4 days experienced delayed cardiovascular effects, such as slow, irregular heartbeats, and a reduction in body temperature *(28)*.

- Muggenburg et al. (2003) reported that exposure to nickel sulfate aerosol at a concentration of 0.05 mg/m³ for 3 h/day for 3 days did not produce significant effects on heart rate in beagle dogs *(29)*.

- Lippmann et al. (2006) reported associations between nickel in ambient air PM and impaired cardiac function. In ApoE^{-/-} mice[35] exposed to CAP, acute changes in heart rate and heart rate variability correlated with the aerosol nickel content. The changes were significant following exposure on days with nickel peaks (nickel aerosol content: ~175 ng/m³) compared with non-peak exposures (mean: 43 ng/m³) *(30)*.

ANSES *(31)* reported that single-exposure studies published after the 2013 REVIHAAP review *(32)* up to February 2016 *(33–39)* provided an inadequate indication of the effects of nickel in ambient air particles on respiratory (changes in cellularity, proteins and/or enzyme activities in bronchopulmonary lavage could not be specifically attributed to nickel) and cardiovascular (no effect on haematocrit and haemoglobin concentrations, coagulation markers, or inflammation markers) end-points.

A6.2.2 Laboratory animals: long-term effects

A6.2.2.1 Respiratory effects

Reports by the ASTDR *(4)*, United Kingdom Department for Environment, Food and Rural Affairs (DEFRA) *(15)* and European Commission *(16)* include the 2-year inhalation studies of nickel oxide, subsulfide and sulfate heptahydrate by the United States National Toxicology Program *(40–42)* that reported effects on the respiratory system and quantified the dose–response relationships. Rats exposed to 0.25 mg/m³ and 0.5 mg/m³ nickel sulfate heptahydrate showed signs of respiratory toxicity in the lungs (e.g. alveolar proteinosis, fibrosis and hyperplasia) related to

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[35]   A mouse model used for studying atherosclerosis, CVD, and fat metabolism.

chronic active inflammation. Similarly, mice exposed to 0.5 mg/m^3 and 1 mg/m^3 nickel sulfate heptahydrate developed lesions in the lungs, including inflammation, hyperplasia, proteinosis and cellular infiltration. Based on these results and a 15-month interim evaluation, the European Commission position paper surmised that the results indicate a LOAEL for mice of 0.06 mg Ni/m^3 (equivalent to 0.25 mg/m^3 nickel sulfate hexahydrate) and a lower LOAEL for rats, whereas a NOAEL for rats or for mice could not be found (16). DEFRA highlighted that the large variability in the NOAEL derived from various studies partly reflected the different solubilities of the nickel compound tested. The NOAEL of insoluble nickel salts was approximately 10-fold higher than the NOAEL of soluble compounds (15).

A6.2.2.2 Cardiovascular effects

The 2019 ANSES report (31) included a 2013 subacute study published after the 2013 REVIHAAP review (32) in which ApoE$^{-/-}$ mice were exposed to filtered air, CAP (69.6 ± 48.4 µg/m^3), filtered air plus Ni or CAP plus Ni (66.5 ± 44.6 µg/m^3) for 6 h/day, 5 days/week for just over 3 months (43). Ni concentrations were 0.9 ± 5.5 ng/m^3 in the CAP group, 440.6 ± 557.3 ng/m^3 in the filtered air plus Ni group and 467.9 ± 601.1 ng/m^3 in the CAP plus Ni group. No effect was noted on markers of systemic inflammation but there was an effect on markers of systemic oxidative stress, as well as on vascular function (aortic contraction).

A6.2.2.3 Reproductive and developmental effects

The 2000 US EPA fact sheet on nickel compounds (17) reported ATSDR data (4) on sperm abnormalities in animals after oral exposure to nickel nitrate and decreased sperm count after inhalation of nickel oxide.

The 2008 DEFRA consultation document (15) cited several animal studies that showed (i) testicular damage, leading to reduced fertility and developmental toxicity in rats and mice exposed to soluble nickel salts (44); (ii) testicular degeneration in rats and mice after inhalation exposure to nickel sulfate (1.8 mg/m^3) or nickel subsulfide (1.6 mg/m^3) for 6 h/day, 12 days (45); and (iii) fetal mortality and malformations following exposure of pregnant hamsters and rats to nickel carbonyl (≥ 0.16 mg/m^3).

A6.2.2.4 Carcinogenicity

The US EPA fact sheet (17), 2000 WHO *Air quality guidelines for Europe* (6), European Commission position paper (16) and DEFRA consultation document (15) all state that nickel sulfate (via inhalation) is not carcinogenic in rats or mice (4,40) but nickel oxide and subsulfide (via inhalation) are (40,46). In United States National Toxicity Program's inhalation studies, exposure to either nickel oxide or nickel subsulfide was associated with higher number of benign (adenomas) and malignant (carcinomas) tumours in rats (40–42).

Inhalation exposure to nickel oxide for 13 weeks was not associated with an increased frequency of micronucleated normochromatic erythrocytes in peripheral blood samples in mice (male and female) (40–42).

IARC Monograph 100C on arsenic, metals, fibres, and dusts reviewed the available evidence from experimental studies and concluded that there is sufficient evidence that nickel metal and nickel compounds (nickel acetate, nickel hydroxides, nickel monoxides, nickel sulfides (including nickel subsulfide)) cause cancer (47). The evidence is limited or inadequate for other nickel compounds.

A6.2.3 In vitro systems

A6.2.3.1 Reproductive and developmental toxicity

Human placental explants were incubated with nickel chloride at concentrations of 1–5 mM for 12 h *(48)*. Tissue permeability (measured by potassium release) and lipid peroxidation increased in a dose-dependent manner.

A6.2.3.2 Genotoxicity

The 2000 WHO *Air Quality Guidelines for Europe (6)*, 2001 European Commission position paper *(16)* and the 2008 DEFRA consultation document *(15)* generally concluded that the results of in vitro bacterial mutation tests are inconsistent, possibly reflecting differences in the test conditions, sensitivity of test strains *(4)* and/or cellular uptake of the particular test compound *(49)*.

Some evidence suggests that the genotoxic effects of nickel compounds may be indirect, through inhibition of DNA repair systems *(50)*. This may reflect the ability of nickel to form complexes with the amino acid histidine (section A6.1.4) and then take part in redox reactions.

IARC Monograph 100C states that nickel compounds are not mutagenic in bacteria and are only weakly mutagenic in mammalian cells under standard test conditions *(47)*. However, exposure to nickel compounds in vitro and in vivo is associated with DNA damage, chromosomal aberrations and micronuclei, and delayed mutagenicity and chromosomal instability in cells a long time after nickel treatment. Since nickel exposure occurs alongside exposure to other co-mutagens that can produce DNA damage, disruption of DNA repair pathways may be a mechanism for nickel-induced carcinogenesis. Other possible mechanisms are the induction of epigenetic changes (e.g. altered DNA methylation patterns) and histone modification. Inflammation is another pathway linking nickel exposure with carcinogenesis.

A6.2.4 Mechanisms of acute toxicity

Nickel compounds can cause oxidation of lipids *(51,52)*, proteins *(53)* and nucleic acids *(52,54)*; intracellular radical production *(53,55)*; and intracellular glutathione depletion *(56–58)*. However, in contrast to other metals, there is little evidence that free nickel undergoes redox cycling reactions.

Hydrated Ni(II) ions react slowly with hydrogen peroxide to form hydroxyl radicals and do not efficient catalyse peroxide decomposition; however, binding to biological ligands decreases their oxidation potential and enables their oxidation to Ni(III) by strong oxidants *(59)*. Such redox cycling generates oxygen radicals that, in turn, cause DNA, lipid and protein oxidation *(60,61)*. This ligand-dependent reaction may also occur with histones, thereby inducing extensive DNA base modification *(62)*. Soluble nickel salts undergo redox reactions and cause oxidative damage through inducing an inflammatory response. Insoluble particulate nickel compounds (e.g. nickel sulfide and nickel subsulfide) may induce ROS release from phagocytic cells *(63)*.

A study into the chemical characterization and redox potential of $PM_{2.5}$ and PM_{10} in underground and ground-level sections of the Los Angeles Metro found that ROS activity strongly correlated with exposure to water-soluble nickel *(64)*.

Other studies support the hypothesis that nickel ions alter epigenetic homeostasis in cells, leading to altered gene expression and carcinogenesis. In various cell lines, nickel compounds (soluble or insoluble) can produce histone phosphorylation *(65)* and ubiquitination *(66)*; among steel workers, histone dimethylation increased with increasing airborne nickel concentrations *(67)*.

Carcinogenicity of nickel compounds relates to their solubility: insoluble salts are more carcinogenic and induce higher levels of intracellular free radical production compared with soluble nickel salts *(53,55)*. As described in section A6.1.4, insoluble nickel compounds are retained in the lungs for much longer than soluble ones.

A6.3 Controlled human exposure studies

The 2013 REVIHAAP review *(32)* reported an association approaching significance between the nickel content of CAP and decreased brachial artery diameter in 24 healthy adults exposed to CAP plus ozone *(68)*. Significant associations were reported for organic and elemental carbon concentrations.

A6.4 Epidemiological studies

A6.4.1 Short-term effects

A6.4.1.1 Mortality: studies in general populations

A 2006 study examined associations between ambient PM components and mortality in two population studies: the United States National Mortality and Morbidity Air Pollution Study (NMMAPS) and the Hong Kong Sulfur-in-Fuel Intervention Study *(30)*. In NMMAPS, daily mortality rates were significantly associated with average levels in air of nickel (and vanadium), but not of other measured species. The Hong Kong sulfur intervention produced sharp drops in nickel (as well as sulfur dioxide and vanadium) levels in air, but not other components, and was associated with the reduction in cardiovascular and pulmonary mortality.

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified three studies on the relationship between nickel exposure and all-cause mortality *(69–72)*. The data were deemed to provide an inadequate indication of effect.

A6.4.1.2 Respiratory effects: studies in occupational populations

The US EPA fact sheet *(17)* reports severe damage to the lungs and kidneys in one person occupationally exposed to an extremely high level of nickel by inhalation *(4)*, and pulmonary fibrosis and renal oedema following exposure to nickel carbonyl *(18)*.

As described in the DEFRA consultation document *(15)*, a worker exposed to an estimated 382 mg/m^3 metallic nickel died from adult respiratory distress syndrome. The report also includes the immediate and delayed acute inhalation effects of nickel carbonyl *(44,73)*. The immediate response after acute exposure includes headache, nausea, dizziness, vomiting, insomnia and irritability. In mild cases, these effects disappear within 1 day. However, more severe acute exposures (≥ 50 mg/m^3) have been associated with delayed symptoms, such as chest pain, dyspnoea and oedema, between 12 h and 5 days after exposure *(16,74)*.

A6.4.1.3 Respiratory effects: studies in general populations

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES (2019) *(31)* identified seven publications examining the associations between short-term nickel exposure from ambient air particles and respiratory health *(69,72,75–79)*. The studies addressed five types of health events, of which three were considered severe: mortality from respiratory causes, hospitalizations from respiratory causes, and asthma and wheezing in children. The data were deemed to provide:

- a strong indication of an effect of nickel exposure on respiratory hospitalizations;

- a moderate indication of effect for mortality from respiratory causes; and

- an inadequate (no association) indication of effects for respiratory symptoms in children (cough and wheezing) and subclinical respiratory health events (decreased ventilatory function and secretion of CC16 protein, a marker of lung tissue damage).

A6.4.1.4 Cardiovascular effects: studies in general populations

The REVIHAAP project identified associations between nickel in ambient air particles and cardiovascular hospital admissions *(70,80–82)*. The strongest indication comes from a case-crossover study on stroke *(81)*. Nickel exposure had the largest (although non-significant) association with stroke incidence, second only to exposure to black carbon. Another study reported that living near a nickel and/or copper smelter is associated with increased cardiovascular mortality *(83)*, but advised caution because the highest nickel emissions had occurred in the past (follow-up: 1982–2005).

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(28)* identified 16 studies examining the association between short-term exposure to nickel in ambient air particles and cardiovascular health *(34,69,72,75,76,79,84–92)*. The studies addressed nine types of health event, two of which were considered severe: all-cause cardiovascular mortality and all-cause cardiovascular hospitalizations. The data were deemed to provide:

- a moderate indication of the effects of nickel exposure on cardiovascular hospitalizations;

- a moderate indication of effects for blood pressure and markers of systemic oxidative stress;

- a weak indication of effects on biomarkers associated with systemic inflammation and vascular endothelial impairment; and

- an inadequate indication of effects on mortality from cardiovascular causes, altered heart rhythm, altered vascular function and altered coagulation markers.

Yang et al. systematically reviewed studies on the associations of short- and long-term exposures to various $PM_{2.5}$ components with morbidity and mortality. The meta-analysis suggested that Ni is among the $PM_{2.5}$ constituents that probably cause cardiovascular adverse health effects *(93)*.

A study in Shanghai (China) examined the short-term associations between various $PM_{2.5}$ constituents and heart rate variability measures *(94)*. Elemental nickel was consistently associated with reduced heart rate variability parameters in both single-constituent models and constituent-$PM_{2.5}$ models.

A study in Guangzhou (China) explored correlations between individual heavy metals in $PM_{2.5}$ and mortality from cardiovascular and cerebrovascular disease *(95)*. Daily exposure to $PM_{2.5}$ and most heavy metals showed significant correlations with cardiovascular and cerebrovascular mortality. Nickel was among the metals for which an interquartile range increase in concentration was associated with the largest cumulative excess risk (1.21%).

A6.4.2 Long-term effects

A6.4.2.1 All-cause mortality: studies in occupational populations

The DEFRA consultation document *(15)* highlighted the difficulty of evaluating the evidence linking chronic nickel exposure to non-cancer mortality because the results are mixed and it is difficult to disentangle the effects of nickel from those induced by co-exposure to other substances.

A6.4.2.2 All-cause mortality: studies in general populations

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified two publications examining the associations between long-term nickel exposure and all-cause mortality *(96,97)*. The data were deemed to provide an inadequate indication of effect.

A study evaluated the association between long-term exposure to ambient PM components and mortality from natural causes in six large administrative cohorts in the framework of the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project *(98)*. The project included almost 27 million participants, who contributed more than 240 million person-years. Nickel was significantly associated with natural mortality (pooled hazard ratio: 1.024 per ng Ni/m^3; 95% CI: 1.006–1.043).

A6.4.2.3 Respiratory effects: studies in occupational populations

The US EPA fact sheet *(17)* and DEFRA consultation document *(15)* described irritation and damage to the upper and lower respiratory tract following occupational chronic exposure to nickel, manifesting as septal damage, chronic sinusitis, chronic bronchitis, reduced ventilatory capacity and pulmonary fibrosis *(99,100)*. A type of asthma specific to nickel exposure has also been described, which may relate to primary irritation of the airways or an allergic response *(4,101)*. The US EPA fact sheet *(17)* states that less-soluble nickel compounds are less toxic to the respiratory tract than more-soluble ones.

A6.4.2.4 Respiratory effects: studies in general populations

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified five publications that examined the relationship between long-term exposure to nickel in ambient air particles and respiratory health *(97,102–105)*. The studies addressed five types of health events, four of which were considered severe: mortality from respiratory causes, asthma or wheezing in children, childhood rhinitis, and respiratory and ear, nose and throat infections in children. The data were deemed to provide:

- a weak indication of the effects of nickel exposure on asthma or wheezing in children; and

- an inadequate indication of effects for other severe childhood events and mortality from respiratory causes.

A6.4.2.5 Cardiovascular: studies in occupational populations

The DEFRA consultation document *(15)* cited a study of boilermakers that reported an association between exposure to transition metals and heart rate variability, although the specific effect associated with nickel was small and not statistically significant *(106)*.

A6.4.2.6 Cardiovascular: studies in general populations

A study of European cohorts did not find associations between the nickel concentration in ambient PM and inflammatory blood markers (fibrinogen and high-sensitivity C-reactive protein) *(107)*.

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified seven publications examining the associations between long-term exposure to nickel in ambient air particles and cardiovascular health *(87,97,107–111)*. The studies addressed five types of health events, two of which were severe: all-cause cardiovascular mortality, and heart attacks and coronary events. The data were deemed to provide:

- a weak indication of an effect of nickel exposure on blood pressure in children;

- an inadequate indication of effect on heart attacks, coronary events and cardiovascular mortality; and

- an inadequate indication of effect on markers of systemic inflammation and vascular endothelial impairment.

A6.4.2.7 Neurological health

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified one study examining the associations between long-term exposure to nickel in ambient air particles and neurological health *(112)*; it addressed a health event considered to be severe: impaired cognitive performance in children. The study provided an inadequate indication of effect.

A6.4.2.8 Reproductive and developmental toxicity: studies in occupational populations

The DEFRA consultation document *(15)* described two studies *(113,114)*:

- one study concluded that nickel can cross the human placenta in vivo *(113)* based on the finding that nickel concentrations were similar in the fetus and the mother's liver – it also suggested that the nickel supply to the fetus depends on nickel levels in the mother; and

- the other reported a higher rate (about double) of spontaneous abortions and congenital malformations in women working in a Russian nickel refinery who had been exposed to nickel (primarily nickel sulfate) concentrations of 80–200 µg/m^3 compared with women working in local construction industries *(114)*.

A6.4.2.9 Reproductive and developmental toxicity: studies in general populations

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified three studies on the relationship between long-term nickel exposure and

perinatal health *(115–117)*. The studies addressed two types of health events, one of which is considered severe: low birth weight. The data were deemed to provide:

- a moderate indication of an effect of nickel exposure on reducing head circumference; and

- a weak indication of effect on the risk of low birth weight.

A retrospective cohort study in Heshan (China) investigated the association of $PM_{2.5}$ components with gestational diabetes mellitus and impaired glucose tolerance *(118)*. Maternal airborne nickel exposure during the second trimester had extremely strong effects on the odds of both health effects.

A study that examined which elemental components of $PM_{2.5}$ were responsible for previously reported associations between $PM_{2.5}$ and neonatal blood pressure consistently found that higher nickel concentrations were associated with significantly higher systolic and diastolic blood pressure *(119)*.

A6.4.2.10 Genotoxicity: studies in occupational populations

The DEFRA consultation document *(15)* cites a study of nickel refinery workers that reported a slight but significant increase in chromosome aberrations (but not breaks or sister chromatid exchange) *(120)*.

A6.4.2.11 Carcinogenicity: studies in occupational populations

The US EPA fact sheet *(17)*, 2000 WHO *Air quality guidelines for Europe (6)* and DEFRA consultation document *(15)* reviewed studies of populations occupationally exposed to airborne nickel compounds (sulfidic, oxidic and soluble ones); the studies consistently reported increased risks for nasal and lung cancers *(121)*, with higher risks for cancers of the nasal cavity. The evidence also clearly showed an exposure–response relationship.

Higher risks were found among workers in nickel smelting, refining or sintering plants *(122)*. Studies of nickel electroplaters or workers in nickel alloy manufacturing plants did not report a significant increase in cancer risk *(123)*. Metallic nickel is believed not to be carcinogenic.

A 2012 study that aimed to quantify lung cancer burden attributable to occupational carcinogens in a general population found that men have an increased lung cancer risk even at low levels of nickel–chromium exposure (odds ratio: 1.18; 95% CI: 0.90–1.53), with increased risk with increasing exposure level *(124)*.

Nickel carcinogenicity has traditionally been associated with exposure to insoluble compounds (nickel oxides or sulfides). However, epidemiological evidence also suggests an association with exposure to soluble compounds, particularly nickel sulfate *(125,126)*.

Evidence about other types of cancer is far less conclusive. Although an assessment in the early 1990s concluded that exposure to airborne nickel compounds is not associated with higher risk for non-nasal and lung cancers *(127)*, later studies suggest an increased risk for stomach *(125,128)* and pancreatic *(129)* cancer.

A6.4.2.12 Carcinogenicity: studies in general populations

In evaluating the evidence published after the 2013 REVIHAAP review up to February 2016, ANSES *(31)* identified two publications examining the associations between long-term exposure to nickel in ambient air particles and health events related to bronchopulmonary cancers *(97,130)*. The data were deemed to provide a weak indication of effect.

A 2021 study evaluated an association between long-term exposure to the elemental components of PM$_{2.5}$ and lung cancer incidence in the ELAPSE pooled cohort *(130)*. The total study population comprised 306 550 individuals, who developed 3916 incident lung cancer events during 5 541 672 person-years of follow-up. A positive association was found between exposure to nickel and lung cancer incidence, with an adjusted hazard ratio of 1.09 per ng PM$_{2.5}$ Ni/m³ (95% CI: 1.02–1.15). Effect estimates were unaffected by adjustment for nitrogen dioxide and slightly attenuated by adjustment for PM$_{2.5}$ mass. These results suggest that industrial and fuel oil combustion particles primarily influence the lung cancer incidence.

A6.5 Information on causality and related evaluations

Table A6.1 summarizes the information available linking exposure to nickel and health effects, such as carcinogenicity assessed by IARC, US EPA and WHO.

Table A6.1 Information on causality by inhalation exposure to nickel

Authoritative body	Air pollutant	Causality	Data upon which causality is based
IARC (1990 (original evaluation), 2012 (most recent evaluation)) *(47,131)*	All Ni compounds	Carcinogenic to humans (Group 1)[a]	Multiple epidemiological studies of occupational exposures in Ni sulfide ore smelting and Ni-refining processes. Multiple studies in experimental animals
	Metallic Ni	Possibly carcinogenic to humans (Group 2B)	
US EPA (1998, 1999) *(132–135)*	Ni refinery dust	Carcinogenic to humans (Group 1)	Four epidemiological studies *(132–135)*
	Nickel subsulfide	Carcinogenic to humans (Group 1)	Rat inhalation study *(46)*
	Nickel carbonyl	Probably carcinogenic to humans (Group 2B)	Rat intratracheal study
WHO Regional Office for Europe (2000) *(6)*	Ni compounds	Classified as human carcinogens	Carcinogenicity in Norwegian Ni refinery workers *(136,137)*

EC: European Commission

[a] Only the inhalation route is associated with cancer, and the tumours are local to the respiratory tract (lung, nasal cavity, paranasal sinuses). Several theories have been suggested for the mechanisms of nickel tumorigenesis, but all assume that the nickel ion is the active agent. The IARC classification was made on the basis that all nickel compounds can generate nickel ions that can be transported to critical sites in target cells.

A6.6 Health-based evaluations and regulatory numbers from authoritative bodies

Table A6.2 presents the guidelines and regulatory levels that have been issued by different authoritative and regulatory bodies to protect human health from nickel exposure.

Table A6.2 Health-based evaluations and regulatory numbers for total airborne nickel (unless otherwise stated) from authoritative bodies

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value (annual mean unless otherwise stated)
Worldwide	WHO (2000) *(138)*	Carcinogenicity in Norwegian Ni refinery workers *(136,137)*	URF: 3.8×10^{-4} An increase lifetime cancer risk by no more than 1:10 000, 1:100 000 and 1:1 000 000 has been calculated to be associated with a lifetime exposure to 250 ng/m³, 25 ng/m³ and 2.5 ng/m³ Ni, respectively	Assuming a linear dose–response, no safe level for Ni compounds can be recommended
United States	ACGIH (1996) *(45)*	–	–	Occupational exposure (TLVs, 8-h average): • 1.5 mg/m³ for elemental Ni • 0.1 mg/m³ for soluble inorganic compounds • 0.2 mg/m³ for insoluble compounds • 0.1 mg/m³ for nickel subsulfide
United States	OSHA (1998) *(139)*	–	–	Occupational exposure: 1 mg/m³ (legal limit over an 8-h working day)
United States	ATSDR (2005) *(4)*	Inflammation in rats	MRLs for nickel sulfate hexahydrate: • intermediate inhalation: 200 ng/m³ • chronic inhalation: 90 ng/m³	–

Table A6.2 contd

Geographical scope	Authoritative body	Health end-point upon which recommendation is based	Guidelines and regulatory levels	Guideline/target/limit value (annual mean unless otherwise stated)
United States (California)	OEHHA (2014) *(140)*	Immune and respiratory system effects in rats exposed to a soluble Ni salt *(40–42)*	Occupational exposure: • REL for Ni compounds: 50 ng Ni/m³ • REL for nickel oxide: 100 ng Ni/m³	–
EU	EC (2001) *(141)*	Carcinogenic and non-carcinogenic effects	–	Limit value: 10–50 ng/m³ Calculated to limit the excess lifetime cancer risk to not more than 1 in 1 million
EU	CSTEE (2001) *(142)*	–	–	Limit value: 20 ng/m³ Suggested to provide reasonable protection for the general population to the carcinogenic effects of Ni compounds in ambient air
EU	EC (2005) *(143)*	–	–	Target value: 20 ng/m³ To be attained as far as possible – adapted from the CSTEE limit value *(142)*
United Kingdom	DEFRA (2008) *(144)*	Exposure–response model *(121)*, Norwegian studies *(126)*	–	Guideline value: 20 ng/m³ Based on an increased risk of cancer for occupational exposure of 20 µg/m³ Ni in air for 40 years and using an uncertainty safety factor of 1000

ACGIH: American Conference of Governmental Industrial Hygienists; CSTEE: Scientific Committee for Toxicity, Ecotoxicity and the Environment; EC: European Commission; MRL: minimal risk level; OSHA: Occupational Safety and Health Administration; TLV: threshold limit value.

Notes: MRL is defined as an estimate of daily human exposure to a substance that is likely to be without appreciable risk of adverse effects (other than cancer) over a specified duration of exposure *(145)*. TLV is defined as a concentration to which most workers may be repeatedly exposed without adverse effect averaged over a normal 8-h working day or 40-h working week over a working lifetime, expressed as a time-weighted average *(146))*. URF is defined as the additional lifetime cancer risk in a hypothetical population after a lifetime exposure to Ni compounds of 1 µg/m³ *(6)*.

A6.7 Future research needs

It is suggested that the chemical composition of PMs may better explain the related health effects than mass alone. However, the findings of epidemiological studies of specific chemical PM components are inconsistent, and may partly relate to exposure assessment limitations.

More epidemiological studies are needed on potential associations between nickel (and different nickel species) in ambient air and health effects. These should include an accurate exposure assessment of highly correlated source components of ambient PM.

Since experimental and epidemiological data indicate that the particular nickel species is important for risk estimation, further studies to characterize the nickel species present in ambient air and their physiochemical properties may be warranted.

Future epidemiological studies in nickel-exposed populations should be underpinned by experimental studies using environmentally realistic doses to determine the biological mechanisms relevant to disease etiology, progression and exacerbation.

A6.8 Concluding remarks

Unit risk estimates *(6,133,134)* and target values *(15,143)* for airborne nickel are based on carcinogenicity data from epidemiological studies on occupationally exposed populations. For the 2000 WHO *Air quality guidelines for Europe,* the critical health end-point used to derive a unit risk for nickel dust and nickel subsulfide were lung and nasal cancers reported in occupational cohorts *(6)*. A guideline value was not based on a linear dose–response, and no safe level for nickel compounds can be recommended.

At low concentrations, nickel is also a common constituent of ambient air and, alongside many other components, is suspected to induce the health effects attributed to $PM_{2.5}$. Indeed, potential associations of nickel exposure through ambient air with health effects have been reported *(31,32,147)*. The most recent review (2019) found most health evidence for cardiovascular and respiratory health *(31)*.

Individual reviews have concluded that the metal content of $PM_{2.5}$ in ambient air, especially the nickel content, and is associated with cardiovascular effects *(148)*.

Although measures to reduce levels of transition metals (including nickel) are likely to improve public health, limited data on the effect of exposure to ambient nickel levels on cardiovascular risk precludes their use in setting WHO air quality guideline standards *(32)*.

It is difficult to identify the effects of individual transition metals because their concentrations correlate strongly because of their shared sources; for example, industry and the combustion of petroleum products are shared sources of iron, nickel and vanadium.

Furthermore, experimental and epidemiological data suggest that risk estimation depends on the particular nickel species the exposure relates to. Several physiochemical factors (e.g. water solubility, particle size distribution, surface enrichment/encapsulation within the aerosol) may affect the bioavailability of nickel compounds and, hence, their toxicity and impact on human health *(16)*. Unfortunately, the limited number of measurement studies means that the species occurring in ambient air and their physiochemical properties are poorly characterized.

All of these factors should be consideration when reconsidering WHO air quality guidelines.

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