Protocol for the selection of health-based reference values (RV)

KATLEEN DE BROUWERE, MIRJA VAN HOLDERBEKE, CHRISTA CORNELIS

01-10-2020

SUMMARY

The Flemish Agency for Care and Health (/http://www.zorg-en-gezondheid.be/EN/) develops and implements the health policy of the Flemish community. One of its tasks is to formulate recommendations regarding environmental health related issues such as drinking water, indoor air quality, hot spot contamination, etc. Hereto, the Agency relies on health-based, toxicological reference values (RV) (like TDI, RfD, MRL) for the general population established by other (in general international) bodies such as WHO, ATSDR, US-EPA, Health Canada, RIVM, etc. Until now, the Flemish Agency for Care and Health has applied a case-by-case evaluation to select the most appropriate health-based reference value for a given substance in a given situation.

Striving for increased transparency and efficiency, the Agency aims at implementing a more systematic and standardized selection of the most appropriate health-based reference value. VITO was asked to support the Agency in developing such a selection strategy. Hereto, VITO drafted this protocol for the selection of health-based, toxicological reference values.

A differentiated approach for the selection of RVs is followed depending on the exposure scenarios for which the health-based reference value will be applied. A decision tree that guides the assessor towards 1) which effects to consider, 2) which types of RV to search for, and 3) which level of detail to apply in the selection of the RVs was set up in Chapter 2.1.

A first type of RV is in the context of a (very) **urgent situation** (incidents, disasters) where one is asked for the assessment on immediate health risks for exposed individuals. How to deal with these situations and a list of agencies and data sources that provide health-based reference values for use in urgent situations is given in Paragraph 2.2. Additionally to immediate health risks, carcinogenicity should be assessed to screen for potential longer-term cancer risks.

If the selection of the reference value is **not in the context of an urgent situation**, the decision on whether using health-based RV for acute, intermediate or chronic duration of exposure should be made case by case (paragraph 2.3.1). Next, it should be considered whether RVs for carcinogenic effects need to be explored. Hereto, existing classification schemes for human carcinogenicity of substances as used by IARC, EU-GHS, US EPA and NTP are given in paragraph 2.3.2. A workflow on how to deal with the information on carcinogenicity as given by the different agencies and the relation to further steps in the selection of the RV is discussed in detail.

If the context of use of the RV (for non-incidents situations) is in a **specific case**, a **default evaluation** according to a standardized protocol is applicable. A tiered approach for the selection of both RVs for carcinogenic and RVs for non-carcinogenic effects is elaborated in Chapter 2.5. Information such as aspects to consider, sources to consult and points of decision are visualised in a flow diagram and discussed step-by-step.

For use in a **generic context** (e.g. establishing indoor air quality guidelines for legal purposes, drinking water quality guidelines) or if the outcome of the default evaluation is inconclusive, it is advised to follow an **in-depth investigation** (Chapter 2.7) for the selection of the health-based reference value.

The protocol relies on the use of health-based reference values available in four different types of sources, going from primary sources on supranational level (e.g. WHO) to secondary sources following a national methodology or a more limited peer review process, tertiary sources originating from a variety of sources and finally quaternary sources which can be used as building blocks to derive HB

RV. In addition, the age of RV derivation is an important criterion since recently derived RVs take into account the most recent advancements of scientific studies which may serve as key study for deriving the RV, and also follow the most recent approaches for selection of assessment and uncertainty factors.

For substances classified as carcinogenic, irrespective of the type of evaluation ('default evaluation' or 'in-depth evaluation'), both carcinogenic and non-carcinogenic effects should be considered.

Chapter 3 shows the reporting format for the selection of RV including a table for reporting the default selection and a table for in-depth investigations. Some examples of how to use the protocol are shown in Chapter 4. Also, a table with the selected Flemish Indoor Air Target and Intervention Guidance values and a table with HB guidance values for outdoor air - following an in depth investigation as described in the protocol - is included in this chapter.

In annex, more information is provided on specific themes such as EFSAs approach to genotoxic carcinogens, OEHHA's evaluation of the carcinogenicity of chemicals and a comparison between DNELs and HB RV.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

ADWG	Australian Drinking Water Guideline
AEGL	Acute Exposure Guideline Level
ANSES	Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail
ATSDR	Agency for Toxic Substances and Disease Registry
BMDL(10)	Benchmark Dose Level 10 % Response (95 % confidence interval)
CAS	Chemical Abstract Service
C&L	Classification and Labelling
CRinhal	Excess carcinogenic risk via air
CRoral	Excess carcinogenic risk via oral intake
DCRF	Dose Rate Correction Factor
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
EFSA	European Food Safety Agency
EU-GHS	European Union Globally Harmonised System of Classification and Labelling
HB (RV)	Health based (Reference Value)
IAQG	Indoor Air Quality Guideline
IARC	International Agency for Research on Cancer
INERIS	Institut National de l'Environnement Industriel et des Risques
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JRC	Joint Research Centre (EC)
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest Observed Adverse Effect Level
MRL	Minimum Risk Level (mg/kg.d of mg/m^3); en Maximum Residue Limit (mg/kg)
MTR	Maximaal Toelaatbaar Risiconiveau
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OEHHA	Office of Environmental Health Hazard Assessment

OEL	Occupational Exposure Limit
OSRTI	US EPA Office of Superfund Remediation and Technological Innovation
OVAM	Openbare Vlaamse Afvalstoffenmaatschappij
PPRTV	Provisional Peer Reviewed Toxicity Values
PTMI	Provisional Tolerable monthly intake
QSAR	Quantitative Structure Activity Relationship
REACH	Registration, Evaluation and Authorisation of Chemicals
REL	Reference Exposure Limit
R(e)V	Reference Value
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RV	Risk Value
TC	Tolerable Concentration
TCA	Tolerable Concentration in Air
TCEQ	Texas Commission on Environmental Quality
TDI	Toelaatbare Dagelijkse Inname, Tolerable Daily Intake
TTC	Threshold of toxicological concern
TWI	Tolerable Weekly intake
US-EPA	United States Environmental Protection Agency
VITO	Vlaamse Instelling voor Technologisch Onderzoek
VMM	Vlaamse MilieuMaatschappij
VR	Verwaarloosbaar Risiconiveau
VTR	Valeur Toxicologiques de Référence
WHO	World Health Organization

CHAPTER 1: RATIONALE FOR A PROCEDURE FOR SELECTION HEALTH-BASED REFERENCE VALUES

The Flemish Agency for Care and Health (/http://www.zorg-en-gezondheid.be/EN/) develops and implements the health policy of the Flemish community. One of its tasks is to formulate recommendations regarding environmental health related issues such as drinking water, indoor air quality, hot spot contamination, etc.

Hereto, the Agency relies on health-based, toxicological reference values (RV) (like TDI, RfD, MRL) for the general population established by other (in general international) bodies such as WHO, ATSDR, US-EPA, Health Canada, RIVM, etc.

These agencies have a long history, and an excellent reputation for their expertise in establishing health-based, toxicological reference values for various chemical substances. In general, these agencies act as advisory bodies, and their advises are implemented in environment – health policies.

Notwithstanding that various bodies establishing RVs follow similar procedures for their derivation of toxicological reference values, differences in the use of key studies, assessment and extrapolation factors have led to (sometimes) wide ranges in RVs for the same substance. A typical example is the divergence in RVs for chronic exposure via inhalation of formaldehyde: WHO Indoor Air Quality Guideline IAQG (2010): 100 µg/m³ versus Exposure limit of 1 µg/m³ developed by JRC in the INDEX project (JRC, 2005).

Until now, the Flemish Agency for Care and Health has applied a case-by-case evaluation to select the most appropriate health-based reference value for a given substance in a given situation.

Striving for increased transparency and efficiency, the Agency aims at implementing a more systematic and standardized selection of the most appropriate health-based reference value. VITO was asked to support the Agency in developing such a selection strategy.

Hereto, VITO made a review of existing procedures for selecting health-based reference values used in neighbouring countries (e.g. ANSES, 2012; INERIS, 2006; RIVM, 1997; RIVM, 2015), and performed a survey within (Belgian) regional agencies and agencies in other countries active in the field of risk assessment. The survey was complementary to the literature review since several agencies apply an unwritten or not-public procedure for the selection of health-based reference values. This review is available in a separate report (in Dutch) (De Brouwere and Cornelis, 2015).

Based on the experiences and practices from other agencies, and after consultation with the Flemish Agency for Care and Health about their needs and required focus, a protocol for the selection of health-based, toxicological reference values was drafted.

With respect to the needs and required focus desired by the Flemish Agency for Care and Health, it should be noted that the protocol aims to achieve a balance between pragmatism and scientific rigour. Pragmatism is required given the time and budget constraints to perform an in-depth analysis in each and every dossier; a systematic strategy (preferentially scientifically underpinned) is a prerequisite for transparency and reproducibility.

The use or selection of legal standards is out of scope of this study; only toxicological, health-based reference values are considered. Neither is a ‘de novo’ derivation of health-based reference values based on toxicological studies subject of this study.

It is noted that the scope of this procedure is limited to reference values for the general public (including potentially sensitive populations such as infants and the elderly); reference values for occupational exposure is out of scope.

Finally, it is realized that several choices in the protocol, or the order of choices, decision points and priorities are based on pragmatic reasons rather than on strong scientific arguments, and therefore may be open to criticism.

In 2016, the first version of the protocol for selection of health-based values was published. The current, revised version (June 2020) is an update of the first version, accounting for additional sources, including the Walloon procedure for selection of health based reference values (ISSeP, 2018), and recommendations following the application of the protocol in various case studies.

CHAPTER 2: PROCEDURE FOR THE SELECTION OF HEALTH-BASED REFERENCE VALUES

A differentiated approach for the selection of RVs is followed for reasons of efficiency (see below):

- a RV for incidents is applied in cases of evaluation of chemicals exposure upon incidents (→ urgency to evaluate and manage the situation);
- the default evaluation is applied in non-urgent case specific evaluations, and
- an in-depth evaluation is made when a RV is needed within a generic context (e.g. for derivation of guidance values, such as indoor air quality guidelines for legal purposes (Binnenmilieubesluit)). The criteria for differentiating between these 3 approaches are further explained below (see Figure 1).

2.1 INITIAL PHASE: CONSIDERATION OF PREVIOUS SELECTIONS AND EXPOSURE SCENARIO

2.1.1 Previous selections

A differentiated approach for the selection of RVs is followed for reasons of efficiency, but notwithstanding this, the assessor should first check whether an in-depth analysis has been conducted previously within the agency in a recent dossier (3-5 years old). If the RV from such a recent in-depth evaluation matches the route and duration of the present case (intended use of the RV), it is advised to use the value selected from this recently performed-depth evaluation, irrespective whether further decision criteria would guide the analysis to a default evaluation' or an 'in depth evaluation' (see Figure 1). A value selected based on an in-depth analysis is always preferred since the full background of the values has been carefully investigated, and the main disadvantage of in-depth investigation (i.e. workload) is withdrawn since these efforts have already been performed previously in another dossier.

It is advised to construct a database where selected reference values and associated level of selection detail (RV for indicent evaluation, default evaluation, or in-depth evaluation) are stored for later consultation.

2.1.2 Exposure scenario

Notwithstanding that this protocol does not aim to provide optimal tools for exposure assessment, it is important to reflect in this initial stage on the exposure scenarios for which the health-based reference value will be applied.

The targeted exposure scenario influences the route and duration for which a RV should be selected, and the depth of the assessment (for use in a case study or a generic context).

The decision tree outlined in Figure 1, which is based on exposure scenario considerations, guides the assessor towards 1) which effects to consider, 2) which types of RV to search for, and 3) which level of detail to apply in the selection of the RVs.

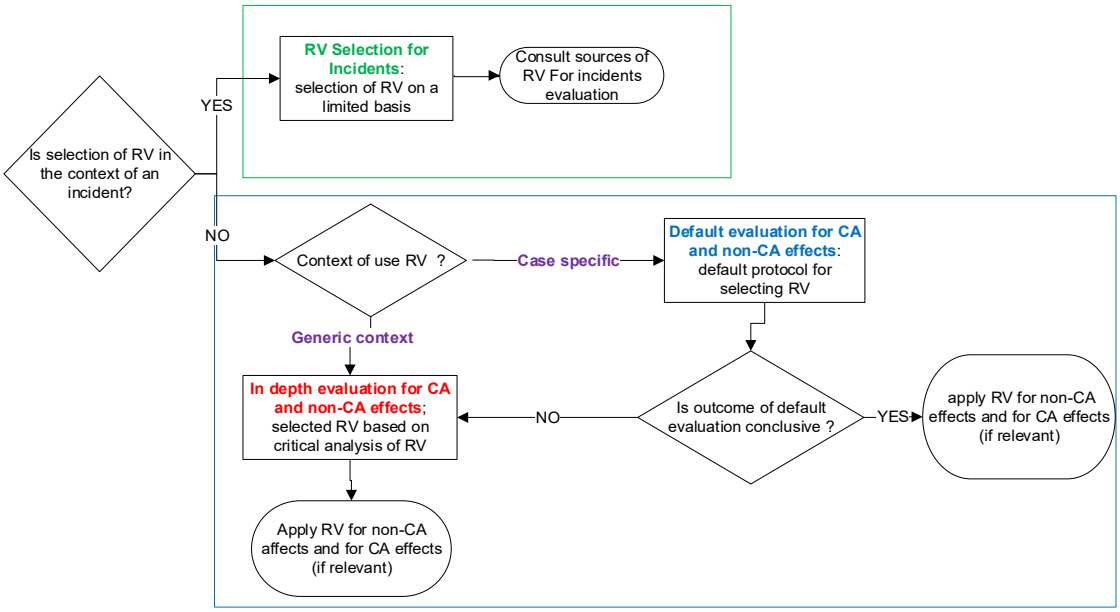


Figure 1: Decision tree for selection approach of health-based reference value (HB RV) for carcinogenic (CA) and non-carcinogenic (non-CA) effect, in view of context of use of the HB RV

A differentiation in RV selection procedures was made in order to apply the most useful, appropriate and efficient method according to the circumstances in which the RV is intended to be used. This is in line with the tiered approach for health-based selection of RVs by several other agencies (ANSES, 2012; INERIS, 2006; DGO 3, 2015).

In a first type of situation, selection of the reference value takes place within the context of a (very) urgent situation (e.g. upon incidental release of contaminants, due to a fire, industrial accident, …) where the one is asked to assess the health risks of exposed individuals. It is anticipated that urgent situations are focussed on the occurrence of (immediate) health effects following the incident. In such situations, a '**RV Incident Selection'** is warranted. This RV incident selection is limited to thresholds for acute exposure and the gravity of effects upon exposure associated with them, and to potential carcinogenic effects on the long-term. Besides the concern for immediate effects following the calamity, health effects that might arise in the long term should also be investigated; hereto-a follow up of the exposure situation is warranted, and evaluation of the (eventually) prolonged exposure should be evaluated using health-based values for intermediate or chronic duration (cfr. Methodology 'fluctuating exposure profiles (De Brouwere et al, 2020).

Examples and specific sources to consult for a 'RV for incidents' are given in Table 1.

If the selection of the reference value is not in the context of an urgent situation (incident, calamity), another type of reference values is required. In such case, we do not want to know gravity of effects above a certain threshold; instead, we search for RV below which no negative effects are expected (either for an acute or chronic duration of exposure). In many cases of non-urgent situations, chronic exposure, or intermediate exposure is subject of the evaluation.

Nevertheless, also in context of non-calamities, acute exposure might be relevant (e.g. short exposure to VOCs during hobby use of glue is a typical 'acute' exposure window).

If the context of use of the RV (for non-incidents situations) is in a **specific case**, a **default evaluation** according to a standardized protocol is applicable. A standardized protocol requires a limited search of RVs – without the need to go into the details of how the RVs have been derived - and it renders the selected value less prune to subjective choices. In case the default evaluation leads to a conclusive answer of risk in the specific case, the exercise may stop here.

However, in situations where a default evaluation leads to an inconclusive answer in a specific case, it might be needed to move to an in-depth evaluation of RV values. For example, if applying RV A established by agency A would lead to the conclusion that the exposure is acceptable, while RV B established by agency B would evaluate the exposure as unacceptable, it is – based on the default evaluation – not possible to come to a conclusive answer. In such case a more in-depth analysis of RVs is needed.

Another example of being inconclusive is that different agencies have different classification for carcinogenicity, this also provokes the need to go to an in-depth analysis of RV for carcinogenic effects.

In such an in-depth analysis, details on how the various RVs have been derived are investigated, allowing to make an informed decision on the most appropriate RV.

For use in a **generic context** (e.g. establishing indoor air quality guidelines for legal purposes, drinking water quality guidelines), it is advised to follow an **in-depth investigation** for the selection of the health-based reference value. An in-depth investigation is advised because the resulting RV will be applied in several divergent exposure situations (which cannot be quantified a priori). This is also in line with in-depth investigations of RVs in other policy contexts, inside and outside Flanders, e.g. for the selection of soil guidance and soil remediation values in Flanders by OVAM, and for the selection of IAQG in France.

The protocol and datasources of the 'default evaluation' and the 'in-depth evaluation' are explained further in 2.6 and 2.7.

Irrespective of the type of evaluation ('default evaluation' or 'in-depth evaluation'), both carcinogenic and non-carcinogenic effects should be considered.

The aspects to consider, and sources to consult for carcinogenic effects are explained in 2.3.1.

2.2 RV FOR USE IN CONTEXT OF INCIDENTS

If the selection of the reference value is in the context of a (very) urgent situation (incidents, disasters) where one is asked for the assessment on immediate health risks for exposed individuals, a screening of exposure limits applicable for incidents is performed. In addition, carcinogenicity is assessed to screen for potential longer-term cancer risks.

In such situations, prompt mitigation and risk controlling actions are needed in case the (preliminary) risk assessment points to a threat for the health of exposed individuals.

Past examples of such very urgent situations are 1) the release of acrylonitrile fumes upon a train disaster (Wetteren) in 2013, 2) accidental chemical contamination of a water supply.

The execution of this 'RV selection for use in context of incidents'' in cases of urgent situations is analogous to the niveau 1 procedure for urgent cases by ANSES (Anses, 2012).

In this step, it is in general not needed to make a formal selection of which is the most appropriate RV; more important is to find one (or more) RV for incidents exposure in order to quickly evaluate the gravity of the calamity. Therefore, no formal priority scheme for exposure limits in context of indicents (see Table 1) has been developed.

In the context of RV selection for use in incidents evaluations, no critical analysis of the background and derivation of the RVs is made; neither is the date of the assessment taken into account, nor is the full scientifical and technical background of the RV to be investigated.

For more details on procedures how to safeguard public health interests in case of incidents (also aspects beyond the selection of RVs), it is adviced to follow the Flemish Decision Support System (Smolders et al., 2014).

2.2.1 Overview of sources exposure with Reference value for incidents

Table 1 gives an overview of data sources for exposure limits available in the context of incidents/calamities

Table 1: Agencies and data sources for health-based reference values for use in urgent situations (incidents; calamities)

Agency	RV name	Route of exposure	Duration exposure	Link
EPA	**AEGL** (acute exposure guideline level)/ **AEGL-1**: Notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure. **AEGL-2**: Irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. **AEGL-3**: Life-threatening health effects or death.	Inhalation	For five relatively short exposure periods : 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours	General description: http://www.epa.gov/aegl/about-acute-exposure-guideline-levels-aegls search functions on: http://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values
EPA	**PAL** (Provisional Advisory Level) **PAL 1**: mild, transient, revisable effects, including changes from baseline biomarker of exposure **PAL 2**: impaired ability to escape increased severity of irreversible serious long-lasting effects **PAL 3**: severe effects, lethality	Inhalation and oral (drinking water)	Acute (24 hours) Short-term (longer than one to 30 days) Long-term (longer than 30 days to two years)	General description: http://www.ncbi.nlm.nih.gov/pubmed/19814653 search functions/easy access: not found
INERIS	**SELS**: seuils des effets létaux significatifs **SPEL**: seuil des premier effets létaux **SEI**: seuil des effets irréversibles **SER**: seuil des effets réversibles	Inhalation	1 minute 10 minutes 20 minutes 30 minutes 60 minutes	https://substances.ineris.fr/fr/page/23#autseu list of substances for which acute toxicity thresholds have been established (downloadable fiche per substance) https://substances.ineris.fr/fr/ database with search function on CASnr or substance name
RIVM	Voorlichtingswaarde (VRW) Alarmeringsgrenswaarde (AGW) Levensbedreigende waarde (LBW)	inhalation	10 min 30 min 1 uur	http://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Nieuwsberichten/2016/Nieuwe_interventiewaarden_voor_gevaarlijke_stoffen https://rvs.rivm.nl/sites/default/files/2018-12/Interventiewaarden%20Incidenten%202018-1%20alfabet.pdf search function on: https://rvs.rivm.nl/zoeksysteem/

Acute Exposure Guideline Levels (AEGLs) developed by EPA are used by emergency planners and responders worldwide as guidance in dealing with rare, usually accidental, releases of chemicals into the air. AEGLs are expressed as specific concentrations of airborne chemicals at which health effects may occur. They are designed to protect the elderly and children, and other individuals who may be susceptible.

AEGLs are calculated for five relatively short exposure periods – 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours – as differentiated from air standards based on longer or repeated exposure.

The differentiation into 3 levels (see Table 1) informs on the severity of expected effects from the corresponding AEGL value onwards, and, if monitoring data are available, should help defining appropriate mitigation and evacuation measures.

Health-based Provisional Advisory Levels (PALs) for homeland security developed by EPA are applicable at federal, state, and local levels, and are intended for use in homeland security efforts, public health, law enforcement, and emergency response, as well as decisions by water utilities, and national and regional EPA offices. PALs have not been promulgated nor have they been formally issued as regulatory guidance. They are intended to be used at the discretion of risk managers in emergency situations when site specific risk assessments are not available. PALs are a tiered set of exposure values used to inform risk-based decision making during a response to environmental contamination involving hazardous chemicals. They are advisory levels for exposure to chemicals by the general public (including susceptible and sensitive sub-populations) and are developed for the following exposures to contaminated air and water:

- Acute (24 hours)
- Short-term (longer than one to 30 days)
- Long-term (longer than 30 days to two years)

The **French Institute INERIS** has developed thresholds for acute toxicity values, for use in the evaluation of accidental release of dangerous substances to the atmosphere. The timespan varies from 1 minute to 60 minutes, and 4 levels of thresholds have been established:

- SELS: “seuils des effets létaux significatifs”: thresholds for significant lethal effects
- SPEL: seuil des premier effets létaux: thresholds for first signs of lethal effects
- SEI: seuil des effets irréversibles: thresholds for irreversible non-lethal effects
- SER: seuil des effets réversibles thresholds for reversible, non-lethal effects

For each substance, a short dossier (fiche) with summary of the 4 values can be consulted from the website of INERIS; also, more in-depth dossier with the full background of the 4 threshold values can be downloaded from the INERIS website http://www.ineris.fr/rapports-d%C3%A9tude/toxicologie-et-environnement/fiches-et-rapports-de-seuils-de-toxicit%C3%A9-aigu%C3%AB

The **Dutch RIVM** recently published new intervention values for dangerous substances (211 of 300 substances have been revised in 2015-2018. Updates for other substances are foreseen in the near future.)

RIVM mentions 3 levels of intervention values

- The Information Value (voorlichtingsrichtwaarde or VRW) represents the air concentration of a substance that will be considered irritating or unpleasant by the exposed population, or that could give rise to mild effects.
- The alarm level (alarmeringsgrenswaarde or AGW) represents the air concentration of a chemical above which irreversible or other serious health effects can occur, or which results in reduced capability of exposed people to bring themselves to a safe place.
- The life-threatening value (levensbedreigende waarde or LBW) represents the air concentration above which death or life-threatening effects are possible.

For each of these levels, 10 minutes, 30 minutes and 1 hour values have been derived.

Some of the Dutch values are based on AEGL values or ERPG values (see https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf)

If none of agencies (RIVM , INERIS EPA-AEGL-, EPA-PAL) has resulted in acute RV for calamities for the substance of interest, it is advised to consult other searches. Ideally, searches in scientific literature should be performed; however, this might not be achievable given the urge of the situation.

Alternatively, databases such as BIG (brandweerinterventieboek - http://www.big.be/) could be consulted, or the REACH database could be explored.

2.2.2 Consideration of carcinogenicity in context of acute exposure events (incidents)

Also in the context of incidents, there might be concern regarding long-term effects following the incidental exposure: the carcinogenicity of a chemical can increase concern and could be accounted for when evaluating the necessity of intervention after incidents.

The above mentioned AEGL values for (very) short term exposure account for both non-carcinogenic and carcinogenic effects. For partim 'carcinogenic risk's the law of Haber has been applied in the derivation of the AEGL values, meaning that the cumulative dose is scale to the desired timespan, in combination with consideration of an assessment factor for vulnerable life stages. More details on the law of Haber and the application for carcinogenic substances is elaborated in the guidance 'fluctuating exposure profiles' (De Brouwere, 2020 draft report). In short, it means that, for example, a chronic exposure level of 1 µg/m³ with a risk of 1.10^{-6} for lifetime exposure, corresponds to the same risk level (1.10^{-6}) if one is exposed during 8 hours to a level of 75.000 µg/m³ of this substance, i.e. the former exposure level (1 µg/m³) is multiplied with the time scaling factor (i.e. lifetime vs. 8 hours : 70 years * 365 days*24h/8h = 77.280 ≈ 75.000).

It is remarked that the AEGL values are in most cases not driven by the partim carcinogen effects. The value derived from partim non-carcinogen effects is in most cases lower than the value for partim carcinogenicity. The lowest from the two values is adopted as AEGL value. In the value selected as AEGL, one cannot see whether the critical part is either carcinogenicity or not.

The principle of dose- time scaling can be extended to other time windows compared to the 10 min, 30 min. 1 h, 4 h and 8 hours timeframes of the AEGL Value.

Hereto, we propose to use a slightly modified version of the principle of Bos et al. (2004) (see also guidance 'fluctuating exposure profiles' (VITO, draft report' 2020)

$$GV_{carc}acute\ (X\ days) = \frac{C(10^{-6}{}_{carc})\ lifetime}{DRCF} \times \frac{25000}{X}$$

With $C(10^{-6}{}_{carc})\ lifetime$: concentration corresponding to a risk of 1.10^{-6} if one is exposed during a lifetime to this concentration.

This formula is similar to the above-mentioned explanation or AEGL partim carcinogenicity, with the addition of a Dose Rate Correction Factor 'DRCF' factor (for sensitive, vulnerable populations) if the period of exposure falls with a vulnerable life stage (Felter et al., 2011). A default factor of 10 for DRCF can be used (De Brouwere, 2020 - draft report' fluctuating exposure profiles').

➔ Conclusion:

1) If substance has an AEGL value, and the time window of the exposure period corresponds to the time window of an AEGL value, one can use the AEGL value, which is also protective for carcinogenic effects. Eventually, divide AEGL value by a factor 10 (DRCF) to be protective for sensitive life stages
2) If substance has no AEGL value, select a unit risk value (using default or in-depth procedure for selection RV), convert it to a $C(10^{-6}{}_{carc})\ lifetime$ and apply the above-mentioned formula for scaling to the appropriate duration of exposure

2.3 RV SELECTION FOR USE IN CONTEXT OF NON-INCIDENTIAL EXPOSURE SITUATIONS

2.3.1 Consideration of exposure duration

One of the first aspects to consider when selecting a health-based reference value, is the duration of the exposure (event) under evaluation. When the exposure window is chronic (often called 'lifelong exposure[1], or at least 10 % of lifetime) reference values for chronic exposure are appropriate.

When evaluating risks from less-than-lifetime exposures, the decision on whether using health-based RV for acute, intermediate or chronic duration of exposure should be made case by case. In order to do so, the decision tree published in the guidance 'fluctuating exposure profiles'[2] can be followed. In short, the appropriate RV (acute, intermediate, chronic) should be selected based on the match with the exposure profile subject for evaluation. In some situations, considerations of toxicodynamics and toxicokinetics may be warranted. More details can be found in the guidance document 'fluctuating exposure profiles' (De Brouwere, 2020).

The method and sources for HB RV (see further in section 2.6) are in principle applicable both for acute, intermediate and chronic HB RV. However, it should be noted that data sources for chronic exposure HB RV are more abundant than for intermediate and acute exposure. In context of health evaluation of environmental pollution, the exposure window is often chronic, and thus chronic HB GV are in place in various environmental contexts.

[1] Definitions of time windows for chronic, intermediate and acute exposure are elaborated more in detail in the guidance document 'evalauting of fluctuating exposure profiles, De Brouwere K., 2020 – draft version)

2.3.2 Consideration of carcinogenicity

In a first stage of the default evaluation and of the in-depth evaluation, it should be considered whether RVs for carcinogenic effects need to be explored.

For consideration of carcinogenicity, no difference is made between the default evaluation and the in-depth evaluation.

Hereto, we make use of the existing classification schemes for carcinogenicity used by 4 agencies: 1) the International Agency for Research on Cancer (IARC), 2) the classification according European Union Globally Harmonised System of Classification and Regulation (EC) No 1272/2008 (EU-GHS), 3) the classification according to the U.S. Environmental Protection Agency (US EPA) and 4) the National Toxicology Program (NTP).

The referenced agencies have developed their own classification system, and class boundaries from one system are not always identical across the systems. An overview of the classification systems is given in Table 2.

A substance is considered carcinogenic (marked red in Table 2) if classified by at least one agency as:

- Human carcinogen
- Probable human carcinogen

A substance is considered as non-carcinogenic (marked blue inTable 2) if classified as:

- Not classifiable with regard to human carcinogenicity
- Probably not carcinogenic

For substances classified as 'possible human carcinogen' or 'suggestive evidence for carcinogenic potential' (marked orange inTable 2), no decision can be made at this stage.

Classification of substances according to the 4 schemes can be consulted using the following resources:

- IARC classification: http://monographs.iarc.fr/ENG/Classification/latest_classif.php[3]
- US EPA classification: http://www.epa.gov/iris/search_keyword.htm

  One may search on agent name, or CAS number. In the search result section, the IRIS summary can be accessed. In section II.A.1 'weight of evidence characterization' of the IRIS summary, the classification is given.

- EU-GHS classification http://echa.europa.eu/information-on-chemicals/cl-inventory-database

One may search on agent name, or other identifiers such as CAS number. The first section of Summary of Classification in the search result gives the harmonized classification according to Annex VI of the CLP Regulation (No 1272/2008).

[3] Best viewed with Google Chrome

Table 2: overview of classification systems for human carcinogenicity of substances (colour code: see text)

IARC	US-EPA - 1986 guidelines	US-EPA - 2005 guidelines	EU – GHS	NTP
group 1: carcinogenic to humans	*group A: human carcinogen*	*carcinogenic to humans*	*carcinogen Cat. 1A: (H350) known to have carcinogenic potential for humans; largely based on human evidence*	*Known To Be Human Carcinogen*: sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure, and human cancer.
group 2A: probably carcinogenic to humans	*group B1*: probable human carcinogen - based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals	likely to be carcinogenic to humans	*carcinogen Cat. 1B*: (H350) presumed to have carcinogenic potential for humans; largely based on animal evidence	*Reasonably Anticipated To Be Human Carcinogen:* Limited evidence in human studies, or sufficient evidence from animal studies, or less than sufficient evidence from human or animal studies, however belonging to a well-defined structurally l related class of substances whose members are human carcinogenic or substances or reasonably anticipated to be human carcinogenic
group 2 B: possibly carcinogenic to humans	*group B2*: (probable human carcinogen - based on sufficient evidence of carcinogenicity in animals	suggestive evidence of carcinogenic potential	*carcinogen Cat. 2*: (H351) suspected human carcinogen	
group 3: Not classifiable as to its carcinogenicity to humans	*group C*: possible human carcinogen	inadequate information to assess carcinogenic potential	*mutagen Cat. 1A* (H340) known to induce heritable mutations in germ cells of humans	
group 4: probably not carcinogenic to humans	*group D:* not classifiable as to human carcinogenicity	not likely to be carcinogenic to humans	*mutagen Cat. 1B*: (H340) should be regarded as if they induce heritable mutations in the germ cells of humans	
	group E: evidence of non-carcinogenicity for humans		*mutagen Cat. 2*: (H341) may induce heritable mutations in the germ cells of humans	

- NTP (National Toxicology Program)
  - report on carcinogens: http://ntp.niehs.nih.gov/pubhealth/roc/index.html

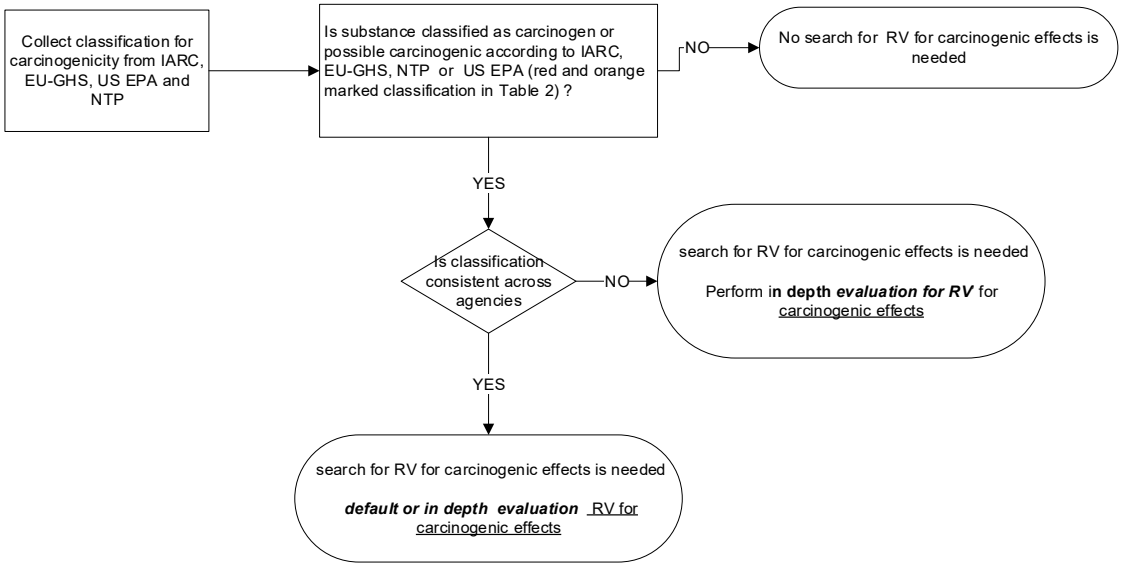
If a substance is classified as carcinogenic (according to classification marked red in Table 2) or possibly carcinogenic (marked orange in Table 2) by one or all agencies, this should trigger a further analysis of the carcinogenic potency and its quantification in the next step. In such a case, the analysis of selecting a Reference Value (RV) for carcinogenicity should be performed, in parallel to the selection of a RV for non-carcinogenic effects.

If a substance is not classified as (possible/probable) carcinogenic (marked in blue in Table 2) by all agencies, further analysis of the carcinogenic potency and its quantification in the next step should not be conducted because of non-relevance; also, it is expected that for such substances no quantified RVs for carcinogenicity will be available at all (see Figure 2).

If at least one agency classifies the chemical as a carcinogen, then RVs for carcinogenic effects should be searched for. If agencies are consistent in their classification, a default evaluation can be the first step. If there is no consistency in evaluation (which means that some agencies classify the substance as carcinogenic and others do not), then an in-depth evaluation of carcinogenic RVs will be required.

This workflow is illustrated in Figure 2.

Figure 2: consideration of carcinogenicity, in relation to further steps in the selection of RV



After having performed a parallel selection of an RV for carcinogenic effects and an RV for non-carcinogenic effects, the two values are combined by taking the most critical one forward. Alternatively, they can be hold separate to be able to separate risks due to non-carcinogenic and carcinogenic endpoints.

2.4 SOURCES FOR CONSULTATION OF HEALTH BASED REFERENCE VALUES

The protocol (see sections 2.5- 2.7) relies on the use of health-based reference values available in different sources. The procedure for the selection is explained further (sections 2.5- 2.7.) In this section, upfront the protocol, an overview is given of data sources referred to in the procotol.

2.4.1 Primary and secondary sources

Primary sources are sources from supranational level, have a very thorough peer review process (over several departments within an agency), and the methods of derivation are transparent and well documented.

RVs from secondary sources are in general also derived in a transparent way and documented (albeit sometimes not in English written versions); however, the extent of the peer review process is more limited, or the procedure follows a national instead of supranational methodology (e.g. in choice of assessment factors)

Table 3: Agencies and data sources for health-based Reference values (RV) (1° - primary sources, 2° - secondary sources)

Agency	Route of exposure[$]	Duration of expsoure	RV name	Website	Type of information/ how to find RV
1° - WHO / Air Quality Guidelines	I	chronic/ (acute)	AQG (Air Quality Guideline)	http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf	- Downloadable text documents covering RV for several substances in one document - Exhaustive rationale for derivation of RV ; - Documents to screen to find RV
1° - WHO / Guidelines for Indoor Air Quality	I	chronic/ (acute)	IAQG (Indoor Air Quality Guideline)	http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2010/who-guidelines-for-indoor-air-quality-selected-pollutants	- Downloadable text documents covering RV for several substances in one document - Exhaustive rationale for derivation of RV ; - Documents to screen to find RV
1° - WHO Cicad	I, O	chronic/ acute	TDI (Tolerable Daily intake Guidance value	https://www.who.int/ipcs/publications/cicad/en/	Alphabetical list of CICADs (Concise International Chemical Assessment Document)
1° - WHO / Drinking Water Quality Guidelines	Ow	chronic/ acute	GV (guideline value)	https://www.who.int/water_sanitation_health/water-quality/guidelines/en/	- Downloadable text documents covering RV for several substances in one document - Exhaustive rationale for derivation of RV ; documents to screen to find RV; - Revisions and updates of guidelines
1° - WHO/JECFA	O	chronic/ acute	TDI (Tolerable Daily intake TWI (Tolerable Weekly intake)	http://www.who.int/foodsafety/publications/jecfa/en/	- Searchable database of all JECFA Monographs and other IPCS Risk Assessment documents
1° - WHO/ JMPR	O	chronic/ acute	ADI (acceptable daily intake) ARfD (acute reference dose)	http://apps.who.int/pesticide-residues-jmpr-database	- Searchable database which contains basic information (ADI, ARID, CAS number etc) for all pesticides evaluated by the Joint Meeting on Pesticide Residues (JMPR) as well as the available publications (reports and monograph) for each compound.

Agency	Route of exposure[$]	Duration of expsoure	RV name	Website	Type of information/ how to find RV
1° - EFSA	O	chronic/ acute	TDI (Tolerable daily intake), TWI (Tolerable weekly intake) , PTMI (provisional tolerable monthly intake)	http://www.efsa.europa.eu/ for RV: http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed http://www.efsa.europa.eu/en/microstrategy/openfoodtox	- Search on the EFSA website for Scientific Opinions for substance of interest. - Search within the Scientific Opinion for RV such as TDI (tolerable daily intake) TWI (tolerable weekly intake) , PTMI (provisional tolerable monthly intake) - EFSA Openfoodtox: searchable database with summary toxicological data and link to EFSA documents, EFSA will update Openfoodtox on a regular basis
1° - US-EPA / IRIS database	I,O(w)	chronic/ acute	RfC, RfD, inhalation unit risk	www.epa.gov/iris drinking water: https://www.epa.gov/dwstandardsregulations/2018-drinking-water-standards-and-advisory-tables https://www.epa.gov/pesticides/updated-list-human-health-benchmarks-pesticides-drinking-water-available (pesticides)	- Online database, search function by CAS number or substance name; resulting in overview of RVs for different duration, route and type effect, and background documents - Summary of EPA's RfD and cancer risk values for drinking water contaminants
1° - ATSDR / MRL	I,O	chronic/ intermediate/ acute	MRL (Minimal Risk Level)	http://www.atsdr.cdc.gov/substances/index.asp, http://www.atsdr.cdc.gov/mrls/mrllist.asp#39tag	- Online database, search function by CAS number or substance name; resulting in overview of classification and downloadable documents where RV and background can be found - List of all MRL values established by ATSDR
2° - US-EPA / PPRTV*	I,O	chronic/ acute	PPRTV* RfC, RfD values; and unit reference values	http://hhpprtv.ornl.gov/	- Online database, accessible from 'PPRTV Quickview' menu; dropdown menu listing alphabetically substances for which PPRTV values have been derived

Agency	Route of exposure[$]	Duration of expsoure	RV name	Website	Type of information/ how to find RV
2 - Cal-EPA OEHHA	I,O(w)	chronic/ acute	REL (Reference Exposure Limit) Unit risk, Slope factor Public Health goal	http://www.oehha.ca.gov/risk/ChemicalDB/index.asp RELs: http://oehha.ca.gov/air/allrels.html cancer risk potency factors: https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009 drinking water: https://oehha.ca.gov/water/chemicals	- Online database, search function by CAS number or substance name; resulting in overview of RV and downloadable versions of supporting material - Overview table of RELs - Overview of cancer risk potency factors (appendix B) - Online database water chemicals, search function substance name; resulting in overview of RV and downloadable versions of supporting material
2 ° - Anses / VTR (in French mostly, English sometimes)	I,O	chronic, subchronic, acute	VTR (Valeurs Toxicologiques de Référence	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses	- Downloadable table with VTR values and downloadable versions of supporting material (report in French, opinion in English and in French)
2° - Health Canada	I,O(w)	chronic	TDI (Tolerable Daily Intake), TC (Tolerable Cocentration), oral slope factor, inhalation slope factor, inhalation unit risk	http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html https://www.canada.ca/en/services/health/publications/healthy-living.html drinking water: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html	- No online databases - RV to obtain by search queries on substance names on Health Canada website - Check also First Priority Substances List (PSL1) Assessments and Second Priority Substances List (PSL2) Assessments. - Downloadable versions of documents with RV and supporting material - Guidance document (can be ordered electronically) with toxicological reference values for chronic exposures - List of publications healthy living, including guidelines drinking water and indoor air - Guidelines for Canadian Drinking Water Quality - Summary Table

Agency	Route of exposure[$]	Duration of expsoure	RV name	Website	Type of information/ how to find RV
2° Texas Commission on Environmental Quality (TCEQ)	I,O	chronic/ acute	ReV (acute and chronic inhalation Reference Values), URF (inhalation Unit Risk factor), RfD (health-based chronic oral reference dose)	https://www.tceq.texas.gov/toxicology/dsd/final	- Online alphabetical list with development support documents
2° National Health and Medical Research Council (NHMRC, Australia)	Ow	chronic/ acute	ADWG (Australian Drinking Water Guideline)	https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1	- Downloadable text document covering RV for several substances in one document
2° Ministry of Health New Zealand	Ow	chronic/ acute	Maximum Acceptable Value	http://www.health.govt.nz/publication/guidelines-drinking-water-quality-management-new-zealand	Downloadable text documents covering RV for several substances in one document Documents to screen to find RV
RIVM (MTR and VR values)	I, O	chronic	Maximaal toelaatbaar risiconiveau (MTR: TDI, CR[4]oral, TCA, CR[4]inhal)) Verwaarloosbaar risiconiveau (VR)	http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf	Reports with MPR values for compounds and compound classes

[$] I: inhalation; O: oral; Ow: oral specific for drinking water

** PROVISIONAL Peer Reviewed Toxicity Values; considered by US-EPA as indicative values to be used if no US EPA or ATSDR values are available*

[4] For genotoxic carcinogens the MTR has been defined as the excess lifetime cancer risk of 1 in 10.000 (1:10[4]).

Table 4: meta databases compiling human health RV from several organizations*

Database	Description	Website
INCHEM Chemical Safety Information from Intergovernmental Organizations	Meta database with access to Environmental Health Criteria, CICAD's and JECFA/JMPR	http://www.inchem.org/
ITER database	Free internet database of human health reference values and cancer classifications for over 680 chemicals of environmental concern from multiple organizations worldwide	http://www.iter.tera.org/
PATCHWORK Public Access to Toxicity data of Chemical hazards to Humans	Portaal site containing 29, free online databases with toxicological data of more 715.000 products and 350.000 substances, relevant for public health expert in the domain of occupational and environmental exposure	http://www.ru.nl/ubn/zoeken/vakgebieden-0/medische/onderverdeling/internetbronnen_op/onderverdeling/farmacologie/indeling/patchwork/
INERIS Portail Substance Chimique	Metadatabase with French and international toxicological reference values	https://substances.ineris.fr/fr/

**It should be noted that none of these meta databases is complete in view of all sources mentioned in Table 3, and it is not clear whether the meta databases do contain the most up to date RVs. However, meta-databases are excellent instruments for a quick first overview of available information.*

2.4.2 Tertiary sources

Health based reference values from tertiary sources are similar in concept as primary and secondary values (I.e. also health based, and transparently derived) but might be originating from a variety of sources (non-limitative list);

Table 5: Tertiary sources of reference values (not exhaustive)

Source	Website	Description
RIVM (MTR and VR values)	http://www.rivm.nl/rvs/Normen	Online database with MTR and VR values (in dutch) Note that the database is not limited to health-based values, but includes also legal standards. Ony the health-based values should be considered.
DEFRA (UK)	https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs	
German Indoor Air Quality Guidelines	http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values	Website with published RW I & II values, and background documentation with rationale
French Indoor Air Quality Guidelines (ANSES)	https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs	Pdf with summary table of IAQG
INDEX project	Index Project (IAQG in Europe) http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_exs_02.pdf	Pdf report
New Zealand Ambient Air quality Guidelines	https://www.mfe.govt.nz/air/air-guidance-and-wood-burners/ambient-air-quality-guidelines	downloadable text document covering RV for several substances in one document
DWI (drinking water inspectorate)	http://www.dwi.gov.uk/index.htm	Search website for substance
EU LCI	https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en https://publications.jrc.ec.europa.eu/repository/bitstream/JRC83683/eca%20report%2029_final.pdf	Pdf report and summary tables
Etc.		

2.4.3 Quaternary sources

These sources are 'building blocks' to derive health-based reference values. These values cannot be adopted as such as health-based reference values because they either lack an 'approval' or peer reviewed procedure (i.e. in case of use of ECHA database), or these values are designed for occupational exposure

Table 6: Quaternary sources of reference values (not exhaustive)

Source	Website	Description
ECHA	https://www.echa.europa.eu/information-on-chemicals/registered-substances	Online database, search for substance by name or CAS nr, go to Reach registered fact sheets, select highest tonnage and full registration type – select toxicological information, summary
Occupational exposure limit values in Belgium and neighboring countries	https://www.werk.belgie.be/nl/onderzoeksprojecten/2019-gegevensbank-met-beroepsmatige-blootstellingsgrenswaarden-belgie-en-de http://www.werk.belgie.be/defaultTab.aspx?id=616	Excel database and report with a list of chemical agents for which there is a occupational exposure limit value in Belgium and three neighboring countries, the Netherlands, France and Germany

2.5 TIERED APPROACH FOR SELECTION OF HEALTH-BASED REFERENCE VALUES (RV)

The scheme for selection of health-based Reference values is applicable for both RVs for carcinogenic and RVs for non-carcinogenic effects. For substances classified as carcinogenic, the scheme should be run in parallel for RVs for carcinogenic effects and for RVs for non-carcinogenic effects.

For non-carcinogenic substances, a health-based Reference value (RV) is a threshold level below which exposure is unlikely to provoke adverse effects. Examples of such RV are Reference Concentration (RfC) and Reference Dose (RfD) values from US EPA; Minimal Risk Levels (MRL) by ATSDR, Tolerable Daily Intake (TDI), Tolerable Concentrations in Air (TCA).

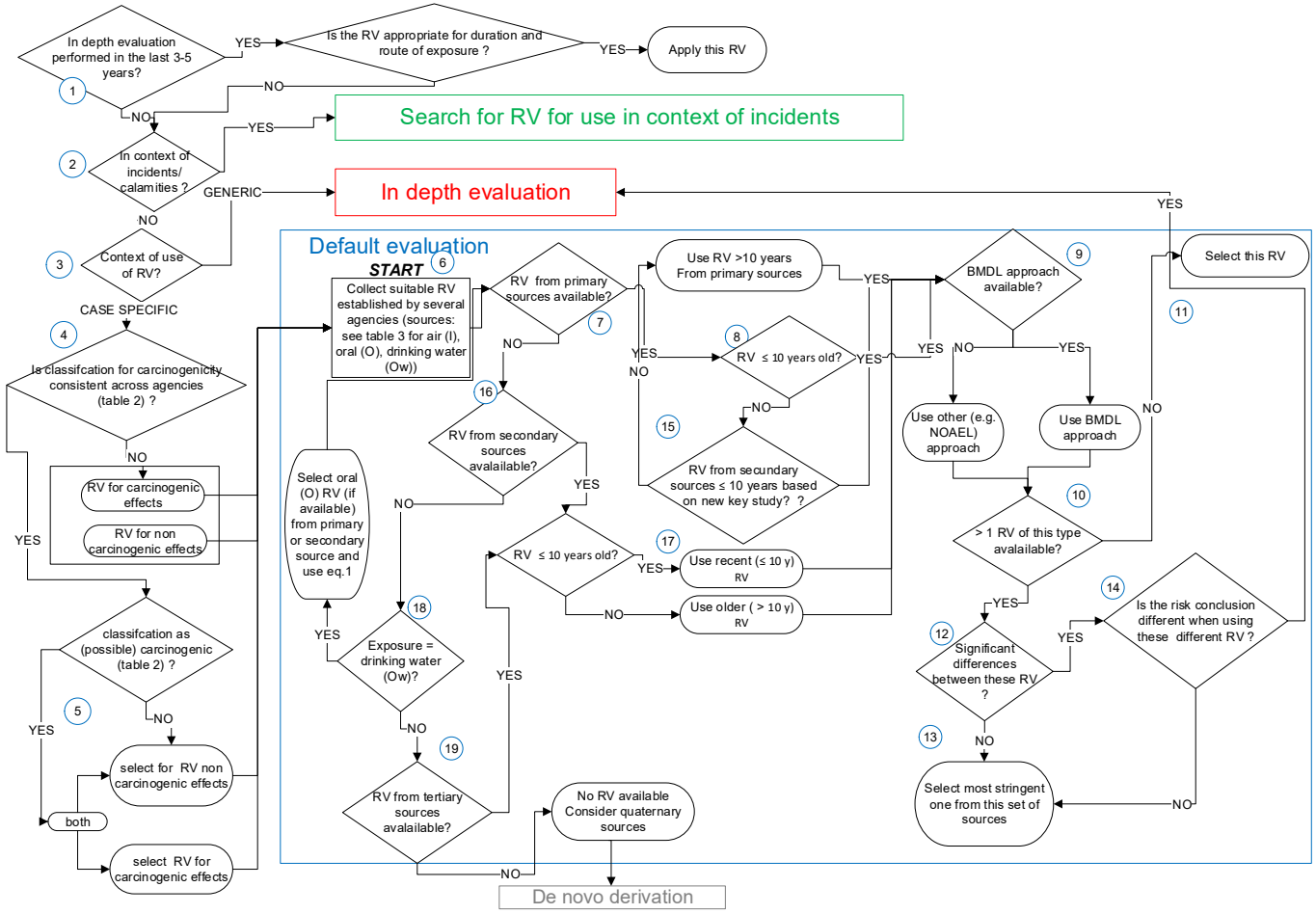
For carcinogenic substances, with a mode of action following a non-threshold mechanism (carcinogenic, genotoxic substances), no safe levels below which exposure does not pose a health risk can be established. For carcinogenic substances with a non-threshold mechanism, the RV for carcinogenicity is very often expressed as a unit risk value or slope factor. The unit risk is defined (by US EPA) as "the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m^3 in air. The interpretation of inhalation unit risk would be as follows: if unit risk = 2 x 10^{-6} per µg/L, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical in 1 litre of drinking water.

It should be noted that some agencies deviate from the use of unit risk or slope factors for carcinogenic substances, and instead, apply a value corresponding to a minimal or acceptable risk level for carcinogenicity (e.g. EFSA: via the margin of exposure: see annex A). This value can be considered as a pseudo-threshold approach.

These different types of RV for carcinogenicity can be compared one to another if account is taken of the levels set for minimal or acceptable risk. They may not be identical because of case-specific differences in low-dose extrapolation methods.

The aspects to consider, sources to consult and points of decision included in the protocol for the selection of health-based reference values is visualized in Figure 3 and explained in the below text.

Figure 3: protocol for selection of health-based reference values for use in human health risk assessment of environmental exposure



Considerations of urgency situation, context of use and carcinogenicity are explained above (see 2.2, 2.3.1) and summarized in steps

(1) (2) (3) (4) (5):

(1): if an in-depth evaluation has been made previously within the agency in a recent dossier (3-5 years old); this value could be applied. Hereto, it should be evaluated whether the route and duration of the previous in-depth assessment matches with the present case (intended use fo the RV). If there is a match, this previously derived in-depth evaluation should be applied. If there is a no match, the scheme should be applied (go to (2))

(2): if the selection the reference value is in the context of a (very) urgent situation (incidents, disasters) where one is asked for assessment of immediate health risks of exposed individuals, a search for risk values designed for evaluation of incidents/calamities is performed

(3): if the RV is intended to be used in a generic context (e.g. derivation of indoor air quality guidelines), an in-depth evaluation should be performed. If the RV is intended to be used in a case specific context, the default evaluation can be used.

(4)

If a substance is classified as carcinogenic (according to classification marked red in Table 2) or possibly carcinogenic (marked orange in Table 2) by one or all agencies, this should trigger a further analysis of the carcinogenic potency and its quantification in the next step. In such a case, the analysis of selecting a Reference Value (RV) for carcinogenicity should be performed, in parallel to the selection of a RV for non-carcinogenic effects.

(4) and (5): if the classification for carcinogenicity is consistent across the agencies (Table 2), and the substances is classified as carcinogenic, 2 types of RV should be selected according to the default evaluation scheme: one for carcinogenic effects, and one for non-carcinogenic effects.

If a substance is consistently not classified as (possible/probable) carcinogenic (marked in blue in Table 2) by all agencies, further analysis of the carcinogenic potency and its quantification in the next step should not be conducted because of non-relevance; also, it is expected that for such substances no quantified RVs for carcinogenicity will be available at all (see Figure 2).

If the classification for carcinogenicity is not consistent across the agencies (which means that some agencies classify the substance as carcinogenic and others do not) the selection of the RV for carcinogenic effects should be done according to an in-depth evaluation.

In addition, an in-depth evaluation for carcinogenic chemicals will be required if a) there is no consensus in conclusion with regard to the threshold / non-threshold assumption between the agencies, b) the final list of valuable RVs for carcinogenic effects contains different types of values like a slope factor, a DMEL or a BMDL with associated MOE.

Unless the selection of a RV fits in a very urgent dossier for assessing risks from incidents/calamities, or in the frame of a generic context (setting guidelines or legal context), the ‘default evaluation’ is the default starting point for selecting RV.

2.6 DEFAULT SELECTION OF HEALTH BASED REFERENCE VALUES

6

The default evaluation starts with the collection of suitable RVs established by several agencies listed in Table 3 (see section 2.4). Suitability of RVs refers to the appropriate duration and route of exposure for which the RV is intended to be applied in the risk assessment.

When collecting suitable RV established by several agencies (Table 3), the duration and route of exposure should be taken into account. Some agencies report mainly risk values for chronic exposure duration, while other agencies have also risk values for acute or intermediate duration of exposure. For inhalation the route of exposure column in Table 3 is marked with 'I', for total oral exposure with 'O' and for exposure via drinking water 'Ow'. Sources that publish RV for both total oral and drinking water exposure are marked with 'O(w)'.

The compilation of the agencies for consultation (Table 3) is based on the lists of agencies consulted by ANSES, INERIS, IsEPP and OVAM in their procedures for selection of RVs, and on the sources mentioned in the WHO Human Health Risk Assessment Toolkit (WHO, 2010).

Meta-databases compiling RVs from several of these agencies exist and can be used as a starting point: Examples of meta-databases are listed in Table 4 (see section 2.4).

The sources of RV in Table 3 are split up into "primary sources" and "secondary sources".

Primary sources are sources from supranational level, have a very thorough peer review process (over several departments within an agency), and the methods of derivation are transparent and well documented.

RVs from secondary sources are in general also derived in a transparent way and documented (albeit sometimes not in English written versions); however the extent of the peer review process is more limited, or the procedure follows a national instead of supranational methodology (e.g. in choice of assessment factors)

Therefore, RVs from primary sources are preferred over RVs from secondary sources (see further)

7

The attribution of 'primary' or 'secondary' can be discussed for some sources; and is indeed not a fully objective criterion. The attribution of 'primary' or 'secondary' in Table 3 is in line with the procedure applied within other Flemish policy domains (Cornelis et al., 2014) and with a procedure developed within a CEFIC-LRI project (De Brouwere et al.,2014).

After collection of available RVs, a flowchart reflecting priority criteria for selecting RV is followed (from 6 to 19).

The first priority criterion 7 is whether the RV is from a primary or secondary source. The second priorty criterion 8 is the year in which the RV has been derived or has been reconfirmed[5].

[5] Reconfirmed: some agencies have re-evaluated the toxicology data in view of updating their RV; if no new information is available, or in the case that the new information leads to the same as previously derived RV, the RV is reconfirmed; in such a case, the date of revision/reconfirmation instead of the date of the first derivation can be regarded as 'age of RV'

The age of RV derivation is selected as an important criterion since recently derived RVs take into account the most recent advancements of scientific studies which may serve as key study for deriving the RV, and also follow the most recent approaches for selection of assessment and uncertainty factors. A cut-off threshold of 10 year as what could be considered as 'recent' is applied here. A ten years period might look rather long as a cut-off for what is considered as 'recent'; however, procedures for deriving and reviewing RVs by above mentioned agencies generally take several years, especially when an exhaustive review procedure is foreseen. Also, most agencies do not update their values in a time span of less than 10 years.

8

Thus, where at least one recent RV is available from a primary source, the older RVs from primary sources are not further considered in the default selection scheme. Analogously, when RVs from secondary sources are considered, priority is given to recent RVs from secondary sources.

9

It should then be investigated whether recent RVs ($\leq$ 10 years) from this level (primary or secondary) have been based on a BMDL approach. Priority should be given to BMDL derived RVs since this is recgonized a a sounder basis compared to the use of NOAEL/LOAEL values as starting point. If not available RVs derived via other approaches (e.g. NOAEL) should be used.

10

A next step is to investigate whether the recent RVs ($\leq$ 10 years) from this level (primary or secondary) have been established by only one or several sources.

11

Where a recent RV ($\leq$ 10 years) has been established by only one source, this value is selected, and the exercise of selection of RVs can stop at this stage.

One exception on this rule pertains to situations for RV selection of carcinogenic effects, where OEHHA is the only source which has established a unit risk value or oral slope factor. In such case, the RV (i.e. a unit risk value) should not be adopted automatically, since there are concerns regarding the uncertainties related to the unit risk factors of OEHHA; instead it is recommended to investigate the rationale of the OEHHA technical document descrbing the derivation of the unit risk/oral slope factor and to consider a number of criteria before selecting the unit risk factor or oral slope factor from OEHHA:

Criteria in favour of using the OEHHA unit risk or slope factor:

- There is sufficient evidence that for the particular exposure route, cancer effects may occur (i.e. in at least in one animal study for this route of exposure, cancer effects have been observerd)

Criteria advising against the use the OEHHA unit risk or slope factor:

- If OEHHA reports substantial uncertainties in view of derivation/application of the unit risk/oral slope factor,
- If primary sources do not consider substance as carcinogenic,
- If primary sources do consider the substances as carcinogenic, but have clear arguments why the concept of unit risk/slope factor is not applicable (i.e. in case of evidence of a threshold mechanism)

If one of these 'advising-against' criteria are met, it is recommended not to use the OEHHA unit risk/slope factor, and instead to rely the selection of the health-based risk value on the non-carcinogenic effects.

More details concerning the rationale of advicing (against) the use of OEHHA's unit risk or slope factors are explained in Annex B.

In the situation where several agencies from that level (e.g. primary or secondary / BMDL or other approach) have recently ($\leq$ 10 years) issued a suitable RV, it should be evaluated to what extent these RVs differ from each other.

No strict criteria can be set for the evaluation of acceptability of the difference between RVs at this step; this might differ from case to case, and should be regarded in view of uncertainty and variability of exposure values; therefore, it is up to the expert to evaluate whether differences between RVs are substantially different or not, and need a further investigation of differences or not.

13

If differences between RVs from the same level (priority of sources) are small, it is advised to stop the analysis of RV at this 'default evaluation' and select the most conservative value.

14

If it is judged that differences between RVs from the same level (priority of sources) are significant, and need further investigations, the selection of the RV should be considered in view of the exposure levels which are subject of the evaluation: it should be evaluated whether the application of each of the considered RVs would lead to a different risk conclusion. If this is not the case (same conclusion using different RV), the most stringent should be used, with an accompanying text explaining that the conclusion by application of various RV from that level is not different (robust conclusion).

In this case, it should be clearly stated that the 'default evaluation' selected RV should not be used beyond the context of that specific situation. In this case, it is worth to mention also the RV values of the other agencies in the conclusion.

If the risk conclusion is affected by the choice of the RV in the risk assessment of the specific case (different conclusion), it should be moved to an in-depth evaluation for selection of RV.

At this stage, when a conclusion differs depending on the choice of the RV, one could also consider to refine the exposure assessment in parallel with – or before – going to a more thorough investigation of appropriate RV (in-depth evaluation).

15

In the case where none of the primary RVs can be considered as recent (≤ 10 years), the selection procedure considers whether recent (≤ 10 years) RVs from secondary sources are available. If yes, the date of the key study underpinning this recent secondary source RV should be investigated. If the publication date of the key study is more recent than the date of the primary sources, one may assume that the more recent secondary source is based on new science published after the date of primary source; since it is based on newer science, it is assumed to be based on an improved scientific background compared to the older primary RV, and in such cases, the more recent secondary RV is preferred over the older primary RV.

In other cases, namely: when a recent secondary sources RV is not based on a key study which is more recent than the date of the primary RV; there is no reason to believe that the more recent secondary source is based on an improved scientific background compared to the older primary RV; in such cases, the older primary source RV(s) are preferred over the recent secondary source RV

If more than one agency from secondary sources has issued recent RV based on recent key studies, the priority protocol similar to the one for the choice of several primary sources should be followed (from 10 to 14)

16

If no RVs from primary sources are available, one should select a RV from available RVs from secondary sources (according to the scheme analogous to primary sources):

17

If recent (≤ 10 years) secondary source RV are avalailable, the recent RV(s) should be used; otherwise 'old' RV from secondary sources may be applied. If more than one RV of this type is available, the same considerations should be made as in case of more than one option for primary sources (see 10 to 14)

18

In the situation where none of the primary or secondary sources from Table 3 has issued a suitable RV for the substance of interest, for exposure via drinking water one should investigate whether a suitable RV for oral exposure is available.

For exposure via drinking water, a guideline value (GV) can be calculated from the oral RV (TDI). After collection of available RVs for oral exposure (O), a flowchart reflecting priority criteria for selecting RV is followed (from 6 to 17).

Equation 1

$$GV = \frac{TDI \times BW \times P}{C}$$

GV = guideline value
BW = body weight, 60 kg for adults (WHO)
P = fraction of the TDI allocated to drinking water, 20% (WHO)
C= daily drinking water consumption, 2 liters for adults (WHO)

19

When none of the primary and secondary sources from Table 3 has issued a suitable RV for the substance of interest for oral (O) and inhalation (I) exposure it is advised to consult tertiary sources (I, O).

Examples of tertiary sources are listed in Table 5 (see section 2.4.2) . This list is neither limitative nor exhaustive, and might be expanded with additional sources; but one should only consider health-based, transparently derived reference values.

If more than one RV from tertiairy sources are available, the same considerations as for secondary sources should be made (recentness, and impact on risk conclusion).

A distinction between secondary and tertiary sources has been made because the list of tertiary sources might be extensive, and merging them with secondary sources would render the default evaluation too exhaustive and not practical in use in many cases. A default evaluation does not require investigating tertiary sources unless no information from primary and secondary sources can be found.

If tertiary sources still do not lead to a RV, one could consider a de novo derivation of a RV. Herein, it could be considered to 1) apply the Threshold of Toxicological Concern (TTC) (Cramer et al., 1978) 2) to derive a RV starting from a RV from analogous compounds (e.g. read-across or QSAR techniques) (IGHRC, 2013) or 3) to perform a de novo analysis in order to derive a health-based reference value.

Methods for performing a de novo derivation are not further elaborated in this report since this topic was out of scope of this study.

However, if case neither primary, secondary nor tertiary sources resulted in the selection fo a health-based value, and a de novo derivation, TTC approach or read across is not feasible, one could also consider the use of quaternary sources.

We define quaternary sources as sources with ‘building blocks’ to derive health-based reference values. These values cannot be adopted as such as health-based reference values because they either lack an ’approval’ or peer reviewed procedure (i.e. in case of use of ECHA database), or these values are designed for occupational exposure, and thus need a conversion to use as health-based reference values for the general public. Therefore, while we consider primary, secondary and tertiairy sources as sources with purely health-based values, the quaternary sources are not necessarly health-based values, and should eventually be adapted to be at similar level of protection of public health as risk values from primary, secondary or tertiary sources. The list and references to quaternary sources is given in Table 6 (see section 2.4.3)

Aspects to take into account when using quaternary sources:

When using the ECHA database, one should in first instance search for general population DNEL values, and the relevant route of exposure (inhalation, dermal, oral) and duration (acute, chronic). If both a DNEL for local effects and systemic effects are available in the database, one should take the lowest of both values.

By preference, one should investigate – if available – the rationale of the derivation of the DNEL. If the rationale is a good quality, and the pivotal study, selection of assessment factor is of sufficient quality, one can use the DNEL as a proxy for a health-based reference value.

If it is not the case, one might consider to use the PoD used in the derivation of the DNEL and apply appropriate assessment factors according expert judgment.

If the confidence in the DNEL value is rather weak, one might consider to apply an additional assessment factor to convert the DNEL to a health based RV equivalent value. By lack of the a well-underpinned value for this ratio, one could use with caution a factor of 10. However, further investigations are needed to derive a well underpinned value for this ratio (see Annex C).

When using occupational exposure limit values as quaternary sources, the following aspects should be considered when using an OEL in risk assessment for the general public:

1. Time window of exposure

   Occupational exposure limits are set for 8 hour time average windows, corresponding to a workshift, while the general public can be continuously (24/days) exposed

2. Safety factor for inclusion of vulnerable populations

   The general public included vulnerable groups (infants, elderly, disabable persons) with potentially a higher sensitivity to environmental pollution, and thus requiring an additional protection level.

3. Non-health-based aspects in derivation of OELs

   While general public HB GV are purely based on health considerations, factors such as technical feasibility, socio-economic aspects, political choices may also play a role in setting OELs, thus leading to values somewhat higher than purely health based protective values.

   In the "MER-richtlijnensysteem mens gezondheid" [6] OEL are converted to general public reference values using following safety factors:
   - 1/10th of the OEL for non-carcinogenic substances
   - 1/x of the OEL for carcinogenic substances. X is the value that brings the risk to 1: 106 for a lifetime exposure. If not enough scientific data are available to determine x, a default value of 1000 is used.

   We propose to adopt these conversion factor to go from an OEL to general public reference value.

Finally, it is stressed that quaternary sources should only be used if searches on primary, secondary, or tertiary sources did not result in a health-based reference value.

[6] https://www.milieuinfo.be/confluence/display/MRMG/Referentiewaarden+voor+de+aftoetsing+van+de+ernst

2.7 IN-DEPTH EVALUATION OF HEALTH BASED REFERENCE VALUES

For use in a generic context, and if the outcome of the default scheme is inconclusive, a more in-depth analysis of the background and rationale of how the RVs have been established is needed in order to make an informed choice on which is the most appropriate reference value.

The information to consider in this step is based on the aspects to consider in a ”niveau 2/3” analysis of RV in the procedure of ANSES (2012).

The following aspects should be considered and discussed for each of the available RVs collected from considered agencies (cfr.Table 3):

General information:

- Year of last revision
- Exposure duration applicable to the risk value
- Critical effects or location of tumors (for carcinogenic effects)

Analysis of the scientific background of the RVs

- Effects considered, and choice of critical effect on which the RV is based
- Choice of pivotal study from which the RV has been derived
- If pivotal study is an animal study or human study (and type of human study)
- Considered population (number of subjects, sensitive populations, etc.)
- Choice and arguments for threshold or non-threshold approach (typically in case of carcinogens)
- Identification of critical doses
- Adjustment factors for extrapolation from intermittent to continuous exposure
- Adjustment factors for differences in metabolic rate between test animals and humans (allometric scaling)
- Uncertainty factors
- Extrapolation methods for high-to-low exposures in case of carcinogens

It is advised to list these aspects in a tabular form for the different available RVs (see **Error! Reference source not found.**).

This information is generally available from the documents in which the derivation of the reference values has been described (e.g. US EPA Toxicological Reviews).

For the aspects leading to conflicts of interpretation and judgement across agencies, the argumentations made by the different agencies should be discussed and carefully analysed. If needed, the original sources of the pivotal studies should be consulted.

For example, if different agencies select other scientific studies as pivotal studies, the reasons for this discrepancy should be analysed:

- Latest scientific studies included
- Completeness of overview of studies before selecting the pivotal study
- Priority given to human studies over animal studies
- Quality of the studies (according to Good Laboratory Practices of OECD)
- Application of framework for evaluating the quality of studies (e.g. Klimisch criteria; Klimisch et al., 1997)

- If animal studies are used: is the effect and mode of action transposable from animals to humans, for the duration and route of exposure considered (if the mode of action is plausible for humans, the construction of the RV can be considered as pertinent.)

In another situation, different agencies might use the same pivotal study, however differing in the choice of the critical dose.

In this case, the presence and the quality of the dose-response relationship should be discussed (e.g. number of tested doses, spacing between doses; attribution of a LOAEL or NOAEL to a tested dose). If a good quality BMD(L) value is available, preference might be given to use the BMD(L) value as critical dose instead of a LOAEL value (EFSA, WHO).

Another important aspect very often leading to divergence in reference values is the use of uncertainty and assessment factors.

Here again, argumentation of the choice of the assessment factors should be carefully investigated. It might be necessary to consult toxicological experts to determine the appropriate selection of assessment factors, in view of type of effect, mechanism or mode of action, and type of exposure.

Taking into account the argumentation of each of the agencies, the assessor makes an informed choice of what is the most robust and pertinent risk value and spells out the argumentation for this choice in the rationale.

An in-depth assessment might also be needed for the selection of RV for carcinogenic effects (see above). In this exercise, a careful investigation of the mode of action/mechanism of and evidence for threshold or non-threshold approach as investigated by the several agencies should be performed. If different types of health-based reference values are reported (e.g. unit risk versus BMDL with associated MOE), the extrapolation methods should be discussed and comparability of results assessed.

Finally, it should be noted that there is a grey zone between a default and in-depth assessment. In a default selection of a HB RV, in principle, one considers only the risk value without considering the point of departure and the applied assessment factors. However, in practice, is it often feasible and valuable to report (shortly) on these factors, and considering these aspects in an 'extended' default selection (without a full elaborated documentation such as in the case of an in-depth assessment). Examples of such 'extended' default selections are available upon request (VITO, and Flemish Agency of Health and Care).

2.8 COMBINING RVS OF CARCINOGENICITY AND NON-CARCINOGENIC EFFECTS

For substances classified as carcinogenic (see Figure 2), parallel selection of RV for carcinogenic and non-carcinogenic effects should be performed according to the default scheme or the in-depth evaluation.

For non-carcinogenic substances and carcinogenic substances with assumed threshold for effects, RVs will be reported in units of exposure: mg/m³,or mg/kg.d. These values can be used as such in the risk assessment.

For non-threshold carcinogens, the dose-response relationship at low exposures is generally expressed as a unit risk or slope factor, assuming linearity in the exposure range for the general population. The units typically are $(mg/m^3)^{-1}$, $(mg/kg\ body\ weight.d)^{-1}$, $(\mu g/l\ drinking\text{-}water)^{-1}$. To use these values in a risk assessment context, either the unit risks/slope factors are used as such and multiplied with available exposure data, resulting in an excess lifetime cancer risk for the population.

This latter value can be compared with cancer risks considered negligible, acceptable or unacceptable (which is a policy choice). Alternatively, unit risks/slope factors can be converted to health-based reference values (corresponding to a set cancer risk) by using the following equation

$$RV_{non-threshol\ \ carcinogen}^{at\ cancer\ risk} = \frac{value\ of\ excess\ lifetime\ cancer\ risk}{unit\ risk/slope\ factor}$$

The value for the excess lifetime cancer risk is a policy decision, for the general population it generally ranges between 1.10^{-6} and 1.10^{-5}. Using the above equation, the magnitude of RVs for non-carcinogenic (or threshold carcinogenic) effects and RVs for non-threshold carcinogenic effects can be compared. The excess lifetime cancer risk should always be mentioned.

In case of non-threshold carcinogens for which a POD (like a BMDL) and a MOE is used, no explicit expression of acceptable cancer risk is made. It is assumed that the risk for the population is of low concern when exposure is below the POD/MOE.

CHAPTER 3: PROCEDURE FOR THE SELECTION OF HEALTH-BASED REFERENCE VALUES

3.1 EXPOSURE SITUATION

Describe here the context of use of the RV. Ideally, report the monitoring data (duration of exposure, route of exposure), and the question to address.

3.2 GENERAL INFORMATION

Substance identifier (name, CAS no)
Date of selection RV
Name/unit of assessor
Route and duration of exposure
Context of use RV

3.3 TIERED LEVEL OF RISK VALUE SELECTION

Choose between options:

- 'RV for incidents' was applied because of of context (incident/calamity)
- 'default selection' was applied because…
- 'in-depth evaluation' was applied because….

3.4 CLASSIFICATION FOR CARCINOGENICITY

Agency	Source/hyperlink to consult	Date	Carcinogenicity classification	Link with retrieved info
IARC	https://monographs.iarc.fr/list-of-classifications open in Chrome			
US EPA	http://www.epa.gov/iris/search_keyword.htm			
EU-GHS	http://echa.europa.eu/information-on-chemicals/cl-inventory-database			
NTP	http://ntp.niehs.nih.gov/pubhealth/roc/index.html			

Conclusion (indicate)

RV to select for non-carcinogenic effects	*RV to select for both carcinogenic and non-carcinogenic effects*

3.5 SELECTION OF RV

Based on the outcome of the tiered level, and the carcinogenicity classification, tables reporting 'RV for incidents', 'default evaluation' or 'in-depth evaluation' should be completed.

A different tier might be relevant for RV for carcinogenic effects versus RV for non-carcinogenic effect for the same substance.

3.5.1 Table for reporting 'RV for incidents'

Agency	Route	Duration	RV name	RV value	RV units	Source/hyperlink

EPA	*I*	*30 min*	*AEGL-1: Life-threatening health effects or death.*	*xx*	*µg/m³*

3.5.2 Table for reporting default selection of health-based reference values

NON- CARCINOGENIC EFFECTs PRIMARY SOURCES				
Agency	**WHO**	**US EPA IRIS**	**EFSA[7]**	**ATSDR**
websites to consult:	Inhalation: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2010/who-guidelines-for-indoor-air-quality-selected-pollutants oraal: https://www.who.int/water_sanitation_health/water-quality/guidelines/en// (drinkwater) https://www.who.int/foodsafety/publications/jecfa/en/ http://apps.who.int/pesticide-residues-jmpr-database inhalatie en oraal : https://www.who.int/ipcs/publications/cicad/en/	www.epa.gov/iris drinkingwater: https://www.epa.gov/dwstandardsregulations/2018-drinking-water-standards-and-advisory-tables https://www.epa.gov/pesticides/updated-list-human-health-benchmarks-pesticides-drinking-water-available (pesticides)	http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed http://www.efsa.europa.eu/en/microstrategy/openfoodtox	http://www.atsdr.cdc.gov/mrls/mrllist.asp#39tag
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites): http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study[8]				
Speciation[9]				
Route and duration				
Name RV[10]				
Critical heatlh effect				
Value RV[11]				
Unit RV				
Source or hyperlink.				
///				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 1) ☐ ***Not applicable since sufficent primary sources are availble***				

[7] if oral route is the relevant route of exposure
[8] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[9] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[10] name of the reference value in the original sources. (for example: RfC (reference concentration))
[11] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	Cal-EPA OEHHA	Anses	Health Canada	US EPA PPRTV
websites to consult:	http://oehha.ca.gov/air/allrels.html http://www.oehha.ca.gov/risk/ChemicalDB/index.asp drinkwater: https://oehha.ca.gov/water/chemicals)	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses	http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php https://www.canada.ca/en/services/health/publications/healthy-living.html https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html (rapport elektronisch aan te vragen) drinkwater: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html	http://hhpprtv.ornl.gov/
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study [12]				
Speciation[13]				
Route and duration				
Name RV[14]				
Critical heatlh effect				
Value RV[15]				
Unit RV				
Source or hyperlink.				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 2)				
Agency	**TCEQ**	**NHMRC Australia**	**Ministry of Health New Zealand**	**RIVM**
websites to consult:	https://www.tceq.texas.gov/toxicology/dsd/final	drinkwater: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1	drinkwater: http://www.health.govt.nz/publication/guidelines-drinking-water-quality-management-new-zealand	http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study[16]				
Speciation[17]				
Route and duration				

12 date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
13 mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
14 name of the reference value in the original sources. (for example: RfC (reference concentration))
15 health-based Reference value (AQG, TDI, RfD, MRL,…)
16 date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
17 mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)

Name RV[18]				
Critical heatlh effect				
Value RV[19]				
Unit RV				
Source or hyperlink.				
//				
TERTIARY SOURCES**: only if primary and secondary sources do ot result into sufficient information indien in primaire en secundaire brelevante info (part 1 – non-limitative list)* ☐ ***Not applicable since sufficent primary or secondary sources are availble				
Agency	**RIVM (MTR en VR)**	**DEFRA (UK)**	**German Indoor Air Quality Guidelines**	**French Indoor Air Quality Guidelines (ANSES)**
websites to consult:	https://www.rivm.nl/rvs/Normen	https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs	http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values	https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs
year RV				
Name + year key study [20]				
Speciation[21]				
Route and duration				
Name RV[22]				
Critical heatlh effect				
Value RV[23]				
Unit RV				
***TERTIARY SOURCES:** only if primary and secondary sources do not result into sufficient (part 2 – non-limitative list)*				
Agency	**INDEX project**	**New Zealand Ambient Air quality Guidelines**	**DWI (drinking water inspectorate)**	**EU LCI**
websites to consult:	http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_exs_02.pdf	https://www.mfe.govt.nz/air/air-guidance-and-wood-burners/ambient-air-quality-guidelines	http://www.dwi.gov.uk/index.htm	https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en https://publications.jrc.ec.europa.eu/repository/bitstream/JRC83683/eca%20report%2029_final.pdf
year RV				
Name + year key study [24]				
Speciation[25]				
Route and duration				

[18] name of the reference value in the original sources. (for example: RfC (reference concentration))
[19] health-based Reference value (AQG, TDI, RfD, MRL,…)
[20] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[21] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[22] name of the reference value in the original sources. (for example: RfC (reference concentration))
[23] health-based Reference value (AQG, TDI, RfD, MRL,…)
[24] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[25] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)

Name RV[26]				
Critical heatlh effect				
Value RV[27]				
Unit RV				
//				
QUATERNARY SOURCES : *only if primary, secondary and tertiary sources not not result in sufficient information*				
Consult info:	https://www.echa.europa.eu/information-on-chemicals/registered-substances DNEL for general population and relvante route and duration of exposure; if DNELs for both systemic and local effects are available, select the lowest one. If derivation of the DNEL is available, asess the quality (selection of pivotal study, Point of departure and assessment factors. If the quality of the DNEL is of poor quality (e.g. use of AF), it is I recommended to apply an additional safety factor.		https://www.werk.belgie.be/nl/onderzoeksprojecten/2019-gegevensbank-met-beroepsmatige-blootstellingsgrenswaarden-belgie-en-de http://www.werk.belgie.be/defaultTab.aspx?id=616 Threshold Limit Values, fort he de algemene bevolking: 1/10e van de TLV voor niet carcinogenen	

[26] name of the reference value in the original sources. (for example: RfC (reference concentration))
[27] health-based Reference value (AQG, TDI, RfD, MRL,…)

CARCINOGENIC EFFECTs (only to consider for substances classified as carcinogenic) PRIMARY SOURCES				
Agency	**WHO**	**US EPA IRIS**	**EFSA**[28]	
websites to consult:	Inhalation: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2010/who-guidelines-for-indoor-air-quality-selected-pollutants oraal: https://www.who.int/water_sanitation_health/water-quality/guidelines/en// (drinkwater) https://www.who.int/foodsafety/publications/jecfa/en/ http://apps.who.int/pesticide-residues-jmpr-database inhalatie en oraal : https://www.who.int/ipcs/publications/cicad/en/	www.epa.gov/iris drinkingwater: https://www.epa.gov/dwstandardsregulations/2018-drinking-water-standards-and-advisory-tables https://www.epa.gov/pesticides/updated-list-human-health-benchmarks-pesticides-drinking-water-available (pesticides)	http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed http://www.efsa.europa.eu/en/microstrategy/openfoodtox	
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites): http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study [29]				
Speciation[30]				
Route and duration				
Name RV[31]				
Critical heatlh effect				
Value RV[32]				
Unit RV				
Source or hyperlink.				
///				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 1) ☒ *Not applicable since sufficent primary sources are availble*				

[28] if oral route is the relevant route of exposure
[29] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[30] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[31] name of the reference value in the original sources. (for example: RfC (reference concentration))
[32] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	Cal-EPA OEHHA	Anses	Health Canada	US EPA PPRTV
websites to consult:	https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009 appendix B: slope factors are always for inhalation exposure unless explicitly stated otherwise. When OEHHA is the only agency with a slope factor (unit risk factor), check rationale and decide whether or not to accept slope factor. contra: when OEHHA itself indicates that there is great uncertainty; primary body (s) consider the substance as carcinogenic, but have clear arguments why a slope or unit risk factor does not apply to quantitatively assess carcinogenicity, e.g. because there is sufficient evidence that there is a threshold (e.g. in the case of formaldehyde); when no information about the derivation of the CPF is available	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses	http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php https://www.canada.ca/en/services/health/publications/healthy-living.html https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html (rapport elektronisch aan te vragen) drinkwater: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html	http://hhpprtv.ornl.gov/
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study [33]				
Speciation[34]				
Route and duration				
Name RV[35]				
Critical heatlh effect				
Value RV[36]				
Unit RV				
Source or hyperlink.				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 2)				

[33] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[34] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[35] name of the reference value in the original sources. (for example: RfC (reference concentration))
[36] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	TCEQ	NHMRC Australia	Ministry of Health New Zealand	RIVM
websites to consult:	https://www.tceq.texas.gov/toxicology/dsd/final	drinkwater: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1	drinkwater: http://www.health.govt.nz/publication/guidelines-drinking-water-quality-management-new-zealand	http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV				
Name + year key study [37]				
Speciation[38]				
Route and duration				
Name RV[39]				
Critical heatlh effect				
Value RV[40]				
Unit RV				
Source or hyperlink.				
//				
TERTIARY SOURCES**: only if primary and secondary sources do ot result into sufficient information indien in primaire en secundaire brelevante info (part 1 – non-limitative list)* ☒ ***Not applicable since sufficent primary or secondary sources are availble				
Agency	**RIVM (MTR en VR)**	**DEFRA (UK)**	**German Indoor Air Quality Guidelines**	**French Indoor Air Quality Guidelines (ANSES)**
websites to consult:	https://www.rivm.nl/rvs/Normen	https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs	http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values	https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs
year RV				
Name + year key study [41]				
Speciation[42]				
Route and duration				
Name RV[43]				
Critical heatlh effect				
Value RV[44]				
Unit RV				
***TERTIARY SOURCES**: only if primary and secondary sources do not result into sufficient (part 2 – non-limitative list)*				

[37] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[38] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[39] name of the reference value in the original sources. (for example: RfC (reference concentration))
[40] health-based Reference value (AQG, TDI, RfD, MRL,…)
[41] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[42] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[43] name of the reference value in the original sources. (for example: RfC (reference concentration))
[44] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	INDEX project	New Zealand Ambient Air quality Guidelines	DWI (drinking water inspectorate)
websites to consult:	http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_exs_02.pdf	https://www.mfe.govt.nz/air/air-guidance-and-wood-burners/ambient-air-quality-guidelines	http://www.dwi.gov.uk/index.htm
year RV			
Name + year key study [45]			
Speciation[46]			
Route and duration			
Name RV[47]			
Critical heatlh effect			
Value RV[48]			
Unit RV			

//

***QUATERNARY SOURCES** : only if primary, secondary and tertiary sources not not result in sufficient information*		
consult info:	https://www.echa.europa.eu/information-on-chemicals/registered-substances DMEL for general population and relvante route and duration of exposure;. If derivation of the DMEL is available, asess the quality (selection of pivotal study, Point of departure and assessment factors. If the quality of the DMEL is of poor quality (e.g. use of AF), it is I recommended to apply an additional safety factor.	https://www.werk.belgie.be/nl/onderzoeksprojecten/2019-gegevensbank-met-beroepsmatige-blootstellingsgrenswaarden-belgie-en-de http://www.werk.belgie.be/defaultTab.aspx?id=616 Threshold Limit Values, for the general public; 1/x of the TLV for carcinogens with x = value reducing the exposure to a risk level of 1.10-6 for lifetime exposure; in case of unsifficient data to derive the value of X, the value of 1000 can be used for X

[45] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[46] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[47] name of the reference value in the original sources. (for example: RfC (reference concentration))
[48] health-based Reference value (AQG, TDI, RfD, MRL,…)

3.5.3 Table for reporting in-depth Investigation

(To be completed for carcinogenic and/or non-carcinogenic effects):

Aspect	Agency X	Agency Y	Agency …
Hyperlink of assessment			
RV			
Year of last revision			
Critical effect as basis for RV			
Effects considered, and choice critical effect on which the RV is based			
Choice of pivotal study from which the RV has been derived			
Is pivotal study an animal study or human study (and type of human study)			
Considered population (number of subjects, sensitive populations, etc.)			
Choice and arguments for threshold or non-threshold approach of the RV			
Identification of critical dose			
Assessment factors (AF)[49]:			
AF Adjustment for exposure duration			
AF Adjustment factor for study length			
AF reliability of dose-response			
AF interspecies (allometric scaling)			
AF interspecies (kinetic & dynamic)			
AF intraspecies (kinetic & dynamic)			
AF sensitive populations			
Other adjustment factors			
Total assessment factor			
…			

The tabular listed information is further elaborated by a textual argumentation for the selected RV:

The aspects leading to conflicts of interpretation and judgement across agencies, the argumentations made by the different agencies should be carefully analysed by the assessor. The motivation for what is considered as the most robust and persistent RV – based on transparency and argumentations used in the derivation of the RV should be clearly stated by the assessor.

[49] Description, explanation and defaults for assessment factors used in the REACH process can be found in the REACH R8 guidance: https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

CHAPTER 4: APPLICATION OF THE PROTOCOL: EXAMPLES

4.1 CASE STUDY: INCIDENT OF ACRYLONITRILE RELEASE TO AMBIENT AIR (30 PPM, 1 DAY)

4.1.1 Exposure situation

Incident of acrylonitrile release resulting in high acrylonitrile levels ambient air levels (worst case measurement was 30 ppm, precautionary assumption that this exposure last for a time span of 1 day. This is an illustration that is not representative for the actual exposure at the disaster); a quick assessment of the health evaluation of acute exposure is asked.

4.1.2 General Information

Substance identifier (name, CAS no)	acrylonitrile – 107-13-1 (CAS)
Date of selection RV	04/01/2016
Name/unit of assessor	Katleen De Brouwere
Route and duration of exposure	inhalation, acute
Context of use RV	Calamity (30 ppm, 1 dag)

Conversion of ppm to mg/m³: (1 ppm = 2.17 mg/m³ at 25 °C): 30 ppm = 65 mg/m³

4.1.3 Tiered level of Risk value selection

Quick screening was applied because of urgency of the situation

4.1.4 Classification of carcinogenicity

Agency	Date	Carcinogenicity classification	Source/hyperlink
IARC	1999 (vol 71)	2B	http://monographs.iarc.fr/ENG/Classification/latest_classif.php
US EPA	1987	B1	http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=206
EU-GHS	CLP 00 (2008?)	1B	http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/77896
NTP	? (in 13th report); NTP study dating from 2001	Reasonably anticipated to be human carcinogen	http://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf

4.1.5 Selection of RV

For non-carcinogenic effects:

Agency	Route	Duration	RV name	RV value	RV units	Source/hyperlink
EPA - AEGL	*I*	*8 hours*	AEGL-1	*No value*		http://www.epa.gov/aegl/acrylonitrile-results-aegl-results
		8 hours	AEGL-2	*0.26*	*ppm*	http://www.epa.gov/aegl/acrylonitrile-results-aegl-results
		8 hours	AEGL-3	*5.2*	*ppm*	http://www.epa.gov/aegl/acrylonitrile-results-aegl-results
INERIS	I	60 minutes	SEL (seuil des effets létaux significant)	ND	ppm	http://www.ineris.fr/rapports-d%C3%A9tude/toxicologie-et-environnement/fiches-et-rapports-de-seuils-de-toxicit%C3%A9-aigu%C3%AB (download the pdf for 'acrylonitrile'): http://www.ineris.fr/substances/fr/substance/getDocument/2631
	I	60 minutes	SPEL (seuil des premiers effets létaux)	139 302	ppm mg/m³	Idem
	I	60 minutes	SEI (seuil des effets irréversibles)	22 48	ppm mg/m³	Idem
	I	60 minutes	SER (seuil des effets réversibles)	ND		Idem
RIVM	I	1 hour	Voorlichtings-grenswaarde (VRW)	3.3	mg/m³	https://rvs.rivm.nl/zoeksysteem/stof/detail/236
		1 hour	Alarmerings-grendwaarde (AGW)	130	mg/m³	
		1 hour	Levensbedreigende waarde (LBW)	220	mg/m³	
		1 hour	Carcinogenic risk potency[50]	328,5 of 1.983	mg/m3	
ATSDR	I	Acute	MRL	0.1	ppm	http://www.atsdr.cdc.gov/mrls/mrllist.asp

AEGL-1: Notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
AEGL-2: Irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape
AEGL-3: Life-threatening health effects or death.

Remarks:

- Also AEGL-1/2/3 values available for shorter duration exposure periods (10 min, 30 min, 60 min and 4 h). the AEGL values for 8 hours were selected because of the best match with the time span of measurements (1 day)
- Also SEL and SPEL values available for shorter duration exposure (1, 10 , 20 and 30 minutes)
- Also VRW, AGW and LBW values available for shorer duration exposure (10, 40 minutes)
- Definition of 'acute' MRL according ATSDR is 1-14 days
- Critical endpoint (cfr. ATSDR overview table): neurological effects

[50] De carcinogenic risk potency (CRP) geeft de luchtconcentratie van een stof bij een kankerrisico van 1 : 10.000 bij een eenmalige 1 uur durende blootstelling.

For carcinogenic effects:

Agency	RV name	Value	Units	Hyperlink
RIVM (2016)	CPR[51]	328,5 - 1983	mg/m³	https://rvs.rivm.nl/zoeksysteem/ (via search on 'acrylonitril')
ECHA	DMEL	No value available		http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d844a2d-b384-4b16-e044-00144f67d249/AGGR-b30161a5-345e-4ce4-9314-9f47227f05ce_DISS-9d844a2d-b384-4b16-e044-00144f67d249.html#AGGR-b30161a5-345e-4ce4-9314-9f47227f05ce
US EPA	Inhalation Unit Risk	6.8 10^{-5}	per µg/m³	http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0206#carc

The CPR (for 1 hour) was converted to a 1 day (24h) equivalent by diviving by a duration factor of 1/24: 328.5/24 mg/m³ → **14 mg/m³**

The Unit risk from US EPA (was converedt according to the CPR method (concentration for a 1 day risk level at 10-4): 14 mg/m³. This is the same value as above (very likely, the RIVM CPR value is based on the unit riks value from US EPA) .

4.1.6 Evaluation of the exposure:

exposure to 30 ppm during 1 day is dangerous to life. The exposure exceeds the 8-h AEGL-3 value (Life-threatening health effects or death) for exposure to acrylonitrile via ambient air (acute effects), and it exceeds the value of 14 mg/m³, which is the 10^{-4} risk level for carcinogenicity, calculated for a single acute 24h exposure event.

4.2 APPLICATION OF THE DEFAULT SELECTION FOR EVALUATION OF INDOOR AIR LEVELS OF 1,4 DICHLOROBENZENE

4.2.1 context of use

chronic exposure (inhalation) to 1,4 dichlorobenzene: to evaluate indoor air monitoring data of in 450 Flemish dwellings (monitored in a campaign 2008-2012) using passive sampling during 1 week, as a proxy for long term exposure.

Monitoring data range from <0.1 µg/m³ to 6.9 µg/m³ (mean value 0.2 µg/m³)

4.2.2 General Information

Substance identifier (name, CAS no)	1,4 dichlorobenzene; 106-46-7
Date of selection RV	15/05/2020
Name/unit of assessor	De Brouwere Katleen VITO
Route and duration of exposure	chronic exposure, inhalation
Context of use RV	indoor air

[51] [51] De carcinogenic risk potency (CRP) is the air concentration corresponding to a cancer risk of 10-4 due to single, acute exposure event of 1 hour.

4.2.3 Tiered level of Risk value selection

Choose between options:

- ~~'RV for incidents' was applied because of of context (incident/calamity)~~
- 'default selection ' was applied because of use in case specific situation (evaluation a montiroing value of 6.9 µg/m³)
- ~~'in-depth evaluation' was applied because~~

4.2.4 Classification for carcinogenicity

Agency	Source/hyperlink to consult	Date	Carcinogenicity classification	link with retrieved infoe
IARC	https://monographs.iarc.fr/list-of-classifications open in Chrome	1999	Group 2B	
US EPA	http://www.epa.gov/iris/search_keyword.htm	2003	Weight of evidence for cancer: not assessed under the IRIS Program.	https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=552
EU-GHS	http://echa.europa.eu/information-on-chemicals/cl-inventory-database	CLP00	Carc 2	https://echa.europa.eu/brief-profile/-/briefprofile/100.003.092
NTP	http://ntp.niehs.nih.gov/pubhealth/roc/index.html	14th RoC	**Reasonably Anticipated To Be Human Carcinogens**	https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf

Conclusion (indicate)

~~*RV to select for non-carcinogenic effects*~~	***RV to select for both carcinogenic and non-carcinogenic effects***

4.2.5 Selection of RV

NON- CARCINOGENIC EFFECTs PRIMARY SOURCES				
Agency	**WHO**	**US EPA IRIS**	**EFSA[52]**	**ATSDR**
websites to consult:	Inhalation: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2010/who-guidelines-for-indoor-air-quality-selected-pollutants oraal: https://www.who.int/water_sanitation_health/water-quality/guidelines/en// (drinkwater) https://www.who.int/foodsafety/publications/jecfa/en/ http://apps.who.int/pesticide-residues-jmpr-database inhalatie en oraal : https://www.who.int/ipcs/publications/cicad/en/	www.epa.gov/iris drinkingwater: https://www.epa.gov/dwstandardsregulations/2018-drinking-water-standards-and-advisory-tables https://www.epa.gov/pesticides/updated-list-human-health-benchmarks-pesticides-drinking-water-available (pesticides)	http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed http://www.efsa.europa.eu/en/microstrategy/openfoodtox	http://www.atsdr.cdc.gov/mrls/mrllist.asp#39tag
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites): http://www.inchem.org/__http://www.iter.tera.org/__https://substances.ineris.fr/fr/			
year RV	/	1994	/	2006
Name + year key study [53]	/	Chlorobenzene Producers Association. 1986. Parachlorobenzene: Two-generation Reproduction Study in Sprague-Dawley Rats. Study 86-81-90605. MRID No. 411088-1. Available from EPA. Write to FOI, EPA, Washington, DC 20460. NOAEL: 301 mg/m³ NOAEL-HEC: 75 mg/m² UF 100 (10 voor gevoelige subpopulatie en 10 interspecies AF)	/	Aiso S, Takeuchi T, Arito H, et al. 2005b; 2-years inhalation study; male and female F344/DuCrj rats + 50 male and female Crj:BDF1 mice
Speciation[54]	/	/	/	
Route and duration	/	Subchronic, inhalation	/	Chronic; inhalation
Name RV[55]	/	RfC	/	MRL chronic
Critical heatlh effect	/	Effects on liver (increased liver weights in P1 males)	/	moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats

[52] if oral route is the relevant route of exposure
[53] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[54] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[55] name of the reference value in the original sources. (for example: RfC (reference concentration))

Value RV[56]	/	800 µg/m³	/	60 µg/m³
Unit RV	/	µg/m³	/	µg/m³
Source or hyperlink.	/	https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0552_summary.pdf	/	https://www.atsdr.cdc.gov/toxprofiles/tp10.pdf
//				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 1)				
☐ ***Not applicable since sufficent primary sources are availble***				
Agency	**Cal-EPA OEHHA**	**Anses**	**Health Canada**	**US EPA PPRTV**
websites to consult:	http://oehha.ca.gov/air/allrels.html http://www.oehha.ca.gov/risk/ChemicalDB/index.asp drinkwater: https://oehha.ca.gov/water/chemicals)	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses	http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php https://www.canada.ca/en/services/health/publications/healthy-living.html https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html (rapport elektronisch aan te vragen) drinkwater: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html	http://hhpprtv.ornl.gov/
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV	list dates from 2019, but if you search further, you find that the date of the latest revision for this substance is 2000	/	/	/ (not applicable because there is a US EPA IRIS value)
Name + year key study [57]	Not mentioned in summary sheet	/	/	
Speciation[58]	/	/	/	
Route and duration	/	/	/	
Name RV[59]	/	/	/	
Critical heatlh effect	Nervous and respiratory; alimentary systems (liver); kidney	/	/	
Value RV[60]	800 µg/m³	/	/	
Unit RV	/	/	/	
Source or hyperlink.	https://oehha.ca.gov/air/general-info/oehha-acute-8-hour-and-chronic-reference-exposure-level-rel-summary	/	/	
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 2)				

[56] health-based Reference value (AQG, TDI, RfD, MRL,…)
[57] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[58] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[59] name of the reference value in the original sources. (for example: RfC (reference concentration))
[60] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	TCEQ	NHMRC Australia	Ministry of Health New Zealand	RIVM
websites to consult:	https://www.tceq.texas.gov/toxicology/dsd/final	drinkwater: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1	drinkwater: http://www.health.govt.nz/publication/guidelines-drinking-water-quality-management-new-zealand	http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV	2015	/	/	/
Name + year key study [61]	TCEQ refers to key study of ATSDR (2006), i.e Aiso et al. 2005; however, TCEQ applies other assessment factors	/	/	/
Speciation[62]		/	/	/
Route and duration		/	/	/
Name RV[63]		/	/	/
Critical heatlh effect	increases in nasal olfactory epithelial lesions in female rats	/	/	/
Value RV[64]	530 µg/m³ for Air Monitoring Comparison Value 160 µg/m³ for ESL (Effect screening Levels)	/	/	/
Unit RV		/	/	/
Source or hyperlink.	https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/dichlorobenzene,%201,4-.pdf			
//				
TERTIARY SOURCES**: only if primary and secondary sources do ot result into sufficient information indien in primaire en secundaire brelevante info (part 1 – non-limitative list)* ☒ ***Not applicable since sufficent primary or secondary sources are availble				

[61] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[62] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[63] name of the reference value in the original sources. (for example: RfC (reference concentration))
[64] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	RIVM (MTR en VR)	DEFRA (UK)	German Indoor Air Quality Guidelines	French Indoor Air Quality Guidelines (ANSES)
websites to consult:	https://rvs.rivm.nl/normen	https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs	http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values	https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs
year RV				
Name + year key study [65]				
Speciation[66]				
Route and duration				
Name RV[67]				
Critical heatlh effect				
Value RV[68]				
Unit RV				
***TERTIARY SOURCES**: only if primary and secondary sources do not result into sufficient (part 2 – non-limitative list)*				
Agency	**INDEX project**	**New Zealand Ambient Air quality Guidelines**	**DWI (drinking water inspectorate)**	**EU LCI**
websites to consult:	http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_exs_02.pdf	https://www.mfe.govt.nz/air/air-guidance-and-wood-burners/ambient-air-quality-guidelines	http://www.dwi.gov.uk/index.htm	https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en https://publications.jrc.ec.europa.eu/repository/bitstream/JRC83683/eca%20report%2029_final.pdf
year RV				
Name + year key study [69]				
Speciation[70]				
Route and duration				
Name RV[71]				
Critical heatlh effect				
Value RV[72]				
Unit RV				
///				
***QUATERNARY SOURCES** : only if primary, secondary and tertiary sources not not result in sufficient information*				

[65] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[66] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[67] name of the reference value in the original sources. (for example: RfC (reference concentration))
[68] health-based Reference value (AQG, TDI, RfD, MRL,…)
[69] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[70] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[71] name of the reference value in the original sources. (for example: RfC (reference concentration))
[72] health-based Reference value (AQG, TDI, RfD, MRL,…)

consult info:	https://www.echa.europa.eu/information-on-chemicals/registered-substances DNEL for general population and relvante route and duration of exposure; if DNELs for both systemic and local effects are available, select the lowest one. If derivation of the DNEL is available, asess the quality (selection of pivotal study, Point of departure and assessment factors. If the quality of the DNEL is of poor quality (e.g. use of AF), it is I recommended to apply an additional safety factor.	https://www.werk.belgie.be/nl/onderzoeksprojecten/2019-gegevensbank-met-beroepsmatige-blootstellingsgrenswaarden-belgie-en-de http://www.werk.belgie.be/defaultTab.aspx?id=616 Threshold Limit Values, fort he de algemene bevolking: 1/10e van de TLV voor niet carcinogenen

CARCINOGENIC EFFECTs (only to consider for substances classified as carcinogenic) PRIMARY SOURCES				
Agency	**WHO**	**US EPA IRIS**	**EFSA[73]**	
websites to consult:	Inhalation: http://www.who.int/phe/health_topics/outdoorair/outdoorair_aqg/en/ http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2010/who-guidelines-for-indoor-air-quality-selected-pollutants oraal: https://www.who.int/water_sanitation_health/water-quality/guidelines/en// (drinkwater) https://www.who.int/foodsafety/publications/jecfa/en/ http://apps.who.int/pesticide-residues-jmpr-database inhalatie en oraal : https://www.who.int/ipcs/publications/cicad/en/	www.epa.gov/iris drinkingwater: https://www.epa.gov/dwstandardsregulations/2018-drinking-water-standards-and-advisory-tables https://www.epa.gov/pesticides/updated-list-human-health-benchmarks-pesticides-drinking-water-available (pesticides)	http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed http://www.efsa.europa.eu/en/microstrategy/openfoodtox	
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites): http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV	/	/	/	
Name + year key study [74]	/	/	/	
Speciation[75]	/	/	/	
Route and duration	/	/	/	
Name RV[76]	/	/	/	
Critical heatlh effect	/	/	/	
Value RV[77]	/	/	/	
Unit RV	/	/	/	
Source or hyperlink.	/	/	/	
//				
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 1) ☐ ***Not applicable since sufficent primary sources are availble***				

[73] if oral route is the relevant route of exposure
[74] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[75] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[76] name of the reference value in the original sources. (for example: RfC (reference concentration))
[77] health-based Reference value (AQG, TDI, RfD, MRL,…)

Agency	Cal-EPA OEHHA	Anses	Health Canada	US EPA PPRTV
websites to consult:	https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009 appendix B: slope factors are always for inhalation exposure unless explicitly stated otherwise. When OEHHA is the only agency with a slope factor (unit risk factor), check rationale and decide whether or not to accept slope factor. contra: when OEHHA itself indicates that there is great uncertainty; primary body (s) consider the substance as carcinogenic, but have clear arguments why a slope or unit risk factor does not apply to quantitatively assess carcinogenicity, e.g. because there is sufficient evidence that there is a threshold (e.g. in the case of formaldehyde); when no information about the derivation of the CPF is available	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses	http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php https://www.canada.ca/en/services/health/publications/healthy-living.html https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html (rapport elektronisch aan te vragen) drinkwater: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality/guidelines-canadian-drinking-water-quality-summary-table.html	http://hhpprtv.ornl.gov/
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV	unclear whether the last revision was in 2001 or 2015	/	/	/
Name + year key study [78]	NTP 1987; study with significant increases in hepatocellular carcinomas or adenomen multistage procedure applied to calcullate a cancer potency and subsequently a human cancer equivalent	/	/	/
Speciation[79]		/	/	/
Route and duration	Inhalation, chronic			
Name RV[80]		/	/	/
Critical heatlh effect	hepatocellular carcinomas or adenomen	/	/	/
Value RV[81]	1 *10^{-5} per µg/m³	/	/	/
Unit RV	Cancer potency	/	/	/

[78] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available

[79] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)

[80] name of the reference value in the original sources. (for example: RfC (reference concentration))

[81] health-based Reference value (AQG, TDI, RfD, MRL,…)

Source or hyperlink.	https://oehha.ca.gov/media/downloads/crnr/appendixb.pdf	/	/	/
If primary sources result in insufficiet basis for selectin of HB RV according to the protocol; consult: SECONDARY SOURCES (part 2)				
Agency	**TCEQ**	**NHMRC Australia**	**Ministry of Health New Zealand**	**RIVM**
websites to consult:	https://www.tceq.texas.gov/toxicology/dsd/final	drinkwater: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines#block-views-block-file-attachments-content-block-1	drinkwater: http://www.health.govt.nz/publication/guidelines-drinking-water-quality-management-new-zealand	http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf
	Overview websites (do not always inclue the most up to date information, it is recommended to consult also the source websites http://www.inchem.org/ http://www.iter.tera.org/ https://substances.ineris.fr/fr/			
year RV	2015			
Name + year key study [82]	TCEQ includes on p30 a rationale why a carcinogenic based ESL has not been derived (according TCEQ there are inadequate data to derive a unit risk)	/	/	/
Speciation[83]		/	/	/
Route and duration		/	/	/
Name RV[84]				
Critical heatlh effect		/	/	/
Value RV[85]	/	/	/	/
Unit RV		/	/	/
Source or hyperlink.	https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/final/dichlorobenzene,%201,4-.pdf	/	/	/
//				
TERTIARY SOURCES**: only if primary and secondary sources do ot result into sufficient information indien in primaire en secundaire brelevante info (part 1 – non-limitative list)* ☒ ***Not applicable since sufficent primary or secondary sources are availble				
Agency	**RIVM (MTR en VR)**	**DEFRA (UK)**	**German Indoor Air Quality Guidelines**	**French Indoor Air Quality Guidelines (ANSES)**
websites to consult:	https://rvs.rivm.nl/normen	https://www.gov.uk/government/organisations/department-for-environment-food-rural-affairs	http://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/german-committee-on-indoor-guide-values	https://www.anses.fr/en/content/indoor-air-quality-guidelines-iaqgs
year RV				
Name + year key study [86]				
Speciation[87]				

[82] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[83] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[84] name of the reference value in the original sources. (for example: RfC (reference concentration))
[85] health-based Reference value (AQG, TDI, RfD, MRL,…)
[86] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[87] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)

Route and duration				
Name RV[88]				
Critical heatlh effect				
Value RV[89]				
Unit RV				
***TERTIARY SOURCES**: only if primary and secondary sources do not result into sufficient (part 2 – non-limitative list)*				
Agency	**INDEX project**	**New Zealand Ambient Air quality Guidelines**	**DWI (drinking water inspectorate)**	
websites to consult:	http://ec.europa.eu/health/ph_projects/2002/pollution/fp_pollution_2002_exs_02.pdf	https://www.mfe.govt.nz/air/air-guidance-and-wood-burners/ambient-air-quality-guidelines	http://www.dwi.gov.uk/index.htm	
year RV				
Name + year key study [90]				
Speciation[91]				
Route and duration				
Name RV[92]				
Critical heatlh effect				
Value RV[93]				
Unit RV				
//				
***QUATERNARY SOURCES** : only if primary, secondary and tertiary sources not not result in sufficient information*				
consult info:	https://www.echa.europa.eu/information-on-chemicals/registered-substances DMEL for general population and relvante route and duration of exposure;. If derivation of the DMEL is available, asess the quality (selection of pivotal study, Point of departure and assessment factors. If the quality of the DMEL is of poor quality (e.g. use of AF), it is I recommended to apply an additional safety factor.		https://www.werk.belgie.be/nl/onderzoeksprojecten/2019-gegevensbank-met-beroepsmatige-blootstellingsgrenswaarden-belgie-en-de http://www.werk.belgie.be/defaultTab.aspx?id=616 Threshold Limit Values, for the general public; 1/x of the TLV for carcinogens with x = value reducing the exposure to a risk level of 1.10-6 for lifetime exposure; in case of unsifficient data to derive the value of X, the value of 1000 can be used for X	

[88] name of the reference value in the original sources. (for example: RfC (reference concentration))
[89] health-based Reference value (AQG, TDI, RfD, MRL,…)
[90] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
[91] mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[92] name of the reference value in the original sources. (for example: RfC (reference concentration))
[93] health-based Reference value (AQG, TDI, RfD, MRL,…)

4.2.6 Conclusion – selection RV and evaluation of exposure

ATSDR (2006), USEPA (1994) and TCEQ (2015) provide a HB RV for 1,4 dichloorbenzene. The key study used in TCEQ (2015) is Aino et al. (2005), the same key study as selected by ATSDR (2006). Since ATSDR is a primary source, and proposes a lower value, we selected teh value of ATSDR (60 µg/m³) for non-carcinogenic effects.

For carcinogenic effects, none of the primary sources derived a unit risk. Two secondary sources reported on this aspect:

TCEQ (2015) provided rationale for not deriving a unit risk (insufficient data). OEHHA derived a risk factor; however, OEHHA did not discuss uncertainties and did not argue why a unit risk is sufficently well underpinned with data. For, this reason, we follow TCEQ (2015) and do not select a RV for carcinogenic effect.

The risk of value of ATSDR (60 µg/m³) for non-carcinogenic effects is selected as RV for 1,4 dichlorobenzene.

The levels of 1,4 dichlorobenzene (ranging from <0.1-6.9 µg/m³) in a monitoring campaign in 450 Flemish dwelling are are below HB RV for 1,4 dichlorobenzene .

4.3 APPLICATION IN CONTEXT OF SELECTION HEALTH BASED GUIDANCE VALUES FOR INDOOR AIR QUALITY IN FLANDERS.

In depth assessments have been made for a series of indoor air pollutants in the context of the Flemish Indoor Air Decree (2018). These values are embedded in a legal context of the Flemish Indoor Air Decree (http://www.ejustice.just.fgov.be/cgi/article_body.pl?language=nl&caller=summary&pub_date=18-09-07&numac=2018013405)

The resulting values are summarized in the below table. The rationale and full details of the in depth assessments are available upon request (reports in Dutch).

Parameter	Basis	Leading health effect; specific critical toxic	Species in the key study	Point of departure, assessment and conversion factors / OR unit risk value or K_L, K_M value $	Flemish Indoor Air Target Guidance value	Flemish Indoor Air Intervention value Guidance value	Exposure period applicable for target and intervention guideline values
2-ethylhexanol	Ad hoc Arbeitsgruppe (2013)	Non cancer effects; Sensory irritation	Human	NOAEC 8 mg/m³ Intraspecies differences: 10 Subacute to chronic: 6	100 µg/m³	810 µg/m³	Chronic*
Acetaldehyde	ANSES (2014a)	Non cancer effects; Degeneration of the olfactory epithelium	Rat	NOAEC 90 mg/m³ Regional Gas Dose Ratio: 0.13 Toxicodynamics and residual uncertainties: 2.5 Sensitive population: 10 Subchronic to chronic: 3	160 µg/m³	480 µg/m³	Chronic*
Asbestos - chrysotile	Health Council of the Netherlands (2010) and Tromp (2016)	Carcinogenicity; Lung cancer and mesothelioma	Human	K_L= 1.64 10^{-2} (fibres/ml yr)$^{-1}$ K_M=0.15 10^{-8} (fibres/ml yr)$^{-1}$	28 fibres/m³	280 fibres/m³	Chronic*
Asbestos - amphibole	Health Council of the Netherlands (2010) and Tromp (2016)	Carcinogenicity; Lung cancer and mesothelioma	Human	K_L= 1.64 10^{-2} (fibres/ml yr)$^{-1}$ K_M=7.95 10^{-8} (fibres/ml yr)$^{-1}$	3 fibres/m³	30 fibres/m³	Chronic*
Asbestos – mixed composition	Health Council of the Netherlands (2010) and Tromp (2016)	Carcinogenicity; Lung cancer and mesothelioma	Human	K_L=1.64 10^{-2} (fibres/ml yr)$^{-1}$ K_M=1.3 10^{-8} (fibres/ml yr)$^{-1}$	$\left(\frac{amphibole\ (F/m^3)}{3\ F/m^3} + \frac{crysotile\ (F/m^3)}{28\ F/m^3}\right) \leq 1$	$\left(\frac{amphibole\ (F/m^3)}{30\ F/m^3} + \frac{crysotile\ (F/m^3)}{280\ F/m^3}\right) \leq 1$	Chronic*
Benzene	ANSES (2014b)	Carcinogenicity; Leukemia	Human	Unit risk: 2.6 × 10^{-5} per µg/m³		0.4 µg/m³**	Chronic*

Parameter	Basis	Leading health effect; specific critical toxic	Species in the key study	Point of departure, assessment and conversion factors / OR unit risk value or K_L, K_M value [$]	Flemish Indoor Air Target Guidance value	Flemish Indoor Air Intervention value Guidance value	Exposure period applicable for target and intervention guideline values
C_4-C_{11}-aldehydes	Ad hoc Arbeitsgruppe (2009) and JRC (2013)	Non cancer effects; Respiratory irritation	rat	LOAEC 360 mg/m³ (Ad hoc Arbeitsgruppe 2009) Adjustment exposure duration: 5.6 Study length: 2 Interspecies difference: 1 Intraspecies difference: 5 Sensitive population: 2 NOAEC: 145 mg/m³ (JRC 2013) Adjustment exposure duration: 5.6 Study length: 2 Intraspecies difference: 10 Quality database: 2	650 µg/m³	1600 µg/m³	Chronic*
C_9-C_{14}-alkanes	Sagunski and Mangelsdorf (2005)	Non cancer effects; Decreased sperm motility	Rat	NOAEL 275 mg/m³ Adjustment exposure duration: 5.6 Interspecies difference: 10 Intraspecies difference: 10 Sensitive population: 2	250 µg/m³	490 µg/m³	Chronic*
Formaldehyde	WHO (2010)	Non cancer effects; Sensory irritation	Human	NOAEL 0.63 standard deviation of nasal pungency thresholds: 5		100 µg/m³	Chronic*
Carbon monoxide	WHO (2010)	Non cancer effects; Acute exposure-related reduction of exercise tolerance and increase in symptoms of ischaemic heart disease	Human	NOAEL carboxyhaemoglobin level of 2%.		8 mg/m³	24 hours
Metallic Hg (vapour)	RIVM (2015)	Non cancer effects; Increased frequency of tremor and reduced cognitive skills	Human	LOAEL 25 µg/m³ Adjustment exposure duration 4,2 Use of LOAEL: 10 Sensitive population: 10	0.05 µg/m³	0.6 µg/m³	Chronic*

Parameter	Basis	Leading health effect; specific critical toxic	Species in the key study	Point of departure, assessment and conversion factors / OR unit risk value or K_L, K_M value [$]	Flemish Indoor Air Target Guidance value	Flemish Indoor Air Intervention value Guidance value	Exposure period applicable for target and intervention guideline values
Naphthalene	US EPA (1998)	Non cancer effects; hyperplasia and metaplasia in respiratory and olfactory epithelium, respectively	Mouse	LOAEL: 52 mg/m³ Adjustment exposure duration: 5.6 ratio of mouse:human blood/gas partition coefficients: 1 Interspecies difference: 10 Use of LOAEL: 10 Sensitive population: 10 database deficiencies: 3	3 µg/m³	31 µg/m³	Chronic*
Ozone	Health Canada (2010)	Non cancer effects; Decreases in pulmonary function and increases in subjective respiratory symptoms	Human	NOAEL 80 µg/m³ Half of the NOAEL (intraspecies difference 10 was not achievable in many Canadian homes)	40 µg/m³	78 µg/m³	Chronic*
PAHs (BaP as indicator)	WHO (2000)	Carcinogenicity; lung tumours	Hamster	Unit risk: 8.7×10^{-2} per µg/m³	0.012 ng/m³	0.1 ng/m³	Chronic*
PM2.5	WHO (2005)	Non cancer effects and cancer effects; cardiopulmonary and lung cancer mortality	Human	annual mean concentration of 10 µg/m³ can be considered to be below the mean for most likely effects	10 µg/m³		Chronic*
Nicotine	Matt et al. (2011)	-	Human	cut off level between dwelling with versus without smokers 0.1 µg/m³	0.1 µg/m³		-
Nitrogen dioxide	Target value: ANSES (2013); Intervention value: WHO (2010)	Non cancer effects; Respiratory symptoms in children with asthma	Human	NOAEL 20 µg/m³	20 µg/m³	40 µg/m³	Chronic*
Styrene	WHO (2000)	Non cancer effects; reductions in visuomotor accuracy and verbal learning skills and subclinical effects on colour vision	Human	LOAEL 107 mg/m³ Adjustment exposure duration: 4.2 Intraspecies difference: 10 Use of LOAEL: 10	260 µg/m³	2500 µg/m³	Chronic*
Tetrachlorethylene	US EPA (2012)	Carcinogenicity; hepatocellular tumors	Mouse	Unit risk: 2.6×10^{-7} per µg/m³	4 µg/m³	38 µg/m³	Chronic*

Parameter	Basis	Leading health effect; specific critical toxic	Species in the key study	Point of departure, assessment and conversion factors / OR unit risk value or K_L, K_M value $	Flemish Indoor Air Target Guidance value	Flemish Indoor Air Intervention value Guidance value	Exposure period applicable for target and intervention guideline values
Toluene	US EPA (2005)	Non cancer effects; neurological deficits	Human	NOAEL 128 mg/m³ Adjustment exposure duration: 2.8 Intraspecies difference: 10	5000 µg/m³	14000 µg/m³	Chronic*
Trichloorethylene	US EPA (2011)	Carcinogenicity; kidney cancer	Human	Unit risk: 4×10^{-6} per µg/m³	0.2 µg/m³	2.5 µg/m³	Chronic*
TVOC	Ad hoc Arbeitsgruppe (1999, 2007)	-	-	Median TVOC concentration in German dwellings	300 µg/m³	1000 µg/m³	Chronic*

$ for substances where non cancer effects are leading for the derivation of target and intervention, the point of departure (NOAEL or LOAEL) is mentioned; for substances where non-threshold cancer effects are leading, the unit risk value used to calculate the guidance and intervention guidance values are displayed in the table; for asbestos K_L (for lung cancer) and K_M values (for mesothelioma) are used, representing the fractional increase of cancer per fibre year/mL

**exposure > 365 days – lifetime exposure*

*** applicable if outdoor air ≤ 0.4 µg/m³, in other circumstances the intervention value is set at the level of the outdoor concentration*

4.4 APPLICATION IN CONTEXT OF SELECTION HEALTH BASED GUIDANCE OUTDOOR AIR QUALITY IN FLANDERS.

In depth assessments have been made for an establishment of health based guidance values for a series of outdoor air pollutants in the outdoor air (arsenic, asbestos, benzene, cadmium, chromium, formaldehyde, carbon monoxide, lead, manganese, nickel, PAHs, PM10, M2.5, NO2, styrene, toluene, H_2S, xylenes, and SO_2. These are advisory values, no legal binding values).

The documents describing the in depth assessment (in Dutch) are available at https://www.zorg-en-gezondheid.be/aandachtsgebieden-en-humane-biomonitoring in the section 'Gezondheidskundige advieswaarden (GAW) voor gebruik in MER.

REFERENCES

ANSES (2012). Valeurs sanitaires de références (VR). Guide des pratiques d'analyse et de choix. Saisine n°2011-SA-0355. https://www.anses.fr/fr/system/files/CHIM2011sa0355Ra.pdf

Cornelis et al. (2014). Werkwijze voor het opstellen van bodemsaneringsnormen en –waarden; richtwaarden en streefwaarden. Tussentijds rapport.

Cramer, G.M., Ford, R.A., Hall, R.L., 1978. Estimation of toxic hazard—a decision tree approach. Food Cosmet. Toxicol. 16, 255–276.

De Brouwere K, Cornelis C, Arvanitis A, Brown T, Crump D, Harrison P, Jantunen M, Price P, Torfs, R. 2014. Application of the Maximum Cumulative Ratio (MCR) as a screening tool for evaluation of mixtures in residential indoor air. Science of the Total Environment 479 – 480: 267-276

De Brouwere K., Baken K. (2020), Methodiek gezondheidskundige beoordeling variabele blootstellingsprofielen, draft report.

Direction générale opérationelle (DGO 3) de l'Agriculture, des Ressources Naturelles et de l'Environnement – Département du Sol et des Déchets – Direction de la Protection des Sols et Direction de l'Assainissement des Sols (2015) Décret du 5 décembre 2008 relatif à la gestion des sols - Code Wallon de Bonnes Pratiques – version 02: Guide de référence pour l'étude de risques. Annex B7

ECHA, 2012. Guidance on information requirements and chemical safety assessment: Chapter R.8: Characterization of dose [concentration]-response for human health https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf

INERIS, 2006. Pratique INERIS de choix des valeurs toxicologiques de reference dans les évaluations de risques sanitair. Rapport d'étude 21/03/2006. N° INERIS-DRC-05-4113-ETSC/R01a

IGHRC (2013). The Interdepartmental Group on Health Risks from Chemicals. Predictive approaches to chemical hazard identification and characterization : Current use by UK Government Depts and Agencies

ISSeP (2018). Procédure pour la Sélection des Valeurs Toxicologiques de Référence et la Prise en Compte du Caractère Cancérogène d ' un Polluant Version 1 – Mai 2018. 1–22.

Klimisch H.-J., Andreae M., Tillmann U. (1997) A systematic approach for evaluating the quality of

experimental toxicological and ecotoxicological data. *Regul Toxicol Pharmacol*; 25:1-5.

OEHHA California Environmental Protection Agency Office of Environmental Health Hazard Assessment Air Toxicology and Epidemiology Branch (2009). Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. https://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

RIVM, 1997. Guidance on the Derivation of Maximum Permissible Risk Levels for Human Intake of Soil Contaminants. RIVM Report 711701006. Auteurs: Janssen & Speijers

RIVM, 2015. Handleiding voor de afleiding van indicatieve milieurisicogrenzen. RIVM rapport 2015-0057. Auteurs : de Poorter et al.

Smolders R., Colles A., Cornelis C., Van Holderbeke M., Chovanova H., Wildemeersch D., Mampaey M., Van Campenhout K. 2014. Key aspects of Flemish system to safeguard public health interests in case of chemical release incidents. Toxicology Letters 231 : 315-323.

Wallonia DGO 3, 2008. Guide de Réference pour l'étude des risques. Annexe B7: Lignes directirces pour l'evaluation du potential cancerigene des polluants non norms et pour la selection des valeurs toxicologiques de reference. P 322-337

WHO (2010). WHO Human Health Risk Assessment Toolkit: Chemical Hazards. Harmonization Project Doc No 8

REVISION HISTORY

Revision January 2020
adjustments clarify the difference between RV for use in incidents evaluation and other acute exposure situations Figure 1: quick screening replaced by 'RV Selection for Incidents'; 'non carcinogenic effects' deleted, 'Is selection of RV in the context of an incident' added
2.2.2 Consideration of carcinogenicity in context of acute exposure events: text about carcinogenic risks updated with information from guidance 'fluctuating exposure profiles' (VITO, draft report' 2019). Paragraph about carcinogenic risk potency values deleted.
chapter 2: new restructure
Table 1: ▼ Link to Ineris updated + link database Ineris added ▼ New link to RIVM added ▼ TCEQ added + information about ReVs added in text
2.2 paragraph added about health-based RV and exposure duration, reference to the guidance 'fluctuating exposure profiles' added
Figure 3 and text in paragraph 2.5 Tiered approach for selection of health-based Reference values (RV) : BMDL approach added, differentiation oral / drinking water / inhalation added, numbers and text were updated in line with the scheme, equation drinking water added
Table 3: For the route of exposure, a differentiation was made between o: total oral, ow: drinking water and o(w): total oral and drinking water Primary sources: ▼ WHO JMPR and WHO Cicad were added as a primary source for RV ▼ WHO Drinking water quality guidelines: link updated ▼ EFSA: link to Openfoodtox database has been added ▼ EPA IRIS: link to Summary of EPA's RfD and cancer risk values for drinking water contaminants document added Secondary sources: ▼ Cal EPA OEHHA: Direct link to overview of cancer potency factors added, link to OEHHA database water chemicals added ▼ Health Canada: advice to check First Priority Substances List (PSL1) Assessments and Second Priority Substances List (PSL2) Assessments, links to publications health living and to summary table Guidelines drinking water quality were added ▼ TCEQ added ▼ NHMRC Australia (drinking water) added ▼ Ministry of Health New Zealand drinking water guidelines added ▼ RIVM moved from tertiary source to secondary source
Table 4: ▼ Furetox deleted (not available anymore) ▼ ITER database: link updated ▼ Ineris chemical Substance Portal added
Table 5: Tertiary sources added ▼ New Zealand Ambient Air quality Guidelines ▼ Drinking water inspectorate
New category: Quaternary sources, Table 6 added + information on how to deal with quaternary sources ▼ Occupational exposure limit values in Belgium and neighboring countries ▼ ECHA portal (DNELs)
Error! Reference source not found. Error! Reference source not found.: default evaluation updated
CHAPTER 4: case studies modified (considering new case studies performed after 2016)
ANNEX B: OEHHA'S evaluations of the carcinogenicity of chemicals added
ANNEX C: comparison between DNELs and health-based reference values added

ANNEX A: EFSA APPROACH TO GENOTOXIC CARCINOGENS

In the case of chemicals that are both carcinogenic and genotoxic, EFSA uses the Margin of Exposure approach (MOE), rather than a slope factor approach to assess health risks (EFSA, 2005)

Preference is given to the use of a BMD[94] approach. If possible, the BMDL[95] at the 10 % effect level (95 % lower confidence interval) is calculated. A MOE to this BMDL (if from animal studies) should then calculated. The MOE should be at least 10,000 in order to conclude that the exposure is of low concern from a public health point (and that the compound is at low priority for risk managers). This MOE covers the inter- and intraspecies differences (each by default a factor of 10), the nature of the carcinogenic effect (10) and the fact that a $BMDL_{10}$ is not equal to a NOAEL. If a T25[96] is used, a higher MOE should be used.

In the case of non-threshold carcinogens, (ECHA, 2012) lowed: the linearized approach and the Large Assessment Factor. Allometric scaling[97] is applied to convert the animal dose into a human equivalent dose. In applying the linearized approach, ECHA considers a BMD at 10 % effect divided by 100,000 or a T25 divided by 250,000 equivalent to a negligible risk level for the general population ($1/10^6$ excess lifetime risk as an indicative tolerable risk level). The Large Assessment Factor is similar to the approach followed by EFSA (ECHA refers to the EFSA approach) and applied to either the $BMDL_{10}$ (default assessment factor 10,000) or the T25 (default assessmenet factor 25,000). The difference with EFSA's approach is that the assessment factors are *applied* to calculate a DMEL (the starting point is divided by the assessment factor) and that a default assessment factor is specified when using a T25.

[94] BMD: Benchmark Dose; dose corresponding to a predefined effect level obtained by fitting a dose-response curve to the experimental effect data

[95] BMDL: Benchmark Dose Low: lower confidence limit to the BMD (generally lower limit of the 95 % confidence interval around the BMD)

[96] T25: dose that will give 25 % of the animals tumours at a specific tissue site after correction for spontaneous incidence

[97] Allometric scaling is used to convert animal doses to human-equivalent doses, accounting for the fact that species characteristics depend upon size and metabolic rate. Scaling factors depend upon the animal species from which conversion is done, but chemical-specific elements and units of exposure should be considered (see ECHA guidance R.8 for more details) .

ANNEX B: OEHHA'S EVALUATIONS OF THE CARCINOGENICITY OF CHEMICALS

OEHHA's Technical Support Document for Cancer Potency Factors (OEHHA, 2009) states that "OEHHA's evaluations of the carcinogenicity of chemicals generally follow the guidelines laid out by IARC for identification and classification of potential human carcinogens, which are described in detail in the most recent revision of the Preamble to the IARC monographs series (IARC, 2006).

Cancer potency values (CPF) included in the Technical Support Document (TSD) for Cancer Potency Factors were from the following sources:

1. Toxic Air Contaminant documents
2. Standard Proposition 65 documents
3. U.S.EPA Integrated Risk Information Systems (Office of Health and EnvironmentalAssessment, U.S.EPA)
4. Expedited Proposition 65 documents
5. Other OEHHA assessments , for example for the drinking water program"

"Although as noted earlier the California Air Toxics programs do not categorize identified carcinogens, it has generally been the practice to regard any agent with an IARC overall classification in Group 1 or Group 2 as a known or potential human carcinogen."

For a number of substances we took a closer look at the derivation described in Appendix B of OEHHA's Technical Support Document for Cancer Potency Factors. The substance evaluations can be split up in reliable and less reliable evaluations, clarified with some examples below.

Reliable:

IARC and US-EPA are unanimous in the carcinogenicity classification of Cr VI (1, A). The oral CPF is derived from animal test studies and well described. Therefore, the oral CPF can be adopted in the standard selection of RV.

For Pb, IARC and US EPA are unanimous in carcinogenicity classification (B2, B2), it is clearly stated that there are no studies demonstrating carcinogenicity by lead inhalation, carcinogenicity by oral intake has been demonstrated in animal studies ("A large number of animal studies have shown kidney tumors following oral exposure to lead compounds, but there are no studies of carcinogenicity due to lead inhalation. "). The oral CPF can be considered as reliable.

Less reliable, yet distracted

As already mentioned above, OEHHA states in appendix B that there are no studies of carcinogenicity due to lead inhalation. However, OEHHA derived an inhalation CPF based on the oral Pb CPF. The unit risk factor was derived assuming that 50% of the inhaled Pb is absorbed (versus 10% of ingested lead) and using the standard assumption that an average adult human has a body weight of 70 kg and an average air intake of 20 m^3 per day. In this case, we do not recommend to select the unit risk as derived by OEHHA due to insufficient scientific evidence.

Ethylbenzene (oral and inhalation) is assessed differently by IARC and US EPA (2A and D). OEHHA itself states "OEHHA therefore concludes that the limited data do not conclusively establish any particular mode of action for ethylbenzene carcinogenesis. However, one or more genotoxic processes appear at least plausible and may well contribute to the overall process of tumor induction.

Because of this, the default linear approach has been used for extrapolating the dose-response curve to low doses. ” The distraction here is thus uncertain and therefore not strong enough to select as a RV.

Formaldehyde (oral) is classified 1 and B1 by IARC and US EPA. An oral slope factor is listed on the OEHHA website (https://oehha.ca.gov/chemicals/formaldehyde), which is equal to the inhalation slope factor. The oral slope factor is not explicitly listed in appendix B and H. Both appendices only mention a “slope factor”, however this refers to the inhalation slope factor. Since no information is available about the derivation of the oral slope factor, it is not strong enough to select as a RV.

Due to possible uncertainties in case only OEHHA has derived a CPF, we recommend to consider a number of criteria before selecting the CPF from OEHHA. These criteria are further explained in the protocol.

ANNEX C: COMPARISON BETWEEN DNELS AND HEALTH BASED REFERENCE VALUES

A DNEL value (**derived no-effect level** (**DNEL**), is a concept under the REACH regulation, being a concentration or exposure level below which a substance does not adversely affect human health. The principle is thus very similar to health-based guidance values, as well as the way a DNEL is derived (i.e selection of a key studie, dose descriptor and application of assessment and uncertainty factors). However, difference in selection of key studies, and selection of assessment factors by different bodies and industry (for DNELs), might lead to differences between DNEL and HB RV for the same route, duration and targeted population.

In literature, we find some comparisons between DNEL values and health-based reference values. The ECA report 29 (JRC, 2013) compared EU-LCI values (which are HB GV, see tertiary sources) with inhalation DNELs for general population (chronic exposure) for 6 VOCs (trimethylbenzene, xylenes, 2-butoxyethanol, styrene, toluene, ethylbenzene), and reported that DNEL values were 10-70 fold higher than the corresponding EU-LCI value. Analogeously, for some other VOCs (formaldehyde, acetaldehyde, 2-ethylhexanol, aceton, dichloromethane, hexane, pentane) DNEL values were 1 to 1000 fold higher than the corresponding values derived by VITO using the protocol for selection of health based reference values. The large range in ratio's DNEL/ HB GV make it hard to propose a default value to convert a DNEL into a health based equivalent RV. In addition, the quality of the DNELs seems to improve other time. While at the time of the ECA report 29 (2013), the DNEL value for styrene was 10,2 mg/m³, the current (2020) DNEL for styrene is 1 mg/m³, and is foreseen with a transparent, well-documented derivation of the DNEL. However, given the rather large range in quality and documentation level of DNELs at the ECHA portal, it is hard to generalize the quality of DNELS.

In the context of occupational exposure health based reference values, Schenk, Deng, & Johanson, (2015) analysed for 235 substances the difference between DNELs and OELs (health base reference values for occupational exposure set by the Swedish authorties) and reported that on average industry's reported DNEL (in ECHA portal) was on average the same as the Swedish OELs, but there was a huge variation (extremes up to 450 fold) in ratio of DNEL/OELs. The choices of key studies, dose descriptors and assessment factors all seemed to contribute ot the descripancies beween DNELs and OEL. Allthoug the comparison of Schenk et al. (2014) is based on occupational exposure risk values, the same issues (selection of key study, dose descriptor and assessment factors) are in place for comparison DNELs with health based rference value. general exposure reference values, and therefore the ratio of occupational DNELs/ health-based worker RV (OELs) shows similarities.

In summary, it is currently not feasible to provide a well underpinned value for conversion a DNEL to a health-based reference value. It is adviced to assess case by case the use of the DNEL, and use additional/other assessment factors.

REFERENCES TO ANNEX A-B-C

ECHA. (2012). Chapter R.8: Characterisation of dose[concentration]-response for human health. In *Guidance on information requirements and chemical safety assessment*.

EFSA. (2005). Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. *EFSA Journal*, *3*(10), 1–31. https://doi.org/10.2903/j.efsa.2005.282

ISSeP. (2018). *Procédure pour la Sélection des Valeurs Toxicologiques de Référence et la Prise en Compte du Caractère Cancérogène d ' un Polluant Version 1 – Mai 2018*. 1–22.

JRC, (European Union Joint Research Centre). (2013). *Urban Air, Indoor Environment and Human Exposure: Harmonisation framework for health based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept*.

Schenk, L., Deng, U., & Johanson, G. (2015). Derived no-effect levels (DNELs) under the European chemicals regulation REACH - An analysis of long-term inhalation worker-DNELs presented by industry. *Annals of Occupational Hygiene*, *59*(4), 416–438. https://doi.org/10.1093/annhyg/meu103