Assessment framework for biological limit values

To: the State Secretary for Participation and Integration

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Health Council of the Netherlands

contents

samenvatting

Blootstelling aan gevaarlijke stoffen op de werkplek kan leiden tot schade aan de gezondheid. In Nederland werkt 1 op de 6 werknemers met gevaarlijke stoffen en naar schatting overlijden jaarlijks 3.000 werknemers vroegtijdig door blootstelling aan gevaarlijke stoffen op het werk. Volgens de Arbowet zijn werkgevers verplicht om werknemers te beschermen tegen nadelige gezondheidseffecten van deze blootstelling. Op verzoek van het ministerie van Sociale Zaken en Werkgelegenheid (SZW) leidt de Gezondheidsraad gezondheidskundige advieswaarden af. Dit zijn concentraties van stoffen in de lucht waarvan verwacht wordt dat blootstelling hieraan gedurende een werkzaam leven niet of in beperkte mate tot gezondheidsschade zal leiden. Het ministerie van SZW gebruikt deze advieswaarden om wettelijke grenswaarden voor de werkvloer vast te stellen. Werkgevers moeten ervoor zorgen dat blootstelling niet boven de luchtgrenswaarden uitkomt.

Biologische grenswaarden kunnen meerwaarde hebben
Voor sommige stoffen biedt een luchtgrenswaarde onvoldoende bescherming, bijvoorbeeld als blootstelling ook plaatsvindt via de huid of de mond. Ook is luchtmonitoring niet voor alle stoffen mogelijk. Voor die stoffen kan de Gezondheidsraad gezondheidskundige biologische grenswaarden afleiden. Dit zijn grenswaarden van stoffen die met biomonitoring in biologisch materiaal zoals urine, bloed of uitgeademde lucht worden gemeten. Het ministerie geeft de voorkeur aan het gebruik van luchtgrenswaarden boven biologische grenswaarden, mits lucht-grenswaarden een minstens even goede bescherming bieden.

Raad gevraagd om afwegingskader te ontwikkelen
De afgelopen decennia is veel vooruitgang geboekt op het gebied van biomonitoring, wat heeft geleid tot een toename in de wetenschappelijke gegevens voor het afleiden van biologische grenswaarden. Er is echter geen systematische methode voor het bepalen van de meerwaarde van biologische grenswaarden ten opzichte van luchtgrenswaarden.
Het ministerie van SZW heeft de Gezondheidsraad gevraagd om een wetenschappelijk afwegingskader te ontwikkelen waarmee bepaald kan worden of een biologische grenswaarde voor een bepaalde gevaarlijke stof op de werkplek toegevoegde waarde heeft als alternatief voor, of als aanvulling op een luchtgrenswaarde. Ook heeft het ministerie de raad gevraagd om het kader ter illustratie toe te passen op enkele stoffen, en om te adviseren over implementatie van biomonitoringsmethoden in de praktijk. Om deze adviesvraag te kunnen beantwoorden heeft de Gezondheidsraad de multidisciplinaire tijdelijke commissie Biologische grenswaarden geïnstalleerd.

Afwegingskader brengt overwegingen in kaart

De commissie heeft zich gericht op zowel de technische als de ethische aspecten van biologische grenswaarden en maakte daarvoor gebruik van bestaande ethische kaders en technische richtlijnen. Het afwegingskader is bedoeld om gebruikt te worden door de commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), onderdeel van de Gezondheidsraad. Deze commissie heeft als taak om gezondheidskundige advieswaarden af te leiden. Met het kader kan de commissie de relevante informatie in kaart brengen, afwegen en bediscussiëren.

Het kader bestaat uit een combinatie van overwegingen die in onderlinge samenhang beoordeeld moeten worden. Hierbij gaat het om:

- **Legitimiteit:** Een gezondheidskundige biologische grenswaarde moet het legitieme doel dienen: het beschermen van werknemers tegen gezondheidsschade door blootstelling aan gevaarlijke stoffen.
- **Effectiviteit:** Het gebruik van een gezondheidskundige biologische grenswaarde moet effectief zijn in het bereiken van het legitieme doel. Er wordt een aantal aspecten overwogen om de effectiviteit van het gebruik van een biologische grenswaarde te vergeleken met die van een op lucht gebaseerde grenswaarde. Daarnaast zijn er voorwaarden om een biologische grenswaarde af te kunnen leiden, zoals de beschikbaarheid van een biomarker.
- **Subsidiariteit:** De minst ingrijpende effectieve methode waarmee het legitieme doel kan worden bereikt heeft de voorkeur.
- **Proportionaliteit:** De toepassing van een gezondheidskundige biologische grenswaarde moet in redelijke verhouding staan tot het legitieme doel.

Op basis van deze overwegingen wordt een beslissing genomen over het afleiden van een gezondheidskundige biologische grenswaarde voor een bepaalde stof in plaats van, of naast, een luchtgrenswaarde. Door het kader toe te passen op een aantal voorbeeldstoffen blijkt dat het kader hiervoor geschikt is.

Neem afwegingskader op in werkwijze

Het afwegingskader is bedoeld als onderdeel van de werkwijze van de commissie GBBS voor het beoordelen van gevaarlijke stoffen op de werkplek. Een gezondheidskundige biologische grenswaarde zal worden afgeleid conform deze werkwijze. Net als bij luchtgrenswaarden is een direct gevolg van het opstellen van een gezondheidskundige biologische grenswaarde dat deze publiek toegankelijk wordt, en door werkgevers gebruikt kan worden om aan hun zorgplicht te voldoen. Daarnaast vormt een gezondheidskundige biologische grenswaarde een basis voor de besluitvorming door het ministerie van SZW over wettelijke biologische grenswaarden, net zoals dat nu het geval is voor luchtgrenswaarden. Voor implementatie van biomonitoringsprogramma's zijn stof-specifieke protocollen voor biomonitoring nodig en training van professionals.

executive summary

Exposure to hazardous substances in the workplace can lead to adverse health effects. In the Netherlands, 1 in 6 workers work with hazardous substances and it is estimated that each year, 3,000 workers die earlier due to occupational exposure to hazardous substances. Employers are required by law to protect employees against these effects. At the request of the Ministry of Social Affairs and Employment, the Health Council derives health-based Occupational Exposure Limits (OELs), which are concentrations of substances in the air at which it is assumed that no or limited health effects are expected. The ministry uses these recommended values to set legally binding Occupational Exposure Limits (OELs) for the workplace. Employers monitor exposure to make sure that it does not exceed these legal limits.

Biological Limit Values can have added value

For some substances, an air-based OEL does not provide sufficient protection, for example when a substance is taken up orally or through the skin, or when air monitoring is not technically feasible. In these cases, the Health Council can derive health-based Biological Limit Values (BLVs). These are limit values for substances measured in human bodily material such as urine, blood or exhaled air, through biomonitoring. The ministry states that air monitoring and OELs are preferred if this provides equal or better protection.

Council asked to develop assessment framework

Recent and ongoing developments in the field of biomonitoring have led to increased availability of scientific data for establishing health-based BLVs. However, there is currently no systematic approach to assess for which substances applying a BLV has added value. The Ministry of Social Affairs and Employment asked the Health Council to develop an assessment framework to help determine whether, for a given hazardous substance, a health-based BLV is of added value either as an alternative to, or in addition to the use of a health-based OEL. Furthermore, the ministry asked the council to put the assessment framework in practice by applying it to a set of relevant substances, and to advise on implementation of biomonitoring methods in practice. To respond to the request, the Health Council installed the multidisciplinary temporary committee Biological Limit Values.

Framework lists considerations for BLVs

The committee has focused on both technical and ethical aspects of biological limit values, using existing ethical frameworks and technical

guidance documents. The framework has been developed for use by the Dutch Expert Committee on Occupational Safety (DECOS), part of the Health Council. This committee is tasked with recommending health-based limit values. The committee can use the framework to map, weigh and discuss the relevant information.

The framework consists of a combination of considerations that must be assessed in relation to each other. It includes:

- **Legitimacy:** A health-based BLV should serve the legitimate goal, which is to protect workers against negative health effects due to exposure to hazardous substances.
- **Effectivity:** The use of a health-based BLV should be effective in achieving the legitimate goal. A number of aspects are considered to compare the effectiveness of using a biological limit value with that of an air-based limit value. Furthermore, there are requirements for derivation of a BLV, such as the availability of a biomarker.
- **Subsidiarity:** The least intrusive of the effective methods to reach the legitimate goal is preferred.
- **Proportionality**: The application of health-based BLVs should be in reasonable proportion to the legitimate goal.

Based on these considerations, a decision is made about the derivation of a health-based BLV instead of, or in addition to, a health-based OEL.
The suitability of the framework was demonstrated by applying it to a number of example substances.

Include framework in DECOS guidance document
The assessment framework is intended to be part of the guidance document of the DECOS for assessing hazardous substances in the workplace. Health-based BLVs will be derived according to this guidance document. As with OELs, a direct consequence of deriving a health-based BLV is that it is made publicly accessible, including its documentation, and thereby available to employers to comply with their duty of care.
In addition, the Ministry of Social Affairs and Employment can use BLVs as a basis for considering legally binding limit values, as is the case for air-based OELs. For implementation of biomonitoring programmes, substance-specific protocols are needed, as well as training of professionals.

01 scope

1.1 Background

Exposure to hazardous substances in the workplace can lead to adverse health effects. To protect workers, employers are required by law to restrict this exposure as much as possible. At the request of the Ministry of Social Affairs and Employment the Dutch Expert Committee on Occupational Safety (DECOS), recommends health-based occupational exposure limits (OELs), which are concentrations of substances in the air below which no or limited adverse effects are expected in the course of and after working life, or in workers' offspring.[1] Informed by these OELs, the ministry can set legally binding OELs for the workplace. Employers must ensure that exposure does not exceed the OEL.

For some substances or situations, air-based OELs do not provide sufficient protection, for instance if a substance accumulates in the body, or if substantial exposure occurs via the oral or dermal route. In such cases, the DECOS can derive a health-based biological limit value (BLV).[1] BLVs are limit values measured in biological materials such as urine, blood or exhaled air. Biomonitoring can be an intrusive method (as it uses bodily material) and entails additional considerations regarding the use of biological material. In addition, according to the Ministry of Social Affairs and Employment, air monitoring fits better with the policy to prevent exposure from occurring via measures directed at the source when possible. Therefore, the Ministry of Social Affairs and Employment states that air monitoring and applying OELs are preferred, if these provide equal or better estimates of exposure than biomonitoring and BLVs.

For substances for which an OEL is not sufficiently protective, a BLV could provide a way to manage occupational exposure. Recent and ongoing developments in the field of biomonitoring have led to increased availability of scientific data for establishing health-based BLVs. However, there is currently no systematic approach to decide, for a given substance, on the derivation of a BLV instead of, or in addition to, an OEL.

1.2 Advisory request

In a request for advice dated 22 December 2022, the Ministry of Social Affairs and Employment asked the Health Council of the Netherlands to develop a scientific assessment framework to determine whether, for a given substance, setting a BLV is of added value to protect workers from adverse effects due to exposure to hazardous substances. This can be either as an alternative to, or in addition to the use of an OEL. Furthermore, the ministry requested the Health Council to illustrate the use of the assessment framework by applying it to a set of relevant substances, and to advise on further implementation of BLVs.

1.3 Committee and approach

To respond to the request, the Health Council installed the temporary Committee Biological Limit Values, hereafter called the committee, with experts in the field of ethics, toxicology, risk assessment, occupational hygiene, occupational medicine and biomonitoring. The members of the committee are listed on the last page of this advisory report.

The committee used available national and international guidance documents on biomonitoring to build an assessment framework for health-based BLVs. The framework is illustrated by the assessment of three substances that have been evaluated in earlier reports from the DECOS or comparable organisations.

The draft advisory report was reviewed by the DECOS and the standing committee of the Health Council.

1.4 Definitions

Air monitoring
Air monitoring is used to measure concentrations of hazardous substances or their breakdown products in the air of the workplace.

Biomonitoring
Biomonitoring can be used to assess exposure to hazardous substances by measuring the substance itself, its metabolites (breakdown products) or its adducts in human biological materials such as urine, blood or exhaled air. The parameter measured is called a biomarker. As the current report focuses on monitoring of occupational exposure, the term biomonitoring is generally used to refer to exposure monitoring. The report also covers biomonitoring of biochemical effects such as haemoglobin- or DNA-adducts, as these are biomarkers of exposure to carcinogens.[2] Biomonitoring of biomarkers of (early) biological effects and disease is outside the scope of the current advisory report.

Health-based Occupational Exposure Limit
A health-based Occupational Exposure Limit (OEL) is an exposure level measured in the air below which no or limited adverse effects are expected during and after working life, or in workers' offspring.[1] Health-based OELs are derived by the Health Council and can form the basis of legally binding OELs set by the ministry.

Health-based Biological Limit Value
A health-based Biological Limit Value (BLV) is a biomarker level below which no or limited adverse effects are expected during and after working life, or in workers' offspring. Internationally, the term Occupational Biomonitoring Level (OBL) is sometimes used, which is comparable to a health-based BLV.[3] The committee uses the EU terminology in this advisory report. Health-based Biological Limit Values are derived by the Health Council and can form the basis of legally binding BLVs set by the ministry.

Substance

Substances in this report are defined as substances as assessed by the DECOS, which can be mono-constituent chemicals, mixtures, complex substances, or emissions from a process. Examples and exceptions are outlined in the *Guidance for recommending classifications and health-based occupational exposure limits*.[1]

02 exposure limit values

Dutch employers are required by law to protect employees against exposure to hazardous substances in the workplace. Control measures in the workplace are aimed at preventing this exposure. At the request of the government, the Health Council derives occupational exposure limits, below which no or limited adverse effects are expected. In general, air-based limit values are derived, but in some situations biological limit values for which exposure is measured in bodily material such as blood, urine or exhaled air might offer better protection.

2.1 Occupational Health and Safety

In the Netherlands, 1 in 6 workers work with hazardous substances. It is estimated that each year, 3,000 workers die earlier due occupational exposure to hazardous substances.[4] Most of the deaths are cancer-related. Of the total burden of occupational diseases, 40% is caused by exposure to hazardous substances.[4,5]

As stated in the Dutch Working Conditions Act (*Arbowet*), all employees have the right to work safely and healthily. Protection of exposure from hazardous substances is part of this act. In all cases where employees are or may be exposed to hazardous substances, the employer must ensure effective protection of the employee's health and safety (art. 4.1b, *Arbowet*). A key element of occupational health and safety is the risk inventory and evaluation (RI&E). Companies in the Netherlands are required to have a RI&E in place (art. 5.1, *Arbowet*). An RI&E is a continuous process in which all potential risks in a company are inventoried, evaluated, and prioritised.[6] Subsequently, an action plan is developed to address all the risks present in the work environment. Exposure to hazardous substances is one of the potential risks addressed next to workplace safety, physical working conditions and psychosocial work pressure. An RI&E needs to be updated if it is rendered outdated, for example due to a change in the working environment. The RI&E is also the basis for the periodic occupational health examinations (PAGO). According to the Dutch Working Conditions Act (art.18, *Arbowet*), the employer is required to offer a PAGO to workers. For working with hazardous substances, the PAGO should be offered before, in between and after potential exposure periods.

2.2 Air monitoring and biomonitoring

The risks of exposure to hazardous substances in the workplace are managed by the hierarchy of control measures which is set in the Dutch Working Conditions Act (art. 3.1b, *Arbowet*). The STOP strategy is a tool to present this hierarchy of control measures (text box STOP strategy). In addition, successful exposure control requires exposure monitoring. Exposure is commonly estimated by measuring or modelling occupational air concentrations of substances. Air monitoring determines potential exposure outside the body, via stationary or portable monitoring equipment. Air monitoring may provide information about the emission patterns from the source of a substance. A disadvantage of air monitoring

is that it may under- or overestimate exposure. It only takes into account potential exposure through inhalation and not via oral and/or dermal uptake. Hence, when oral and/or dermal uptake plays a role, air monitoring may underestimate total exposure.[7,8] On the other hand, when personal protective equipment (such as respiratory masks) is used, air measurements outside the equipment may overestimate exposure.
In addition, air monitoring may not be feasible for all substances or under certain workplace conditions (e.g. working in small spaces).

Biomonitoring is used to assess exposure to hazardous substances by measuring the substance itself, its metabolites (breakdown products) or adducts, in biological materials such as urine, blood or exhaled air.
By using biomonitoring, the internal exposure to a substance is assessed. An advantage compared to the external measurements in air, is that biomonitoring integrates exposure from all exposure routes.
Another advantage of biomonitoring is that the internal exposure provides information on the total body burden that is more directly related to the systemic effect. Furthermore, via biomonitoring, also non-occupational or previous exposures to a hazardous substance may be detected.
Disadvantages of biomonitoring may be the intrusiveness of the method (as it uses bodily material) and that it entails additional considerations regarding the use of biological material. A more extensive description of the advantages and disadvantages of exposure assessment methods is available elsewhere.[7] Since air monitoring and biomonitoring have different advantages and disadvantages, the methods are often used complementary to each other.

STOP strategy

The STOP strategy reflects the principle of the hierarchy of control measures from the Working Conditions Act aimed at minimising workplace risks.[9] Based on this principle, interventions to control the exposure are deployed, with the highest measures to be implemented where possible.

1. Substitution: The hazard or hazardous substance is removed or replaced with a less hazardous alternative.
2. Technical measures: Workers' exposure to the hazard or hazardous substance is prevented or reduced through modifying equipment or the workspace, using protective barriers, ventilation, and more.
3. Organisational measures: Work practices are adapted to reduce the duration, frequency, or intensity of workers' exposure to the hazard or hazardous substance.
4. Personal protective equipment: personal protective equipment, such as gloves, safety glasses, and respirators, is used to limit workers' exposure to the hazard or hazardous substance.

2.3 Current applications of biomonitoring

Occupational biomonitoring is currently applied on a small scale in the Netherlands. It is directed towards evaluation of exposure control measures such as the use of personal protective equipment against exposure to hazardous substances such as chrome, benzene, and polycyclic aromatic hydrocarbons.[7] Researchers have described biomonitoring as an underused tool for exposure assessment in occupational settings.[10] Biomonitoring can also be used for monitoring biological effects. Although not yet widely applied, effect biomonitoring is seen as promising for assessment of effects to complex mixtures of substances.[3]

Among the general population, biomonitoring programmes are increasingly used for measuring exposure to substances. This is partly driven by the progress that has been made in the field of biomonitoring research and monitoring programmes. Biomonitoring is seen as a valuable complementary tool to air or environmental monitoring.[11,12] In 2024, the Health Council advised the Dutch government to develop and implement a structural biomonitoring programme to measure exposure to hazardous substances in the general population.[13]

2.4 Occupational exposure limits

The Health Council has been evaluating the toxicity of hazardous substances in the workplace at the request of the Ministry of Social Affairs and Employment since 1993. The evaluations are currently done by the Dutch Expert Committee on Occupational Safety (DECOS; Dutch GBBS) according to its guidance document.[1] The committee evaluates substances of concern that are used in, or produced or process-generated in the Netherlands. This includes mixtures (e.g. ink), complex substances (e.g. crude oil), emissions from industrial processes (welding fumes, diesel engine exhaust, wood dust and emissions from iron and steel founding), and groups of substances (e.g. polycyclic aromatic hydrocarbons, and diisocyanates). DECOS recommends health-based OELs which are exposure levels in air below which no or limited adverse effects are expected during and after working life, or in workers' offspring. Effects can be local or systemic, immediate or long term (see text box *Derivation of health-based Occupational exposure limits* on the next page). The evaluations form health-based, scientific recommendations for the ministry as a basis for setting legally binding limit values.

2.5 Biological limit values

When OELs do not provide sufficient protection, the DECOS can recommend a health-based BLV. Analogous to an OEL, a health-based BLV is a concentration in a biological sample, such as blood, urine or exhaled air, below which no or limited adverse effects are expected. There are different approaches to derive health-based BLVs.[3] Most organisations who derive BLVs use data on the direct relationship between biomarker and health effect or data on the association between air concentrations and biomarker levels as a basis.[3]

There is currently one EU-wide legally binding BLV, which is for lead, (art. 4.20, *Arbeidsomstandighedenregeling*) due to a decision at EU level based on an assessment by the Scientific Committee for Occupational Exposure Limits (SCOEL).[14] The BLV of lead was favoured over an OEL as the occupational exposure through oral uptake was seen as

Derivation of health-based Occupational Exposure Limits

The derivation of health-based Occupational Exposure Limits is described in detail in DECOS' *Guidance for recommending classifications and health-based occupational exposure limits*.[1] In brief, the DECOS decides on the critical adverse effect(s), the type of OEL to be set, the choice between a threshold- or risk-based approach in deriving OELS, the selection of the key study or studies for the point of departure in deriving OELs, the derivation method and the use of adjustment factors and defaults. The type of OEL may be a particular air-based OEL (8h time-weighted average or short-term exposure limit or ceiling value) and also includes the option of a biological limit value (BLV).

The assessment process starts with a literature search, followed by an assessment of the quality of the individual studies and evidence synthesis on the existence of a relationship between exposure and adverse effect. To propose a health-based OEL, the DECOS searches for evidence of a relationship regarding all possible adverse effects (local and systemic effects; acute, short-, mid- and long-term effects) and for studies with data on quantitative relationships or associations between exposure and identified adverse effects. These data are then used to derive a health-based OEL and to consider whether a skin notation should be issued if a substance can cause adverse effects upon dermal exposure.

relevant.[14,15] Over the years, the DECOS derived a number of BLVs (cadmium and inorganic cadmium compounds, 4,4'-methylene bis (2-chloroaniline) and 4,4'-methylenedianiline), but these were not legally implemented.[16-19]

In its reports, the DECOS has provided the rationale for the added value for deriving these BLVs. However, a systematic approach to consider the added value does not exist. In their advisory report on biomonitoring, the Social and Economic Council (SER) points out that legally binding BLVs should be grounded on a science-based framework in which criteria are used to decide whether a BLV would add to the protection of workers' health.[8] In line with the SER report, the Ministry of Social Affairs and Employment has expressed the need for a systematic approach to assess the added value of a BLV in protecting the health of workers. In the next chapter, the committee outlines a systematic, science-based framework to decide on derivation of health-based BLVs for hazardous substances.

03 assessment framework

The committee developed a science-based framework to decide on derivation of a BLV for a given hazardous substance. The framework consists of a set of ethical considerations: the derivation of a health-based BLV should serve a legitimate goal, achieve this goal effectively, be the least intrusive, and should be proportional to the legitimate goal.
The framework has been developed to be included in the workflow of the DECOS.

3.1 Scope and use

The science-based assessment framework is meant as a tool to decide on the derivation of a BLV to contribute to the protection of workers from adverse effects due to exposure to hazardous substances. The BLV may be derived either instead of, or in addition to an air-based OEL.
The framework has been developed to guide decisions of the DECOS on deriving a BLV for a given substance. The derived BLV is intended to be used in practice, as a basis for the ministry to decide on setting legal limits and as a publicly available health-based limit value to inform employers.

An ethical framework to guide decisions on deriving a BLV was not available from the literature. Therefore, the committee developed such a novel framework that integrates ethical and technical aspects of exposure monitoring. Reports of the Social and Economic Council (SER), the Dutch National Institute for Public Health and the Environment (RIVM), and the DECOS guidance documents were used as input.[1,7,8] The committee also reviewed documents on BLVs from other countries and organizations and scientific literature on added value of biomonitoring and BLVs.[3,10,20-24]
The rationale of the set of ethical considerations to guide decisions on monitoring methods is described in detail in the RIVM report.[7]
The relevant scientific and technical aspects for these considerations were extracted from the cited documents.

The framework consists of a set of ethical considerations to evaluate or compare specific types of interventions or measures (Figure 1 on the next page). Scientific information is needed as input for these ethical considerations. The framework is to be regarded as a sequence of considerations for selecting the preferred methods that serve the legitimate goal. The legitimate goal for deriving limit values is to protect the worker against adverse health effects caused by the exposure to hazardous substances. The ethical considerations in the framework are legitimacy, effectivity, subsidiarity (in terms of intrusiveness), and proportionality. The order of the considerations in the framework is such that each of the subsequent considerations takes the former into account. This means that the method should be effective in achieving the legitimate goal, the subsidiarity of the method is considered in the context of effectivity of the method, and all prior considerations are taken into account to decide whether the method is proportional to the goal.
Each consideration should lead to a conclusion before the subsequent consideration is evaluated.

Assessment framework for biological limit values (BLVs)

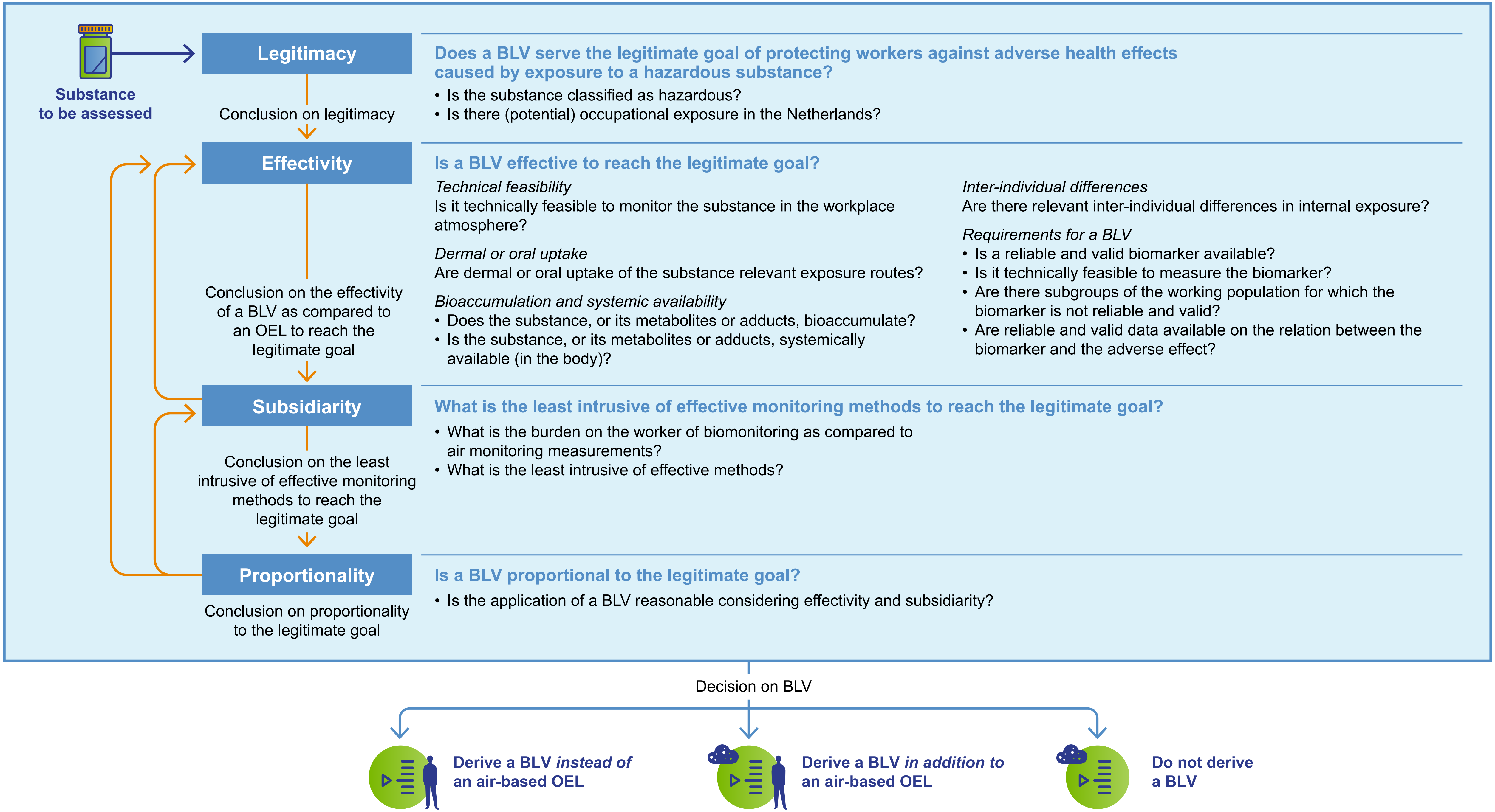

Figure 1 Assessment framework

For each ethical consideration, the framework lists specific questions (described in 3.2-3.5) (Figure 1). The framework is a tool to collate, weigh and discuss the relevant information, rather than a decision tree. As such, the framework facilitates systematic and transparent choices regarding the preferred method. Systematic in this context means that for any substance evaluated by the DECOS the added value of derivation of a BLV should be assessed consistently using the considerations described in this assessment framework. Transparent means that the considerations behind the decision whether to derive a BLV are made explicit in the DECOS' advisory reports.

The DECOS' considerations are science-based. As such, they include evidence on the hazard of the substance, the effectiveness of the method, and on analytical and methodological aspects (with consequences for intrusiveness, such as the number of biological samples needed). DECOS does not consider workplace-specific aspects and costs associated with the practical implementation of biomonitoring. Based on all aspects considered, a final decision is made about derivation of a BLV instead of, or in addition to, an OEL.

3.2 Legitimacy

The starting point of the assessment framework is considering whether a BLV for a certain substance serves a legitimate goal. The legitimate goal is the protection of the worker against adverse health effects caused by the exposure to hazardous substances. The questions to be addressed here are whether the substance is potentially hazardous and whether there is potential exposure. The requests for limit values from the ministry generally concern substances to which workers in the Netherlands can be exposed and the exposure is suspected to be hazardous. In the existing DECOS workflow, the hazardous nature of the substance is evaluated before derivation of limit values.

3.3 Effectivity

The use of a BLV should be effective in serving the legitimate goal of protecting workers against adverse health effects caused by exposure to hazardous substances. Therefore, the effectivity considerations refer to the effectivity of biomonitoring as a tool to quantify the exposure to hazardous substances. In addition, deriving a BLV requires the availability of a biomarker that is related with the adverse effect. The effectivity of the method is a decisive aspect for determining the added value of a BLV.
A BLV can only be derived when it is effective in quantifying exposure, and when the requirements for derivation are met. Several factors contribute to the effectivity of a BLV. These factors are summarized in paragraphs 3.3.1-3.3.5.

3.3.1 Technical feasibility of air monitoring

For substances for which air monitoring is technically not feasible, biomonitoring and a BLV may offer an alternative. For hazardous substances with a low vapor pressure (<100 Pa) measurement of gas/vapor phase exposure in air may be difficult at lower concentrations. In addition, for some substances air concentrations are so low that air monitoring becomes technically challenging. There may also be practical reasons why air monitoring is not suitable, for example when air monitoring interferes with work activities.

The committee notes that even if air monitoring is feasible, there may be reasons which make air monitoring a less effective method for assessing workers' exposure. These reasons are described in the following paragraphs.

3.3.2 Dermal or oral uptake

Substances may penetrate the skin or can be ingested. For hazardous substances for which dermal or oral absorption is a relevant route of exposure, air monitoring is insufficient, and biomonitoring provides added value.[8,10]

Dermal uptake may take place when the worker is in direct contact with the hazardous substance or in direct contact via contaminated materials. The DECOS evaluates the significance of dermal absorption and recommends on adding a skin notation.[1] A skin notation for a given substance indicates a substantial contribution of dermal exposure to systemic adverse effects. A skin notation is added when the amount absorbed by both hands and forearms in 1 hour is more than 10% of the amount that can be absorbed by the lungs when exposed to the health-based OEL for 8 hours.[1]

Despite mitigation measures such as not eating, drinking and smoking in the workplace and decontamination, oral ingestion may occur. If occupational exposure through ingestion is substantial, a health-based BLV may be of added value. For some groups of substances, the oral uptake route is known to be substantial. Some hazardous substances, such as certain metals, pesticides, pharmaceuticals and radionuclides are typically ingested orally with a substantial contribution to the overall internal exposure.[25] For substances for which dermal or oral absorption is not a relevant route of exposure, a BLV may be of added value for reasons described in other paragraphs.

3.3.3 Bioaccumulation and systemic availability

Systemic availability is a requirement for the identification of a biomarker in blood and an indicator of the potential for causing adverse systemic effects.

Some hazardous substances, such as PFAS, lead, or cadmium, can accumulate in the human body for years up to a lifetime.[10] When previous exposure plays a role in the total exposure, air monitoring and the application of an OEL do not provide sufficient protection. Therefore, the use of a health-based BLV may be of added value for substances that bioaccumulate.[8,10]

The committee is aware that non-occupational or previous exposures may add to the internal exposure of hazardous substances that bioaccumulate. In some cases, the contribution of non-occupational exposure could be separated from occupational exposure via baseline measurements. However, regardless of whether the exposure is occupational or not, according to the committee, derivation of a health-based BLV for bioaccumulating substances has added value as it protects the health of the worker. For substances that do not bioaccumulate, a BLV may be of added value for reasons described in other paragraphs.

3.3.4 Inter-individual differences

A health-based BLV can have added value in the protection of workers if there is inter-individual variability in internal exposure.[10] With biological monitoring people can be identified who are more susceptible to a hazardous substance because their body metabolises or eliminates the substance differently. The application of a BLV in such a scenario can be of added value to protect people whose internal exposure to the toxic substance or its toxic metabolite would be relatively higher at the same level of external exposure.

The SER has stated that substances with large inter-individual differences in metabolism of, and sensitivity to, the substance do not qualify for legal BLVs as such differences might impede the interpretation of biological values.[8] The committee, however, notes that air monitoring is not suited to detect inter-individual differences in internal exposure. Therefore, a standard safety factor is applied when deriving an air-based OEL to account for inter-individual differences. Application of a BLV in biomonitoring programmes facilitates addressing this inter-individual variation via direct measurements. Guidance for setting up an occupational biomonitoring programme is addressed by other organisations and lies outside the scope of this advisory report.[3,8,26]

For substances for which inter-individual differences do not play a substantial role, a BLV may be of added value for reasons described in other paragraphs.

3.3.5 Requirements for a BLV

For derivation of a BLV, a biomarker needs to be available that is reliable, valid and specific to the hazardous substance. The technical feasibility to measure the biomarker may also play a role. Furthermore, it is to be considered whether there are subgroups of the working population for which the biomarker may not be reliable. Criteria for biomarker selection have been extensively described in the Organization for Economic Co-operation and Development (OECD) guidance document.[3]

To derive a BLV, sufficient scientific literature should be available as a basis for this. It is part of the DECOS workflow to first consider whether limit values from other organisations, if available, meet DECOS' quality standards.[1] Existing risk assessments from other organisations may also be used as a starting point for an updated literature search and subsequent derivation of a limit value. If there are no limit values from other organisations available, the DECOS derives one based on their own literature search of original studies and reviews. BLVs can be derived from data on the direct relationship between biomarker and health effect or from data on the association between air concentrations and biomarker levels.[3] Equivalent to OELs, the committee anticipates the derivation of threshold-based BLVs as well as risk-based BLVs. A threshold-based limit value represents an exposure level below which no significant effect is observed. Risk-based limit values are derived when such a threshold cannot be established because exposure to the substance is considered to always pose a health risk. Risk-based limit values are based on predefined risk levels.[1]

3.3.6 Conclusion on effectivity

After all individual aspects of effectivity have been considered, a conclusion is to be drawn on the effectivity of the use of a BLV and the biomarker, in comparison to an OEL, in serving the legitimate goal of protecting workers against exposure to hazardous substances. When biomonitoring is not effective as a tool to quantify exposure, the decision will be not to derive a BLV. When requirements of a valid biomarker or data needs are not met, a BLV cannot be derived and the DECOS may recommend further research. If it is concluded that a BLV is at least as effective as an OEL, it will be further evaluated for subsidiarity and proportionality.

3.4 Subsidiarity

The consideration of subsidiarity means that in general, the least intrusive of the effective methods is preferred. The intrusiveness involves the individual burden for the worker caused by the monitoring measurements. The burden of biomonitoring measurements as compared to air monitoring is weighed in the context of the effectiveness. A more intrusive measurement may be well acceptable if this offers more effective protection against hazardous substances. However, if all effective methods are highly intrusive, it should be reevaluated whether a less effective, less intrusive method would be more acceptable. At the same time there is an obligation to explore new (technical) developments that allow the BLV to be set based on a less intrusive sample (such as measurements in dried blood spots). In many situations, air-based monitoring may be seen as less intrusive than measurements in blood. A biomarker in urine or exhaled air is often considered less intrusive than a biomarker in blood. However, the individual burden also depends on the measurement method for the biomarker. For example, repeated collection of urine samples or wearing portable air sampling devices may be perceived as more intrusive than drawing one blood sample.

When assessing the subsidiarity, it should be taken into account that worker participation in a biomonitoring programme remains voluntary. If individual workers choose not to participate in a biomonitoring programme, the obligation of the employer to protect the workers against exposure to hazardous substances remains in force. This can be achieved by implementing measures prompted by the group level biomonitoring results of the (other) workers and by following the hierarchy of control measures. In addition, the produced occupational biomonitoring results are personal data, which are protected by data privacy laws.

The consideration of subsidiarity will lead to a weighed conclusion on intrusiveness and effectiveness of monitoring methods.

3.5 Proportionality

Finally, it is to be evaluated whether the application of a BLV in the context of a biomonitoring programme is proportional given the legitimate goal. The question to be addressed here is whether there is a reasonable relationship between the legitimate goal and the means to achieve that goal. To draw this conclusion, the collated information on effectiveness and subsidiarity is taken into account. There is also the option of reconsidering a method if it is not proportional to the goal. In an iterative process, it is to be considered whether less effective and/or less intrusive methods would be proportional.

3.6 Decision on BLV derivation

Based on all considered aspects, a decision is made about the derivation of a BLV. The committee anticipates that the framework enables a science-based decision about the preferred method for all substances. For a given substance, different methods may be complementary but will not be evaluated as equal. Hence, the collated information will inform DECOS' decision about derivation of a BLV *instead of* an OEL or *in addition to* an OEL. For example, for substances for which it is decided to derive a BLV and exposure via inhalation has local effects in the lung, a BLV may be derived *in addition to* an OEL. When air monitoring is technically not feasible, a BLV may provide an alternative to an OEL and may be derived *instead of* an OEL.

04 illustration of the framework

The committee selected the following substances to illustrate the use of the framework: lead and its inorganic compounds, benzene, and isocyanates. For lead and benzene, it was concluded that a BLV should be derived in addition to an OEL. For isocyanates, derivation of a BLV would have added value, but adequate scientific data are lacking and hence a BLV would not be indicated. The suitability of the framework to guide decisions on the derivation of BLVs was demonstrated by using these example substances.

4.1 Scope

In this chapter the assessment framework is applied to a set of example substances. This illustrates how the framework's considerations converge into a decision on the derivation of a BLV. The framework is a tool to collate, weigh and discuss the relevant scientific information, which requires expert knowledge. During the development of the framework the example substances were also used to improve the applicability of the framework. The committee selected three substances which were previously evaluated by the DECOS and/or a comparable organisation. The information and conclusions were based on these earlier evaluations and hence the conclusions do not necessarily reflect the current state of science (Table 1).

Table 1. Overview of example substances

Substance	References
Lead and its inorganic compounds	ECHA-RAC 2020 [15]
Benzene	DECOS, Health Council 2014 [27] ECHA-RAC 2018 [28]
Isocyanates	DECOS, Health Council 2018 [29] ECHA-RAC 2020 [30]

4.2 Lead and its inorganic compounds

Lead and its inorganic compounds are a group of substances which contain the heavy metal lead, either in its pure form or as an inorganic salt or oxide.[15] At the moment, this is the only substance for which a legally binding BLV is implemented in the Netherlands.[31] The committee has applied the assessment framework to this substance to illustrate how the framework can be used. The individual questions and detailed answers, as well as the conclusions for the different ethical considerations and the decision on derivation, can be found in the text box (on the next page).

Assessment framework applied to

lead and its inorganic compounds

Legitimacy

- *Is the substance classified as hazardous?*
  Lead and its inorganic compounds are classified as reprotoxic and have known neurotoxic and adverse renal, cardiovascular and haematological effects.[15]
- *Is there (potential) occupational exposure in the Netherlands?*
  Exposure to lead and its inorganic substances in Dutch workplaces may occur during use, production and recycling of lead-containing products such as paint and building materials.

Conclusion on legitimacy: Deriving a BLV for lead serves a legitimate goal.

Effectivity

- *Is it technically feasible to monitor the substances in the workplace atmosphere?*
  It is possible to measure lead and its inorganic compounds in the air through a suitable filter in a sampling probe connected to a suction pump. There are several standardized protocols available.[15]
- *Are dermal or oral uptake of the substance relevant exposure routes?*
  Next to inhalation, the oral route is considered a primary occupational exposure route for lead and its inorganic compounds by hand to mouth exposure in case of insufficient workplace hygiene. Dermal absorption of lead and its inorganic compounds through healthy human skin is minimal.[15]
- *Does the substance, or its metabolites or adducts, bioaccumulate?*
  Inorganic lead accumulates primarily in bones and teeth. The relatively large pool of lead in bone maintains elevated blood lead levels long after exogenous exposure has ended.
- *Is the substance, or its metabolites or adducts, systemically available?*
  Lead is systemically available.[15]
- *Are there relevant inter-individual differences in internal exposure?*
  Uptake can be influenced by concurrent food intake, and the iron- and calcium status of the individual. There are genetic polymorphisms influencing the toxicokinetics of lead leading to higher blood lead levels under the same external exposure.[15,32]
- *Is a reliable and valid biomarker available?*
  Lead and its inorganic compounds have biomarkers in blood, bone, urine, hair and nails. Lead in venous blood (PbB) is the most prominent and best validated biomarker for exposure to lead and its inorganic compounds.[15] Lead in bones, nails and hair reflects long-term cumulative exposure. Lead in bones can be measured either through biopsies or by x-ray fluorescence, which are not routine measurements. Lead in urine is another potential biomarker, but the correlation with blood levels shows a wide variation and there are insufficient data on the association with toxic effects.[15] Lead in blood measurements via capillary blood sampling (via a finger puncture) are being studied, but have not yet been validated for occupational settings.[33,34]
- *Is it technically feasible to measure the biomarker?*
  Lead can be measured to a sufficiently low limit of quantification in venous blood.[15]
- *Are there subgroups of the working population for which the biomarker is not reliable or valid?*
  There is no indication that the biomarker is not reliable or valid in any subpopulation.[15] For women of childbearing age, the biomarker is reliable but for derivation of a BLV it is to be taken into account that exposure to lead has the additional risk of developmental toxicity for the offspring.[15]

- *Are reliable and valid data available on the relation between biomarker and adverse effect?*
  For lead in venous blood and bones, but not urine, there are reliable and valid data from biomonitoring studies in the occupational and general population.[15]

Conclusion on effectivity: Measurement of lead and its inorganic compounds in the air is possible and an OEL protects against exposure via inhalation, but not via the oral route. A BLV would be effective in protecting the worker against exposure from all routes, including oral exposure and the potential for bioaccumulation. Lead levels in venous blood are considered the most reliable and valid biomarker and there are reliable and valid data on the relationship with adverse effects. A BLV for lead in venous blood is effective to reach the legitimate goal, in addition to an OEL.

Subsidiarity

- *What is the burden for the worker of biomonitoring as compared to air monitoring?*
  As compared to air monitoring, measurement of lead in blood may be perceived as a higher burden for the worker.
- *What is the least intrusive of effective methods?*
  Measurement of lead in blood is more effective for capturing total exposure but the method is more intrusive. There are different biomarkers for lead and its inorganic compounds (in blood, bone and urine). Although lead in bones reflects long-term exposure best, and better than in blood, bone measurements are not yet usable for practical application in occupational setting. Capillary blood and urinary measurements may be perceived as less intrusive, but are currently less effective.

Conclusion on subsidiarity: A BLV based on lead in blood is the least intrusive effective method to reach the legitimate goal.

Proportionality

- *Is application of a BLV reasonable considering effectivity and subsidiarity?*
  Of the available sampling methods, lead in venous blood offers the best balance between effectiveness to protect the worker and intrusiveness to the workers body integrity. Measuring lead in blood is a reasonable method to reach the legitimate goal.

Conclusion on proportionality: The application of a BLV for lead in blood is proportional to reach the legitimate goal of protecting workers against adverse effects from exposure to lead.

Decision: Based on the framework, the decision for lead and its inorganic compounds is to derive a BLV *in addition to* an OEL.

4.3 Benzene

Benzene is a low molecular aromatic hydrocarbon which is a colourless liquid with a sweet odour at room temperature.[27] The DECOS has previously concluded that there are suitable biomarkers of benzene and ECHA-RAC derived a BLV in addition to an OEL.[27,28] The committee has applied the assessment framework to this substance to illustrate how the framework can be used. The individual questions and detailed answers, as well as the conclusions for the different ethical considerations and the decision on derivation, can be found in the text box.

Assessment framework applied to **benzene**

Legitimacy

- *Is the substance classified as hazardous?*
  Benzene is classified as mutagenic and carcinogenic.[27]
- *Is there (potential) occupational exposure in the Netherlands?*
  Benzene exposure can occur in Dutch workplaces via air during the combustion of organic materials.. Furthermore, benzene is present in crude oil, natural gas condensate, light petroleum products and products derived through cracking of petroleum, and it is used as feedstock for synthesis of materials such as styrene and pharmaceuticals. Workers in fossil fuel industries may be exposed to benzene but there is also exposure from road traffic and wood burning stoves.[27]

Conclusion on legitimacy: Deriving a BLV for benzene serves a legitimate goal.

Effectivity

- *Is it technically feasible to monitor the substances in the workplace atmosphere?*
  Air monitoring is technically possible, and measurement methods are well established.[27,28]
- *Are dermal or oral uptake of the substance relevant exposure routes?*
- Benzene is readily absorbed via inhalation, and via dermal and oral routes, of which inhalation is the most important route for exposure.[27] Oral uptake is considered negligible in occupational situations. Dermal exposure is considered possible and relevant.[27,28] When air levels are controlled better, dermal exposure becomes a more important route of exposure.[35]
- *Does the substance, or its metabolites or adducts, bioaccumulate?*
  Benzene is quickly absorbed by inhalation and distributed, but does not accumulate in the human body.[35]
- *Is the substance, or its metabolites or adducts, systemically available?*
  Benzene is systemically available and metabolized to benzene oxepine, which is unstable and rearranges to phenol which can be further metabolized to a series of urinary metabolites.[35]
- *Are there relevant inter-individual differences in internal exposure?*
  No relevant inter-individual differences between external and internal exposure have been reported.[36]
- *Is a reliable and valid biomarker available?*
  Yes, biomarkers of benzene exposure include benzene levels in blood, urine and exhaled air. In addition, benzene and its metabolites in urine and adducts of benzene have been used as biomarkers of exposure.[27,28,35] For all biomarkers analytical methods are available which are sufficiently sensitive. However, for low benzene concentrations (<1 ppm), benzene and SPMA (a benzene mercapturic acid metabolite) in urine seem to be the most reliable biomarkers.[27,28]
- *Is it technically feasible to measure the biomarker?*
  Well validated methodologies are available for the urinary biomarkers at the current low OELs.[28]
- *Are there subgroups of the working population for which the biomarker is not reliable or valid?*
  In the available literature, none have been identified.

- *Are reliable and valid data available on the relation between biomarker and adverse effect?*
  Not directly, but a sound correlation between external exposure (airborne benzene levels), for which OELs have been derived, and internal exposure (urinary concentrations of biomarkers) has been established. OELs have been derived based on relationships with the adverse effect.[27,28]

Conclusion on effectivity: Benzene exposure occurs primarily via inhalation, but dermal absorption is a relevant additional route of exposure. Reliable biomarkers for benzene in urine do exist. So far, there is insufficient information to link the proposed biomarker directly to the adverse health effect, but a BLV can be derived based on established OELs. Considering the substantial dermal uptake of benzene, a BLV would provide effective protection against adverse health effects caused by exposure to benzene, in addition to an OEL.

Subsidiarity

- *What is the burden for the worker of biomonitoring as compared to air monitoring?*
  Urinary measurements require sampling at the end of exposure or the end of work shifts. Biomonitoring in urine implies a higher burden for workers than air monitoring.
- *What is the least intrusive of effective methods?*
  Urine sampling is considered to have a relatively low burden for the worker as compared to blood and exhaled air measurements.

Conclusion on subsidiarity: Urinary measurements have minimal burden for the worker, and they effectively measure the total benzene exposure.

Proportionality

- *Is application of a BLV reasonable considering effectivity and subsidiarity?*
  The application of a BLV based on urinary measurements would be reasonable to the goal, considering that the total benzene exposure can be measured more effectively in urine than in air, while intrusiveness of urine sampling is limited.

Conclusion on proportionality: The application of a BLV for benzene based on urinary measurements would be reasonable to reach the legitimate goal.

Decision: Based on the framework, the decision for benzene is to derive a BLV in addition to an OEL.

4.4 Isocyanates (di- and triisocyanates)

Isocyanates are a group of organic compounds containing one or more functional groups with the molecular formula R–N=C=O. For this example, the general term isocyanates refers to isocyanates with two (diisocyanates) or three (triisocyanates) functional groups.[29] In their earlier reports the DECOS and ECHA-RAC derived an OEL but no BLV for isocyanates.[29,30] The committee has applied the assessment framework to this substance to illustrate how the framework can be used. The individual questions and the detailed answers, as well as the conclusions for the different ethical considerations and the decision on derivation, can be found in the text box.

Assessment framework applied to **isocyanates**

Legitimacy

- *Is the substance classified as hazardous?*
  Yes. Isocyanates are substances that are known to induce allergy signs and symptoms of the airways when inhaled.[29] Furthermore, the degradation products and metabolites of 4,4′-methylenediphenyl diisocyanate (MDI) and toluene diisocyanate (TDI) have been classified as mutagenic and carcinogenic.[29,30]
- *Is there (potential) occupational exposure in the Netherlands?*
  Yes. Isocyanates are used in a variety of occupational settings worldwide.[37] In Dutch workplaces, it is estimated that approximately 716,000 workers work with isocyanates.[38]

Conclusion on legitimacy: Deriving a BLV for isocyanates serves a legitimate goal.

Effectivity

- *Is it technically feasible to monitor the substances in the workplace atmosphere?*
  The measurement of isocyanates in air is considered challenging as these substances are highly reactive and therefore unstable.[29,30] A number of air measurement methods are available to assess isocyanate exposure, but these all have certain limitations with respect to both sampling and analysis.
- *Are dermal or oral uptake of the substance relevant exposure routes?*
  Occupational biomonitoring studies indicate that dermal exposure could be a relevant exposure route.[37] Since dermal exposure can lead to sensitisation and development of respiratory allergenic signs and symptoms, the DECOS applied a skin notation.[29] Oral uptake may occur via hand-to-mouth behaviour but oral exposure is expected to be negligible in comparison to inhalation exposure.[37]
- *Does the substance, or its metabolites or adducts, bioaccumulate?*
  Diisocyanates are reactive compounds and therefore quickly metabolised or conjugated. Biomonitoring studies have reported urinary amine levels, which reflect isocyanate-derived diamines released by hydrolysis of protein adducts in urine or plasma. The half-lives of amines are relatively short (i.e. in the range of 2-5 hours). In plasma of exposed workers, toluene di-isocyanate (TDI) was found to be primarily bound to albumin and these albumin adducts remain in the circulation for about 20-25 days.[39]
- *Is the substance, or its metabolites or adducts, systemically available?*
  Isocyanate protein adducts are found in plasma after absorption.
- *Are there relevant inter-individual differences in internal exposure?*
  Yes, large inter-individual differences in urine concentrations were observed among in auto body shop workers exposed to hexamethylene diisocyanate (HDI).[40] This variability might be due to differences in respiration rate, diisocyanate uptake and absorption and diamine clearance rates.[40]
- *Is a reliable and valid biomarker available?*
  Biological monitoring methods are available for the most common isocyanates.[29] However, the DECOS concluded in 2018 that the biomonitoring methods developed so far for isocyanates did not provide reliable values. Since then, a review paper has been published which reported a fair correlation between urinary amines and airborne measurements.[37] It has not yet been sufficiently established whether current biomarkers for isocyanates provide reliable results needed for a quantitative risk assessment.

- *Is it technically feasible to measure the biomarker?*
  Yes, methods are available to measure isocyanate adducts in plasma and metabolites in urine.[29]
- *Are there subgroups of the working population for which the biomarker is not reliable or valid?*
  Reliability of current biomarkers is not yet established for the working population or subgroups thereof.
- *Are reliable and valid data available on the relation between biomarker and adverse effect?*
  Bronchial hyperreactivity is regarded as the most informative effect to estimate the occurrence of occupational asthma due to exposure to isocyanates. ECHA-RAC has concluded that there are no reliable markers of (respiratory) sensitisation to diisocyanates that could be used to identify either a threshold or a dose-response relationship for induction of sensitisation.[30] It is therefore recommended for now, according to the advice of the DECOS, that BLVs for isocyanates be used only as biological indicators.[29]

Conclusion on effectivity: Air monitoring of isocyanates is considered technically challenging. A BLV may have added value given that, next to inhalation, dermal uptake is a relevant exposure route. Biomarkers for isocyanates are available, but the reliability is not yet established. Moreover, data to determine a quantitative relationship between a biomarker and the critical adverse effect bronchial hyperreactivity, are lacking. Based on earlier evaluations by the DECOS and ECHA-RAC, it is concluded that a BLV for isocyanates is not effective.

Subsidiarity

- A BLV was found not to be effective and therefore the evaluation of subsidiarity is not relevant.

Conclusion on subsidiarity: Not applicable

Proportionality

- A BLV was found not to be effective and therefore the evaluation of proportionality is not relevant.

Conclusion on proportionality: Not applicable

Decision: Based on the framework, the decision for isocyanates is not to derive a BLV as it is not effective. Further data on the relationship between the urinary biomarker and bronchial hyperreactivity to isocyanates are needed.

05 implementation

5.1 Implications of the assessment framework

The assessment framework has been designed to be used by the DECOS to systematically assess whether a BLV is to be derived instead of, or in addition to, an air-based limit value to protect the worker from adverse health effects due to exposure to hazardous substances. The assessment framework has been developed to become part of the DECOS guidance for recommending health-based occupational exposure limits.[1] The framework allows a systematic and transparent assessment of considerations to derive health-based BLVs.

The Ministry of Social Affairs and Employment intends to adopt the BLVs derived by the DECOS similar to the current procedure of air-based OELs. In case the ministry decides to implement legally binding BLVs, these will be implemented *in addition to* legally binding OELs, unless otherwise advised by the DECOS. The current procedure is that when the DECOS establishes a health-based limit value, the ministry uses this as a basis to set a legally binding OEL or BLV. Limit values can be derived on a risk-based or a threshold-based approach. For substances for which limit values are derived on a risk-based approach, exposure to the substance always poses a certain health risk. For risk-based limit values, considerations of feasibility are made by the SER Subcommittee on Limit Values of Substances in the Workplace based on feasibility studies and the discussion with representatives of the Dutch government, worker unions and employers.[8] For limit values derived with a threshold-based approach, it is assumed that there is a safe level for the substance in question and currently they are directly used by the ministry to set legally binding limit values.[1]

A direct consequence of limit values derived by the DECOS is that these, including documentation, will be publicly accessible and thereby available to employers to comply with their duty of care. According to the Working Conditions Decree, if employees can be exposed to a hazardous substance in the workplace for which there is no legally binding limit value, the employer is required to derive a suitable limit value which protects the worker. They can use the limit values derived by the DECOS or other trusted organisations. In addition, the assessment framework itself may be used by employers who register substances, including limit values, under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation, and by the Ministry of Social Affairs and Employment to inform discussions at the EU level concerning BLVs.

Limit values, whether air-based or biological, contribute to the health of workers only when implemented and complied with in working practice. The Netherlands Labour Authority concluded in 2024 that improvement in the handling of hazardous substances in the workplace is needed.[41] Areas for improvement include monitoring of exposure and compliance to limit values, next to improving awareness and implementing preventive measures. According to the Labour Authority, a healthy workplace is the shared responsibility of the employers, workers, occupational health professionals, policymakers and the Labour Authority themselves.[41]

5.2 Using health-based Biological Limit Values in practice

The implementation of the framework by the DECOS can lead to the availability of BLVs for more substances, thereby facilitating the application of occupational biomonitoring in the Netherlands.

The application of occupational biomonitoring in companies requires a thought-out plan that is part of an already established occupational health and safety plan. Furthermore, biomonitoring protocols are to be developed by multidisciplinary teams with expertise in toxicology, exposure sciences, epidemiology, ethics and law, occupational hygiene and occupational medicine. Within the interdisciplinary Human biomonitoring for Europe Initiative (HBM4EU), protocols were developed and biomonitoring guidance values were derived which has advanced human biomonitoring on the European level. The work is continued in the European Partnership for the Assessment of Risks from Chemicals (PARC) project which involves biomonitoring studies across Europe. Existing guidance documents from international organisations and the guidance currently under development from the European Agency for Safety and Health at Work (EU-OSHA) provide general guidance on implementation of biomonitoring programmes.[3,26] In addition, the International Society for Exposure Science develops indicators for guidance of biomonitoring of specified substances.[42]

At the national level, the Dutch Association of Occupational Hygiene (*Nederlandse Vereniging voor Arbeidshygiëne*, *NVvA*) and the Dutch Association for Occupational Medicine (*Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde*, *NVAB*) published a guide to periodic medical examinations of workers exposed to hazardous substances which also contains instructions on the development of a biomonitoring plan.[43] Further risk-based guidance on biomonitoring needs to be developed by these or other organisations or knowledge institutions. In addition, to support occupational hygienists, occupational health professionals and toxicologists in their tasks to apply occupational biomonitoring, there is a need for advanced education and training.

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Assesment framework for biological limit values

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[a] Consulted experts are consulted by the committee because of their expertise. Consulted experts and observers are entitled to speak during the meeting. They do not have any voting rights and do not bear any responsibility for the content of the committee's advisory report.

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