Limit Value Setting in Different Areas of Regulatory Toxicology

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Abstract

Standards for the protection of human health are important tools used for risk management. They represent the *limit value*, the maximum level of exposure deemed acceptable or tolerable, under the particular exposure circumstances for which they are set. Usually, there is a formal assessment process by which the standard is set. From a toxicological point of view, limit values reflect a *risk characterization* for an available database. Because assessments by individual scientists can differ, limits are usually based on a consensus. Although they must meet a scientific rationale, limit values also have to take into account political considerations, technical feasibility, and economic consequences.

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Exposure Limit Setting in the Context of the Regulatory Framework

According to the NAS/NRC (and IOMC) risk assessment/management paradigm, the risk characterization (the qualitative and, wherever possible, quantitative determination of the probability of occurrence of known and potential adverse effects of an agent under defined exposure condition) is the final stage of the risk assessment. The development of alternative regulatory options and the weighing of their economic, social, and political consequences are elements of risk evaluation (IOMC), which is the first stage of risk management. The US NAS/NRC report was concerned principally with risk assessment, and the EPA does not break down risk management into the three components identified by IOMC, namely, risk evaluation, emission and exposure control, and risk monitoring.

A principle way to regulate harmful substances is to manage exposures in order to prevent the exceedance of an acceptable or tolerable level of risk. For the regulator this includes setting and enforcing limit values. In this context, risk assessment and risk management are two related but independent processes. The *risk assessment* is based exclusively on scientific principles, while risk management (and, in particular, the risk evaluation) has to balance problems of socioeconomic costs and benefits, technical feasibility, societal perception, and public policy. The *risk management* process includes identification of the procedures that should be adopted to control exposure (engineering controls, use of protective equipment, remediation, etc.), the setting of limits, and the enforcement of the procedures and limits. Decoupling of political management and scientific analysis ensures clear responsibilities.

In the narrowest sense, limit values are measurable, quantitative thresholds representing uptake at the receptor or site of action within the body for hazardous substances. In practice the human's body burden of toxic chemical compounds, elements, or their metabolites is measured in biological samples (exhaled air, blood, urine, sweat, hair) or is estimated by extrapolation from measurements on exposure in various media such as air, water, soil, or food. The limit values have been recommended by the regulatory body established under the appropriate legal framework. *Legal limits* represent "tolerable" or "acceptable" risks, depending on their definition and the framework within which they are utilized.

The general public uses a very general understanding of the generic term *limit value*. Its scope is extended to guidance values, threshold values, ceiling values, etc. (see chapter "► The Regulatory Process in Toxicology" in this book), many of which are not enforceable. In contrast, if limit values are treated as values set within a legal framework established by the state, binding thresholds are defined and exceeding these thresholds triggers specific consequences. In contrast, normally adherence to *guidance values* (whether from nongovernmental organizations or from government) is voluntary.

The approach used for establishing limit values generally distinguishes between populations. It may also distinguish different levels of protection. A clear definition of the group "at risk" and of the type and level of risk being addressed is one of the

most important requirements when setting limits. Thus, health-based limit values can protect different groups of people (to different extents) depending on the circumstances of the exposure; these include:

- Workers.
- Consumers.
- The general public via environmental exposure (including human health-based standards aimed at protection of the environment as a whole or specific compartments (soil, groundwater/surface water, ambient air) within the environment).

The general methodology for establishing health-based limits should be equally applicable both in workplace and non-workplace scenarios. There should be a clear distinction between scientific and other aspects in the practice of setting limit values. Transparency of derivation, flexibility and ease of use, and defined rules for reevaluation and updating all help to build public acceptance of governmental limit values for the regulation of toxic chemicals. It should be noted that, although apparently different approaches for the risk assessment of chemicals in the workplace and in other scenarios have emerged on the international and the national level, these differences are due to, *inter alia*, the standards being for different populations (healthy workers, without children or the elderly and with the possibility of excluding the more susceptible individuals, versus everyone), often with different attitudes to risk, and different exposure scenarios (8-h workplace shifts versus continuous).

The Setting of Occupational Exposure Limits

Occupational Exposure Limit values (OELs) are set by national authorities or national institutions as limits for concentrations of hazardous compounds in the workplace air. Most of the industrialized countries establish and maintain OEL lists that regulate hazardous substance concentration levels to which workers may be exposed via inhalation, ingestion, or skin contact for specified time periods without being at risk over a working lifetime. These limits can be binding or indicative. For workplace airborne exposures to gases, vapors, and particulates, there are three principal limits in widespread use. They are based on different durations of exposure:

- The 8-h *time-weighted average* (*TWA*) *exposure limit* – the maximum average concentration of a chemical in air for a 8-h working day and 40-h week
- The *short-term exposure limit* (*STEL*) – the maximum average concentration to which workers can be exposed for a short period (usually 15 min)
- The ceiling value – a concentration that should not be exceeded at any time

In addition, *Biological Exposure Indices* (*BEIs*) represent the body burden, i.e., the concentration of chemicals in the body that would correspond to inhalation exposure at a specific concentration in air. Theoretically, biological effects indices are also possible, but they are unlikely to be set on the grounds that the aim is to prevent harmful effects occurring, and harmful effects are occurring if the measure is one of minimal harm.

Fundamental work to develop a systematic and comprehensive approach to setting occupational exposure limits was done by the American Conference of Governmental Industrial Hygienists (ACGIH). The conception of the ACGIH to derive Threshold Limit Values (TLVs) is one of the earliest developments aimed at managing workplace exposures. The ACGIH first published Maximum Allowable Concentrations (MACs) in 1946. These were later renamed TLVs and are republished annually by the ACGIH. TLVs are subject to a health-based view only and are not legally binding. ACGIH is not a regulatory authority. The US Occupational Safety and Health Administration (OSHA), which is a regulatory body, adopts mandatory limits, the *Permissible Exposure Limits* (*PELs*), and OSHA is supported in this process by the National Institute for Occupational Safety and Health (NIOSH). NIOSH develops its own health-based Recommended Exposure Limits (RELs). Together with ACGIH's TVLS, the RELs of NIOSH contribute to the setting of PELs by the OSHA; however, OSHA makes its own independent judgment regarding the final value of PEL. PELs arise from a comprehensive and well-documented rule making that takes into account significant health risks, sampling and analytical procedures, as well as technological and economic feasibility.

Similar approaches to that of ACGIH and NIOSH were adopted by the Deutsche Forschungsgemeinschaft (DFG) in Germany (non-enforceable maximum workplace concentration, MAK), the Netherlands, and Scandinavia.

The UK Health and Safety Executive (HSE, a regulatory authority with enforcement responsibilities) pursued a dual system of maximum exposure limits (MELs) and occupational exposure standards (OESs), each of which carried different exposure management requirements, until 2005. In 2005, UK's two-OEL system has nominally been replaced by a single-OEL system of *workplace exposure limits* (*WELs*), in which most of the existing MELs and OELs have been converted to WELs, but the different management approaches previously applicable to MELs and OESs have been maintained using EU classification and labelling requirements to identify which management approach is appropriate. The list of approved workplace exposure limits, which have been approved by the Health and Safety Executive (HSE), is legally binding.

On the European scale, the European Commission decided to set up a formal base for the work on the scientific evaluation of the health risks posed by exposure to chemical substances in the workplace with its Decision 95/320/EC of 12 July 1995 to encourage OELs. OELs are proposed by the Scientific Committee on Occupational Exposure Limits (SCOEL). The major task of the SCOEL is to give advice on the setting of OELs based on scientific data and, where appropriate, propose values. SCOEL's approach is documented in its *Methodology for the Derivation of Occupational Exposure Limits*: *Key Documentation* (2009).

The SCOEL may recommend OELs, which can be supplemented by further notations as:

- Eight-hour time-weighted average (TWA – 8 h)
- Short-term exposure limits (STEL)
- Biological limit values (BLVs)

The SCOEL aims to give health-based OELs that can be recommended when the available scientific data suggest that a clear threshold value can be identified for the adverse effects of the substance in question.

For some adverse effects (in particular genotoxic carcinogenicity, respiratory sensitization, and genotoxicity), it is deemed that, according to current knowledge, it is not possible to identify thresholds. In these cases, the SCOEL recommends a pragmatic OEL, which is established at levels considered implying sufficiently low risk. Since the late 1990s, SCOEL has developed the concept of "practical thresholds" in the derivation of OELs for carcinogens (Bolt 2008). For some carcinogens health-based OELs have been recommended, while a quantitative assessment of the substance-related carcinogenic risk is made for others. Non-genotoxic carcinogens and/or non DNA-reactive carcinogens are deemed to have a true threshold associated with a clearly founded NOAEL. The remaining carcinogens are categorized into three groups: genotoxic carcinogens for which a practical threshold is supported by studies on mechanisms and/or toxicokinetics and a health-based OEL can be derived based on an established NOAEL; genotoxic carcinogens, for which the existence of a threshold cannot be supported currently and the linear non-threshold model is applied as a default assumption; and non-threshold carcinogens for which a linear non-threshold model appears appropriate.

For respiratory sensitizers, the SCOEL evaluates data on a case-by-case basis and provides further information to the Commission.

An overview of existing OELs in the EU is given on the website of the European Agency for Safety and Health at Work (EU-OSHA). The so-called *Indicative Occupational Exposure Limit Values* (*IOELVs*) are health-based limits set under the Chemical Agents Directive (98/24/EC). IOELVs are listed in Directives which Member States are obliged to take into account when implementing by introducing national limits for the chemical agents in question, taking into account the European values. For chemicals for which a *binding OEL value* (*BOELV*) is established at Community level, Member States have to introduce a corresponding national binding limit based on, but not exceeding (i.e., higher than), the BOELV value.

When carrying out an assessment of human health effects for the chemical safety assessment under Regulation (EC) No 1907/2006 (REACH), the regulation requires the derivation of a "*Derived No Effect Level*" (*DNEL*) or "*Derived Minimal Effect Level*" (*DMEL*) by the registrant. DNEL or DMEL should be derived for all relevant routes of exposure (inhalation, dermal, or oral). Inhalation is usually considered an important potential route of exposure in the workplace. A (generic) maximum "safe" inhalation exposure level can be developed from the appropriate DNEL/DMEL using the recommended (in Guidance from ECHA) standardized procedure and assessment factors. If no OEL is available, the adequacy of the protective measures used in the workplace can be assessed by comparing the predicted or actual exposure levels with the maximum "safe" exposure level derived from this REACH-based procedure.

Health-Based Limit Values for Environmental Contaminants

Air Pollutants

The World Health Organization (WHO) defines air pollution as "contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere." Effects of air pollutants can impair human health either directly via inhalation exposure or indirectly via atmospheric deposition on edible plants and thus entering the food chain. Outdoor (ambient) and indoor air quality are usually considered separately.

WHO's *air quality guidelines* (for ambient air quality) were first published as "Air Quality Guidelines for Europe" in 1987 (WHO 1987), followed by the "Guidelines for Air Quality" in 2000. WHO emphasizes that these guidelines are not intended as standards. In moving from guidelines to standards, the prevailing exposure levels and environmental, social, economic, and cultural conditions in a country or region should be taken into account. The guideline setting process has been described in detail in the "Guidelines for Air Quality" (WHO 2000). In short, toxic effects are considered to be of two types, threshold and non-threshold. For substances where the critical effect is considered to have a threshold (including non-genotoxic carcinogenesis for which there is adequate mechanistic data), a *Tolerable Intake* (TI) expressed as airborne concentrations (i.e., μg or mg/m^3) is developed usually on the basis of an NOAEL. The derivation of guidance values for compounds present in other environmental media than air will require the allocation of proportions of the TI to such as air, food, and water, which will be based on sound information on relative exposure via different routes. A default approach, low-dose risk extrapolation, was conducted for carcinogens of IARC classification groups 1 and 2A, and an uncertainty factor approach applied in the case of substances in groups 2B and 3. The mechanism of action was the determining factor for the method of assessment. Hence, it was decided that compounds classified under 1 or 2A could be assessed using uncertainty factors, if evidence for a *threshold mechanism* of carcinogenicity existed. In contrast, compounds classified under 2B could be assessed by low-dose extrapolation methods, if a *non-threshold mechanism of carcinogenicity* in animals was proven.

WHO has revised its air quality guidelines in 2005 for key parameters of contamination (particulate matter, ozone, nitrogen dioxide, and sulphur dioxide). Whereas the previous guidelines (published in 1987 and 1997) concentrated on Europe, the 2005 revision included information from low- and middle-income countries worldwide. They are designed to offer global guidance on reducing adverse health impacts of air pollution. WHO air quality guidelines are not legally binding, but constitute an important basis for the regulation of air pollution. National air quality *standards* will vary from country to country. They depend on each country's attitude to health risk and its specific approaches to balancing risks to health and technological feasibility. They also take into account economic considerations and political and social factors.

Recently, WHO proposed its guidelines for selected indoor air pollutants (WHO 2010). The substances considered, i.e., benzene, carbon monoxide, formaldehyde, naphthalene, nitrogen dioxide, benzo(a)pyrene, radon, trichloroethylene, and tetrachloroethylene, have indoor sources or sources sub-adjacent to the building and are often found indoors in concentrations of health concern. WHO's guidelines for indoor air quality provide the scientific basis for legally enforceable standards.

The US *National Ambient Air Quality Standards* (NAAQS) are standards established by the US EPA under authority of the Clean Air Act (CAA) that apply to outdoor air. EPA has set NAAQS for the following principal pollutants: carbon monoxide, lead, nitrogen dioxide, ozone, particulate matter (PM), and sulphur dioxide. The standards are listed in Title 40 of the Code of Federal Regulations Part 50. CAA established two types of national air quality standards. Primary standards set limits to protect public health with an adequate margin of safety to allow for the health of vulnerable populations such as individuals suffering from respiratory disorders, children, and the elderly. Secondary standards set limits to protect public welfare, including protection against visibility impairment and damage to animals, crops, vegetation, and buildings.

The European Union has legislation concerned with ambient air quality. Directive 2008/50/EC of 21 May 2008 on ambient air quality consolidated as much existing legislation on objectives for ambient air quality in relation to sulphur dioxide, nitrogen dioxide and oxides of nitrogen, particulate matter (PM10, PM2.5), lead, benzene, carbon monoxide, and ozone, and Directive 2004/107/EC (which was not included in the consolidation) set objectives for arsenic, cadmium, mercury, nickel, and polycyclic aromatic hydrocarbons (PAHs) in ambient air.

Water Quality Criteria and Standards

Quality standards for ground and surface water may reflect either or both ecological criteria and quality criteria for drinking water. Either water resources used as sources of drinking water, and their related water ecosystems, should be protected from pollution, or they have to be purified during supply.

The European Union has implemented the Water Framework Directive (EU Directive 2000/60/EC) establishing a framework for Community action in the field of water policy. Its ultimate objective is to achieve a "good ecological and chemical status" for all community waters by 2015. The Directive establishes a list of 33 priority substances, including cadmium, lead, mercury, nickel, and its compounds, benzene, PAHs, and DDT, for action. The corresponding *environmental quality standards* (EQS) for priority substances and certain other pollutants have been laid down in Annex I of the Directive 2008/105/EC on environmental quality standards in the field of water policy. Generally, groundwater is the most sensitive and the largest body of freshwater and, in particular, is a main source of public drinking water supplies. The Directive 2006/118/EC on the protection of groundwater against pollution and deterioration comprises *groundwater quality standards* for nitrates and active substances in pesticides, including their relevant metabolites,

degradation, and reaction products. It also requires Member States to establish threshold values for groundwater pollutants and indicators of pollution on the basis of a minimum list of pollutants and their indicators (arsenic, cadmium, lead, mercury, ammonium, chloride, sulfate, trichloroethylene, tetrachloroethylene, and conductivity [which is indicative of saline or other intrusions]) considering the guidelines outlined in Annex II/Part A.

Section 304(a) (1) of the US Clean Water Act is the legal basis for the development of criteria for water quality for the protection of aquatic life as well as for human health (including organoleptic effects) in the USA. US EPA's *National Recommended* ***Water Quality Criteria*** defines the human health criterion as the highest concentration of a pollutant in water that is not expected to pose a significant risk to human health (US EPA 2013). The criteria consider human health for the consumption of water and organisms or organisms only. The methodology for deriving *Ambient Water Quality Criteria for the Protection of Human Health* has been revised in 2000 with revisions in the assessment of exposure to carcinogens, exposure to noncarcinogens, and exposure assessment and bioaccumulation. For noncarcinogens the effective EPA guidance on assessing noncarcinogenic effects of chemicals and for the Reference Dose (RfD) derivation should be used. More sophisticated methods are recommended for cancer risk assessment, including identification of the likely mechanism of human carcinogenicity and use of the most appropriate low-dose extrapolation.

WHO's water-related activities cover a broad range of activities, including water and drinking-water quality and infectious agents, toxic chemicals, and radiological hazards and general aspects of water supply and sanitation as well. A comprehensive framework, the *Guidelines for Drinking-Water Quality* (GDWQ), has been published regularly by the WHO. Two approaches to derive guideline values are used: one for "*threshold chemicals*" and the other for "*non-threshold chemicals*" (mostly genotoxic carcinogens). In establishing GDWQ, the IARC evaluation of carcinogenic compounds, where available, is taken into consideration. The principles in the derivation of ADIs (acceptable daily intakes) developed by FAO, JECFA, and JMPR have been adopted, where appropriate, in the derivation of TDIs used in developing guideline values for drinking-water quality. GDWQ are kept up to date through an ongoing "*rolling revision*" process. Increasingly the preferred approaches for the derivation of TDIs/ADIs for threshold chemicals include the benchmark dose (BMD) or the benchmark dose lower confidence limit (BMDL) and chemical specific adjustment factors. In order to make the distinction with respect to the underlying mechanism of carcinogenicity, compounds that have been shown to be a carcinogen (i.e., chemicals classified in group 1 or group 2A by IARC) are evaluated on a case-by-case basis. The evidence of genotoxicity, the range of species affected, the relevance of the tumors observed in experimental animals to humans, and the toxicokinetics of the substance are considered when determining the mode of action and therefore the approach taken. For carcinogens for which there is evidence to suggest a non-genotoxic mechanism or to suggest that detoxification mechanisms require to be overwhelmed by high doses, guideline values are derived using the threshold chemicals approach. WHO's normal allocation of 20 % of the TDI/ADI to

drinking water has changed from the allocation of 10 % used in the third edition of the GDWQ. The latter was found to be excessively conservative and the new value will be incorporated in new guidelines and revisions of existing guidelines (WHO 2011).

The current EU binding framework for Member State national standard setting for the quality of *water intended for human consumption at the point of deliver* is contained in the revised Council Directive 98/83/EC. The numerical values for chemical parameters in Annex I are generally those of WHO's GDWQ. The Commission must review Annex I at least quinquennially and has to make proposals for amendments in the light of scientific and technical progress.

Drinking Water Standards and *Health Advisories* (DWSHA) are issued periodically by US EPA. The Health Advisory (HA) Program publishes concentrations of drinking-water contaminants at Drinking Water Specific Risk Level Concentration for cancer (10^{-4} cancer risk) and concentrations of drinking-water contaminants at which noncancer adverse health effects are not anticipated to occur over specific exposure durations – one-day, ten-day, and lifetime. The *lifetime HA* for the drinking-water contaminant is calculated from its associated *Drinking Water Equivalent Level* (DWEL), obtained from its Reference Dose (RfD), and incorporates a drinking-water Relative Source Contribution (RSC) factor of contaminant-specific data or a default of 20 % of total exposure from all sources. *One-day HAs*, *ten-day HAs*, and *lifetime HAs* are not to be construed as legally enforceable federal standards. In contrast, an enforceable *Maximum Contaminant Level* represents the highest level of a contaminant that is allowed in drinking water. MCLs are set as close as feasible to the *Maximum Contaminant Level Goal* (MCLG) using the best available analytical and treatment technologies and taking cost into consideration (US EPA 2012).

Soil Values (Contaminated Land)

Land contamination may occur naturally or through anthropogenic activities. A distinction is often made between soil contamination originating from clearly confined sources (local or point source contamination, e.g., abandoned hazardous sites) and that caused by diffuse sources. In general, land contamination and remediation is a newer field of environmental legislation, and control is currently mainly through land use planning legislation. Different policies (e.g., on water, waste, chemicals, industrial pollution prevention, pesticides, agriculture) have contributed to preventing land being contaminated. However, as these policies have other aims, they are not sufficient to ensure an adequate level of protection. On the European scale, a proposal for a framework Directive (COM (2006) 232) exists which sets out common principles for protecting soils across the EU. Within this common framework, the Member States will be in a position to decide how best to deal with issues associated with contaminated land, its potential, uses, and its remediation. According to Article 11 of COM (2006) 232, a soil status report shall be issued including the concentration levels at which there are sufficient reasons to believe that the dangerous substances concerned pose a significant risk to human

health or to the environment, but special soil trigger values have not been proposed. Specific *soil trigger values* have been set in recent times at the national level, notably in Canada, Germany, the Netherlands, Switzerland, and United Kingdom.

The US EPA developed the Soil Screening Guidance to help standardize and accelerate the evaluation and cleanup of contaminated soils. This guidance provides a methodology to calculate risk-based and site-specific *Soil Screening Levels* (SSLs) for contaminants in soil. To calculate SSLs, the exposure equations and pathway models are run in reverse to back calculate an "acceptable level" of a soil contaminant. For ingestion, dermal, and inhalation pathways, toxicity criteria are used to define an acceptable level of contamination in soil, based on a 10^{-6} individual excess cancer risk for carcinogens and a hazard quotient (HQ) of 1 for noncarcinogens. SSLs are back calculated for migration to groundwater pathways using groundwater concentration limits (MCLGs, MCLs, or health-based limits (HBLs) (10^{-6} cancer risk or a HQ of 1, where MCLs are not available)). Generic SSLs are not national cleanup standards.

Future Perspectives

Increasingly, scientific quantitative risk assessment succeeds in identifying and reducing uncertainties that are inherent in all stages of the risk analysis. For substances with adverse health effects, alternative methods such as the benchmark dose method are being incorporated into the determination of dose–response relationships. These alternatives can reduce the shortcomings of the classical concept of determining tolerable body doses based on a NOAEL or LOAEL. Recent assessments of carcinogenicity are based on the complete analysis of all available biological information, including that on the mechanism of action. This is an improvement on the older risk quantification in the low-dose range using the linearized multistage model, which often led to an overestimation of risk. Exposure assessment methods are beginning to allow a more realistic description of exposure. However, better exposure models require an expanded database. Current issues include the use of multiple "worst case" (or "reasonable worst case") assumptions by regulatory authorities, leading to unrealistically precautionary overall risk assessments. Probabilistic approaches, such as Monte Carlo analysis, yield more realistic overall risk assessments. Emerging issues include approaches to considering the extrapolation to low doses in a sound manner, low-dose effects in toxicology/non-monotonic dose–response, and the development of scientific state-of-the-art approaches to mixtures of chemicals.

References

Bolt HM (2008) The concept of "practical thresholds" in the derivation of occupational exposure limits for carcinogens by the scientific committee on occupational exposure limits (SCOEL) of the European Union. Genes Environ 30:114–119

EU Directive 2000/60/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:327:0001:0072:EN:PDF
European Commission (2006) Proposal for a directive of the European parliament and of the council establishing a framework for the protection of soil and amending Directive 2004/35/EC. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2006:0232:FIN:EN:PDF
European Commission Employment, Social Affairs and Inclusion (2009) Methodology for the derivation of occupational exposure limits methodology for the derivation of occupational exposure limits. Key documentation (version 6). http://ec.europa.eu/social/main.jsp?catId=148&langId=en&internal_pagesId=684&moreDocuments=yes&tableName=INTERNAL_PAGES
US EPA (2012) 2012 edition of the drinking water standards and health advisories. http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf
US EPA (2013) National recommended water quality criteria. Last updated on Tuesday, June 11, 2013. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm#hhtable
World Health Organization (1987) Air quality guidelines for Europe. Copenhagen, WHO Regional Office for Europe, 1987 (WHO Regional Publications, European Series, No. 23)
World Health Organization (2000) Guidelines for air quality. Geneva, 2000. http://www.airimpacts.org/documents/local/AQGUIDE.pdf
World Health Organization (2005) WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide Global update 2005. http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf
World Health Organization (2010) WHO guidelines for indoor air quality: selected pollutants. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf
World Health Organization (2011) Guidelines for drinking-water quality, 4th edn. http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/index.html

Resources

European Agency for Safety and Health at Work (EU-OSHA). http://osha.europa.eu/en/topics/ds/oel/members.stm
Summaries of EU legislation > Environment. http://europa.eu/legislation_summaries/environment/index_en.htm
UK Health and Safety Executive. http://www.hse.gov.uk/
U.S. Department of Labor, Occupational Safety & Health Administration. http://www.osha.gov/
US Environmental Protection Agency. http://www.epa.gov/
World Health Organization. http://www.who.int/en/