Distribution: General

Final report

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

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Study accomplished under the authority of the Flemish Agency for Care and Health

2016/MRG/R/0469

Januari 2016

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LIST OF ACRONYMS

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
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
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/m³); en Maximum Residue Limit (mg/kg)
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
OEHHA	Office of Environmental Health Hazard Assessment
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
RfC	Reference Concentration
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RV	Risk Value
TCA	Tolerable Concentration in Air
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
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 Agency 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.

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

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 (see below):

- a quick screening is applied in cases of urgency;
- the default evaluation is applied in non-urgent case specific evaluations, and
- an in-depth evaluation is made whena 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).

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 fo 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 'quick screening' or 'default evaluation' (see Figure 2). 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 (quick screening, 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 list of sources to consult (e.g. RV for oral or inhalation exposure; RV for acute exposure or chronic exposures), the types of effects to consider (carcinogenicity?), and the depth of the assessment.

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.

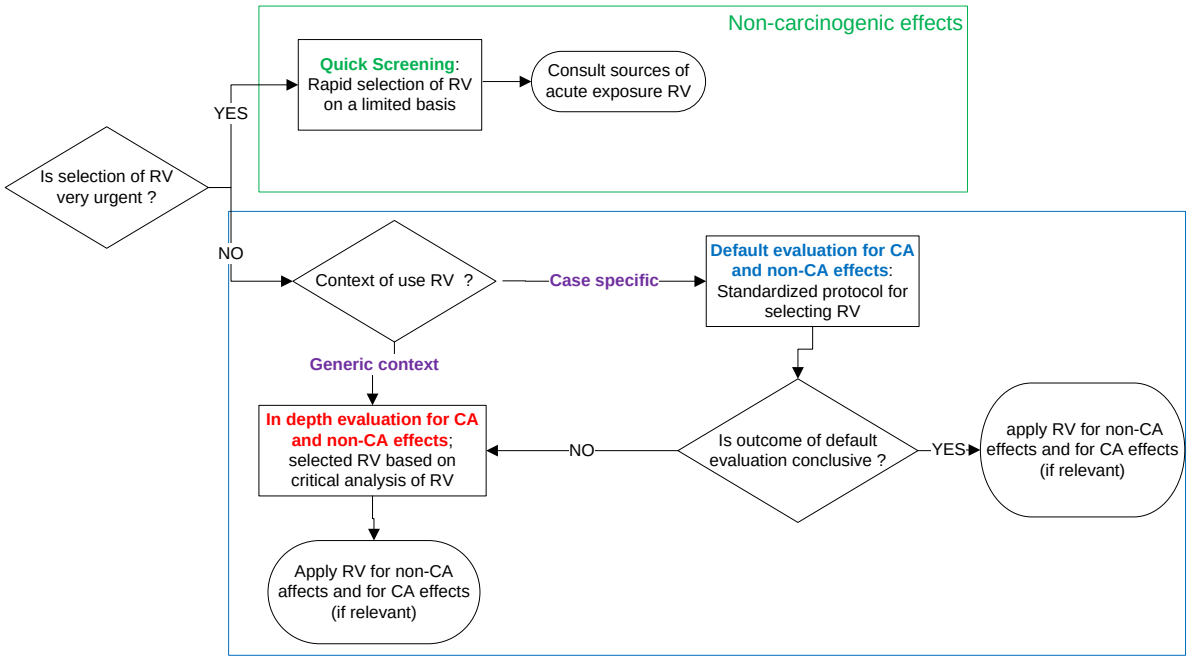


Figure 1: Decision tree for selection approach of health-based reference value for carcinogenic (CA) and non-carcinogenic (non-CA) effects

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).

If the selection of the reference value takes place within the context of a (very) urgent situation where the Agency is asked for advice on the health risks of exposed individuals, there is little time to perform a default evaluation or in-depth evaluation. It is anticipated that urgent situations are focussed on the occurrence of health effects after acute or short-term effects. In such situations, a '**quick evaluation'** is warranted. This quick evaluation 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.

Examples and specific sources to consult for a 'quick screening' are given in Table 1.

If the selection of the reference value is not in the context of an urgent situation, there is more time, allowing for a more time consuming, sound analysis. Also, in many cases of non-urgent situations, chronic exposure instead of acute exposure is subject of the evaluation. For chronic exposure, other sources of RV (see Table 3) compared to RV for acute exposure are applicable.

If the context of use of the RV 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 carcinogencity, 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 2.4 and 2.5, respectively.

For cases related to chronic exposure subject to '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.

2.2. QUICK SCREENING OF ACUTE EXPOSURE LIMITS

If the selection of the reference value is in the context of a (very) urgent situation (incidents, disasters) where the Agency is asked for advice on immediate health risks of exposed individuals, a quick screening of acute exposure limits 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. These situations generally do not allow the time for a time consuming assessment of the most appropriate RV.

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 'quick screening step' in cases of urgent situations is analogous to the niveau 1 procedure for urgent cases by ANSES (Anses, 2012).

In a quick screening exercise, 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 acute exposure in order to quickly evaluate the gravity of the calamity. Therefore, no formal priority scheme for acute exposure limits from Table 1 has been developed. Moreover, the 'choice' in RVs for acute exposure is less abundant compared to RVs for chronic exposure.

In this quick screening step, no critical analysis of the background and derivation of the RVs is made; neither is the date of the assessment taken into account.

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).

Table 1 gives an overview of data sources for acute exposure limits.

Table 1: Agencies and data sources for health-based reference values for use in urgent situations (acute exposures; 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	Inhalation	1 minute 10 minutes 20 minutes 30 minutes	http://www.ineris.fr/rapports-d%C3%A9tude/toxicologie-et-environnement/fiches-et-rapports-de-seuils-de-toxicit%C3%A9-aigu%C3%AB

Agency	RV name	Route of exposure	Duration exposure	link
	létaux SEI: seuil des effets irréversibles SER: seuil des effets réversibles		60 minutes	list of substances for which acute toxicity thresholds have been established (downloadable fiche per substance)
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 search function on: https://rvs.rivm.nl/zoeksysteem/
ATSDR	Acute MRL (Minimal Risk Levels)	Inhalation and oral	Acute (1-14 days)	http://www.atsdr.cdc.gov/mrls/mrllist.asp
ECHA*	Acute DNEL (consumer/general public)	Inhalation and oral	Acute (exact time span: see REACH dossiers)	http://echa.europa.eu/information-on-chemicals/registered-substances

*DNELs derived by industry, and accompanying data for acute toxicity (e.g.LD50 values) are reported on the website of ECHA.

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) 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 (2016) published new intervention values for dangerous substances (122 of 300 substances have been revised in 2015. 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)

The **Agency for Toxic Substances & Disease Registry** (ATSDR) has also established acute exposure MRLs for a large number of substances. The timespan referring to for acute exposure is 1-14 days; the ATSDR MRLs do – in contrast to AEGS and PALs – not discriminate between severity of effects. MRL correspond to the minimal dose at which effects for the most sensitive endpoints are expected, and thus are rather comparable to AEGL-1 and PAL-1 levels.

It should be noted that other agencies establishing RV (see Table 3) focus on RV for chronic exposure (e.g. RfC derived by US EPA, IAQG by WHO). In some situations, consideration and protection to short term exposure is considered, however, the focus – and critical effect – is generally chronic exposure.

If none of agencies (ATSDR, EPA-AEGL-, EPA-PAL) has resulted in acute RV 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.

Notwithstanding the use of DNELs (Derived no effect levels) developed by industry might be critized by (sometimes) lack of transparency and lack of peer review process, the data (e.g. acute DNELs for consumers) found on the ECHA portal could serve as a quick screening value – in cases of lack of any other database.

2.2.1. CONSIDERATION OF CARCINOGENICITY IN CONTEXT OF ACUTE EXPOSURE EVENTS

Quick screening of acute exposure limits

Quick screening focusses on situations corresponding to incidents or accidents. Health-based reference values are targeted towards health effects after acute or short-term exposure. Although carcinogenicity is not considered to be an acute or short-term health effect, the potential carcinogenicity of a chemical can increase concern and could be accounted for when evaluating the necessity of intervention after incidents.

At present, there are no health-based reference values for carcinogenicity after short-term exposure. However, within the framework of the Dutch Intervention Values for Hazardous Chemicals (interventiewaarden voor gevaarlijke stoffen), carcinogenic risk potency values (CRP) for 1 hour exposure have recently been published (https://rvs.rivm.nl/zoeksysteem/Stof/Index) as part of the Dutch system on Disaster Intervention Values. It should be noted that these values are very recent and have not yet been published for all carcinogenic chemicals on the list (e.g. benzene has not yet a CRP value on date of 07/01/2016). The CRP values are published for *inhalation* and are derived as follows:

$$CRP(1\ hour) = \frac{C(1.10^{-4}) * 613200}{2.8}$$

CRP is the carcinogenic risk potency concentration for 1 hour exposure, C is the concentration corresponding to an excess lifetime cancer risk of 1.10^{-4}, the factor of 613200 corresponds to the extrapolation factor from lifelong to 1 hour exposure: 24 h/d * 365 d/yr * 70 yr. It is currently unclear to what the factor 2.8 is a dose rate conversion factor which accounts for the fact that the factor "concentration * time" is not a constant when extrapolating from long to short-term exposures (information received from the RIVM helpdesk Centrum Veiligheid van Stoffen en Producten, 13/01/2016).

Seen the urgency with which values have to be searched for in case of incidents, the carcinogenicity assessment of the default evaluation is not feasible within this context. Therefore the following approach is proposed to evaluate the carcinogenicity of a chemical either in qualitative and quantitative way.

1. Consultation of the Dutch database on Risks of chemicals (which is expected to be consulted in case of incidents anyway) (https://rvs.rivm.nl/zoeksysteem/Stof/Index);
    a. if a CRP value is listed
    → if 1 hour exposure is to be considered: take the value →if longer exposure times are to be considered: divide the value by the number of hours to be considered
    b. if no CRP values is listed, go to step 2.
2. Consultation of the ECHA database (most extended list of chemicals) on chemicals whether the substance is classified as carcinogen 1a, 1b or 2 (http://echa.europa.eu/information-on-chemicals/cl-inventory-database)
    a. if the chemical is classified as such: search for a DMEL for the general population in the database (http://echa.europa.eu/information-on-chemicals) – registered substances – on the tab Toxicological information
        i. if value is present: convert it to a value at 1.10^{-4} by multiplying it with 10-100 and further to a CRP using the above equations and factors
        ii. if no value is present, go to step 3
    b. if not classified, go to step 3
3. Consultation of the US-EPA IRIS database (www.epa.gov/iris):
    a. if a concentration / dose corresponding to an excess cancer risk of 10^{-4} is present, use the value to calculate a CRP (if a slope factor is present, convert it to a concentration/dose at 10^{-4}), list carcinogenicity classification

   b. if no value is present, go to step 4
4. Consult the IARC database (http://monographs.iarc.fr/ENG/Classification/) and report carcinogenicity classification:
   a. if classified as 1 (carcinogenic to humans) or 2A (probably carcinogenic to humans): mark as carcinogen – quantitative assessment of carcinogenicity (IARC generally does not derive slope factors)
   b. if not classified or classified in other groups: not considered a carcinogen

2.3. CONSIDERATION OF CARCINOGENICITY FOR DEFAULT EVALUATION AND IN-DEPTH EVALUATION

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

- 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).

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

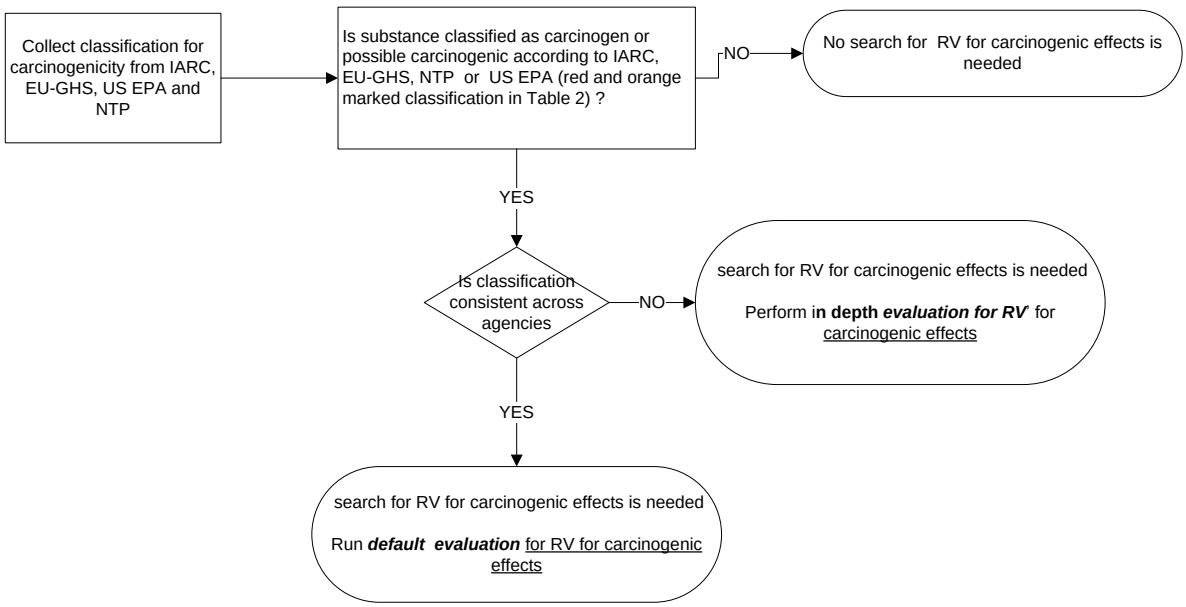
If a substance is classified as carcinogenic (according to classification marked red in Table 2) or possibly carcinogenic (marked orange in Table 2) by one or all agencies, this should trigger a further analysis of the carcinogenic potency and its quantification in the next step. In such a case, the 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. DEFAULT EVALUATION FOR SELECTION OF HEALTH-BASED REFERENCE VALUES (RV)

The scheme for default evaluation 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).

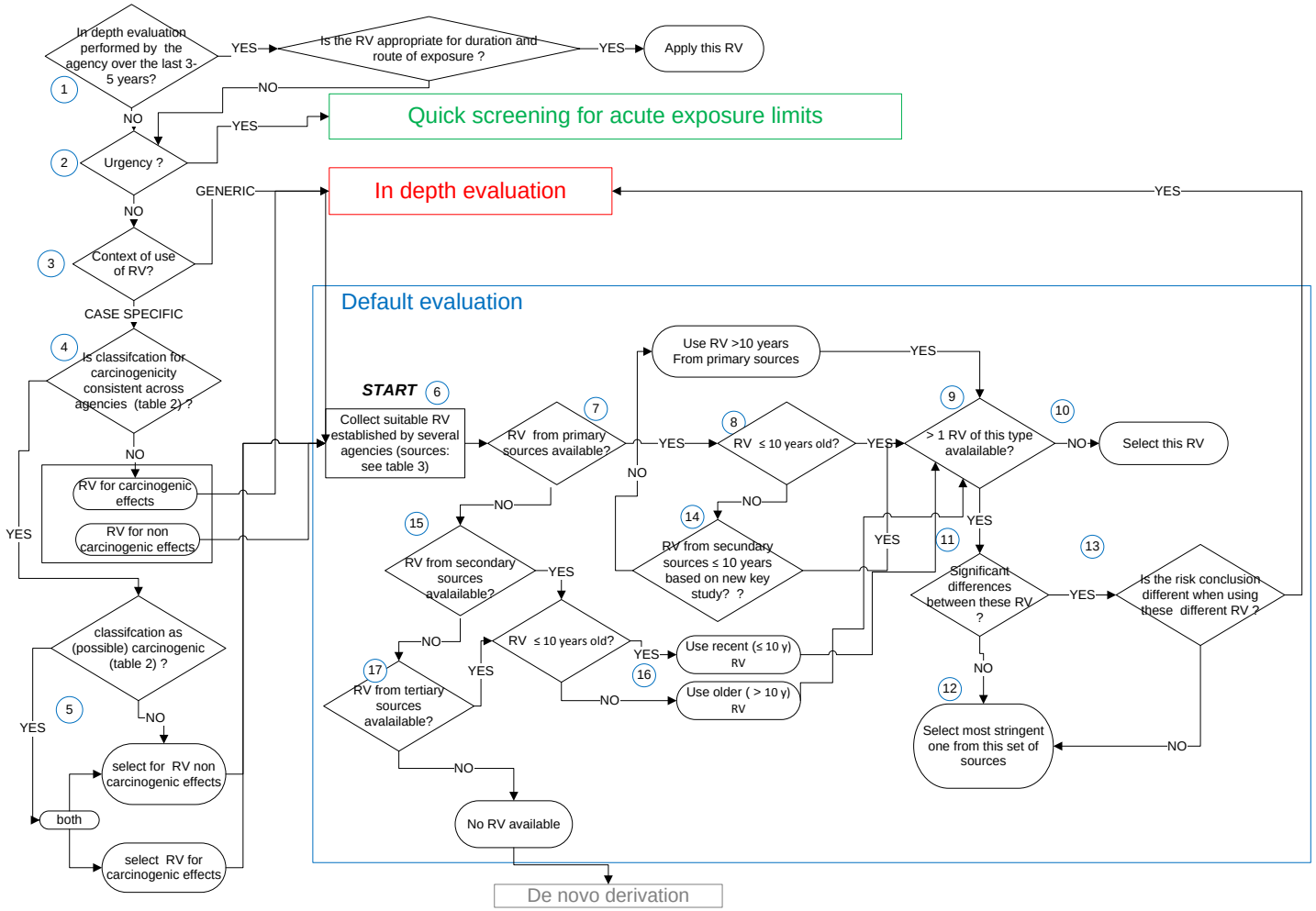
For carcinogenic substances, with a mode of action following a non-threshold mechanism (carcinogenic, genotoxic substances), no safe levels below which exposure does not pose a health risk can be established. For carcinogenic substances with a non-threshold mechanism, the RV for carcinogenicity is very 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 the daily activities of the Flemish Agency for Health



Considerations of urgency situation, context of use and carcinogenicity are explained above (see 2.1, 2.2, 2.3) 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 the Agency is asked for advice on immediate health risks of exposed individuals, a quick screening of acute exposure limits 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 in a quick screening exercise for acute exposure guidelines , or in the frame of a generic context (setting guidelines or legal context), the ‘default evaluation’ is the default starting point for selecting RV.
(6)

The default evaluation starts with the collection of suitable RVs established by several agencies listed in Table 3. 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.

The compilation of the agencies for consultation (Table 3) is based on the lists of agencies consulted by ANSES, INERIS 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.

Table 3: Agencies and data sources for health-based Reference values (RV) (1° - primary sources, 2° - secondary sources: see text; tertiary sources: see Table 5)

Agency	Route of exposure[$]	RV name	website	Type of information/ how to find RV
			PRIMARY SOURCES	
1° - WHO / Air Quality Guidelines	I	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	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-pollutantshttp://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 / Drinking Water Quality Guidelines	O	GV (guideline value)	http://www.who.int/water_sanitation_health/dwq/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	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° - EFSA	O	TDI (Tolerable daily intake), TWI (Tolerable	http://www.efsa.europa.eu/ http://www.efsa.europa.eu/ for RV:	Search on the EFSA website for Scientific Opinions for substance of interest. Search within the Scientific Opinion for

Agency	Route of exposure[$]	RV name	website	Type of information/ how to find RV
		weekly intake) , PTMI (provisional tolerable monthly intake)	http://www.efsa.europa.eu/en/topics/topic/contaminantsfoodfeed	RV such as TDI (tolerable daily intake) TWI (tolerable weekly intake) , PTMI (provisional tolerable monthly intake)
1° - US-EPA / IRIS databank	I,O	RfC, RfD, inhalation unit risk	www.epa.gov/iris	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
1° - ATSDR / MRL	I,O	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
			SECONDARY SOURCES	
2° - US-EPA / PPRTV	I,O	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
2 - Cal-EPA OEHHA*	I,O	REL (Reference Exposure Limit)	http://www.oehha.ca.gov/risk/ChemicalDB/index.asp http://oehha.ca.gov/air/allrels.html	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
2 ° - Anses / VTR (in French	I,O	VTR (Valeurs Toxicologiques	https://www.anses.fr/fr/content/valeurs-toxicologiques-de-référence-vtr	Downloadable table with VTR values and downloadable versions of supporting

Agency	Route of exposure[$]	RV name	website	Type of information/ how to find RV
mostly, English sometimes)		de Référence	https://www.anses.fr/fr/content/liste-des-valeurs-toxicologiques-de-r%C3%A9f%C3%A9rence-vtr-construites-par-l%E2%80%99anses https://www.anses.fr/en/content/trvs-toxicity-reference-values https://www.anses.fr/en/content/list-toxicity-reference-values-trvs-established-anses	material (report in French, opinion in english and in french)
2° - Health Canada	I,O		http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/index-eng.php	No online databases RV to obtain by search queries on substance names on Health Canada website Downloadable versions of documents with RV and supporting material

- [$] I: inhalation; O: oral
- * PROVISIONAL Peer Reviewed Toxicity Values; considered by US-EPA as indicative values to be used if no US EPA or ATSDR values are available

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/
Furetox	Metadatabase with French and international toxicological reference values	http://www.furetox.fr/
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.tera.org/iter/
PATCHWORK	Portaal site containing 29, free online databases with toxicological	http://www.ru.nl/ubn/zoeken/vakgebieden-

Public Access to Toxicity data of Chemical hazards to Humans	data of more 715.000 products and 350.000 substances, relevant for public health expert in the domain of occupational and environmental exposure	0/medische/onderverdeling/internetbronnen_op/onderverdeling/farmacologie/indeling/patchwork/

*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.

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).

It is noted that DNEL values developed by industry under REACH are not considered as primary or secondary sources. The main reason is that the derivation of DNELs is up till now not transparent and insufficiently detailed publically available. Therefore, DNELs are not considered as reference values for use in practices of the Flemish Agency for Health and Care.

After collection of available RVs, a flowchart reflecting priority criteria for selecting RV is followed (from 6 to 13).
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[1].

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.

[1] 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’

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 established by only one or several sources.

10

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.

11

In the situation where several agencies from that level (e.g. primary or secondary) 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.

12

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 value from WHO or EFSA (if available); and otherwise select the most conservative value. WHO and EFSA values are preferred since their supranational nature and policy relevance within the European context.

13

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).

14

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 9 to 13)

15

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: from

16

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 9 to 13

17

In the situation where none of the sources from Table 3 has issued a suitable RV for the substance of interest, it is advised to consult tertiary sources.

Examples of tertiary sources are listed in Table 5. 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).

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

source	Website	Description
RIVM (MTR and VR values)	http://www.rivm.nl/rvs/Normenhttp://www.rivm.nl/rvs/Normen http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf http://www.rivm.nl/bibliotheek/rapporten/711701092.pdf	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 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 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
Etc.		

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 should 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.

2.5. 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 CHAPTER 3). 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.

2.6. 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, mg/kg body weight.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

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

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 REPORTING FORMAT FOR THE SELECTION OF 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:

'quick screening' was applied because of urgency of the situation

'default evaluation' was applied because…..

'in-depth evaluation' was applied because….

3.4. CLASSIFICATION OF CARCINOGENICITY

Agency	Date	Carcinogenicity classification	Source/hyperlink
IARC			
US EPA			
EU-GHS			
NTP			

Conclusion: RV to select for
- Carcinogenic effects
- Non carcinogenic effects

(/scratch 'RV to select for carcinogenic effects if no classification for carcinogenicity)

3.5. SELECTION OF RV

Based on the outcome of the tiered level, and the carcinogenicity classification, tables reporting 'quick screening', '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 'QUICK SCREENING'

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 EVALUATION'

Non-carcinogenic effects									Source/Hyperlink
agency	Date RV	Name and date of key study[6]	Speciation[5]	Route and duration	RV name[1]	Critical endpoint	RV value	RV units	
Primary sources									

WHO	
US EPA IRIS	
EFSA[3]	
ATSDR	
Secondary sources	
OEHHA	
ANSES	
Health Canada	
US EPA PPRTV	
Tertiary sources[4]	
RIVM	

				carcinogenic effects (to be completed if substances is classified as carcinogenic)				
agency	date	speciation	Route	RV name[1]	Type of effects/tumour site	RV value[2]	RV units	Source/Hyperlink
Primary sources								
WHO								
US EPA IRIS								
EFSA[3]								
Secondary sources								
ANSES								
Health Canada								
US EPA PPRTV								

OEHHA	
Tertiary sources[4]	

[1]name of the reference value in the original sources. (for example: RfC (reference concentration))
[2]unit risk value (slope factor) or pseudo-threshold value
[3] if oral route is the relevant route of exposure
[4] tertiary sources to consult where no suitable reference values from primary or secondary sources are available
[5]mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[6] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available

Conclusion 'default evaluation' RV selection:

Either:

- **RV: X (units), Agency, Date**
- Critical effect on which is the RV is based:

Or

The outcome of TIER 2 analysis in non-conclusive, a TIER 3 analysis is needed

Overall conclusion integrating carcinogenicity and non-carcinogenicity:

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)[2]:			
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			
…			

[2] 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

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.

CHAPTER 4 APPLICATION OF THE PROTOCOL AND REPORTING FORMAT: EXAMPLE

4.1. CASE 1: 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	

Agency	route	Duration	RV name	RV value	RV units	Source/hyperlink
		1 hour	Carcinogenic risk potency[3]	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

For carcinogenic effects:

agency	RV name	value	units	hyperlink
RIVM (2016)	CPR[4]	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	$6.8\ 10^{-5}$	per µg/m³	http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0206#carc

[3] 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.
[4] [4] 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.

agency	RV name	value	units	hyperlink
	Unit Risk			

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. CASE 2: ACRYLONITRILE IN WELL WATER USED AS DRINKING WATER

4.2.1. EXPOSURE SITUATION

Acrylonitrile levels in well water : 0.004 mg/mL (one well was positive; just above detection limits).

This question is less urgent. Question: what is the health risk of consumption of well water contaminated with acrylonitrile?

4.2.2. 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	Oral; acute and chronic
Context of use RV	Evaluation of safety of use as drinking water

4.2.3. TIERED LEVEL OF RISK VALUE SELECTION

'default evaluation' was applied as default approach in a case specific evaluation

4.2.4. 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

Conclusion: RV to select for

- Carcinogenic effects
- Non carcinogenic effects

classification for carcinogenicity is not consistent (IARC lists as possibly carcinogenic) →
in principle: go to an in-depth analysis for carcinogenicity

4.2.5. SELECTION OF RV

→ **Non-carcinogenic effects**

agency	Date RV	Name and date of key study[6]	Speciation[5]	Route and duration	RV name[1]	Critical endpoint	RV value	RV units	Source/Hyperlink
Primary sources									
WHO	No value (not included in 4th edition DW)								http://www.who.int/water_sanitation_health/publications/dwq_guidelines/en/
US EPA IRIS	RfD not assessed under IRIS programme								http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=206
EFSA[3]	No value								
ATSDR	**1990**	**TBD**		**Oral, chronic**	**MRL**	**Nervous system**	**0.04**	**mg/kg bw/day**	**http://www.atsdr.cdc.gov/mrls/mrllist.asp#78tag**
ATSDR	**1990**	**TBD**		**Oral, intermediate**	**MRL**	**Nervous system**	**0.01**	**mg/kg bw/day**	**http://www.atsdr.cdc.gov/mrls/mrllist.asp#78tag**
ATSDR	**1990**	**TBD**		**Oral, acute**	**MRL**	**Nervous system**	**0.1**	**mg/kg bw/day**	**http://www.atsdr.cdc.gov/mrls/mrllist.asp#78tag**
Secondary sources									
OEHHA	2001	No value for oral route							
ANSES	Substance not present on ANSES list VTR								
Health Canada	1998	No value for oral route							http://toxnet.nlm.nih.gov/cgi-bin/sis/search2
US EPA	Substance not present on the PPRTV list								

agency	**Date RV**	**Name and date of key study[6]**	**Speciation[5]**	**Route and duration**	**RV name[1]**	**Critical endpoint**	**RV value**	**RV units**	**Source/Hyperlink**
PPRTV									
Tertiary sources[4]									
ITER PR	2003	Gagniaire et al., 1998		Oral, chronic	RfD	Nervous system	0.05	mg/kg/day	http://toxnet.nlm.nih.gov/cgi-bin/sis/search2 (via ITER tox net search op 'acrylonitrile)

The Sapphire Group (under the ITER PR column), on behalf of The Acrylonitrile (AN) Group (an industry trade group), derived a chronic oral reference dose (RfD) of 0.05 mg/kg-day based on neurological effects observed in rats in a 12 week gavage study (Gagnaire et al., 1998). Notwithstanding it's a tertiary source value, and does not get priority over the primary source RV (ATSDR, 1990: 0.04 mg/kg/day), it is worth to mention that the value from the Sapphire Group which based on newer scientific data (rat study published by Gagniaire et al.,1998) is very similar to the (older) value from ATSDR (primary source).

Conclusion RV selection according to 'default evaluation' for non-carcinogenic effects:

Chronic: 0.04 mg/kg/bw day (ATSDR, 1990); effects: nervous system
Intermediate: 0.01 mg/kg/bw day (ATSDR, 1990): effects: nervous system
Acute: 0.1 mg/kg/bw day (ATSDR, 1990): effects: nervous system

→ ***carcinogenic effects***

in principle, an in-depth evaluation of RV for carcinogenicity is needed because of inconsistent classification for carcinogenicity.
However, within the timeframe of the project, an in-depth assessment was not possible.

Therefore, the selection is done based on a default evaluation. In a later stage (outside of this project), it is advised to perform an in depth evaluation.

Default evaluation:

agency	date	Name and date of key study	speciation	Route	Type of tumour/effects	RV name[1]	RV value	RV units	Source/Hyperlink
Primary sources									
WHO			No value (not included in 4th edition DW)						http://www.who.int/water_sanitation_health/publications/dwq_guidelines/en/
US EPA IRIS	**1987**	**TBD**		**Oral**	**Tumour site: nervous, gastro-intestinal**	**Slope factor** **Drinking water unit risk**	**5.4[$]** **1.5 10^{-5}**	**Per mg/kg bw/day** **Per µg/L**	**http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=185659** **http://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=496213**
EFSA[3]			No value						Not found by performing search on EFSA website
Secondary sources									
ANSES			Substance not present in ANSES list VTR						
Health Canada	1998	TBD		oral	Central nervous system	TD05 (LCL) (= tumorigenic dose at 5 %	1.4	mg/kg bw/day	Via search on toxnet http://toxnet.nlm.nih.gov/cgi-bin/sis/search2 and http://www.hc-sc.gc.ca/ewh-

agency	date	Name and date of key study	speciation	Route	Type of tumour/effects	RV name[1]	RV value	RV units	Source/Hyperlink
						level)			semt/pubs/contaminants/psl2-lsp2/acrylonitrile/index-eng.php#a33322
US EPA PPRTV		No value (substance not present on PPRTV list)							
OEHHA	2011	TBD (see text below)			Not mentioned in summary	Slope factor	1.0	mg/kg bw/day	http://oehha.ca.gov/air/hot_spots/pdf/CPFs042909.pdf
Tertiary sources[4]									

[1]name of the reference value in the original sources. (for example: RfC (reference concentration))
[2]unit risk value (slope factor) or pseudo-threshold value
[3] if oral route is the relevant route of exposure
[4] tertiary sources to consult where no suitable reference values from primary or secondary sources are available
[5]mention speciation if for various species, different RV are applicable (e.g. Cr3+ versus Cr6+)
[6] date and name of key study to complete in case of absence of recent (< 10 years old) RV, while recent secondary sources are available
TBD: to be determined in case if needed in flowchart

The RV from primary source (US EPA IRIS, 1987) is 5.4 per mg/kg bw/day. A more recent secondary source slope factor (OEHHA, 2011), i.e. slope factor 1.0 mg/kg bw/day , which is significantly different from the older US EPA slope factor is available.
Therefore, the date of the key study of each of these slope factors is essential in order to select the most appropriate value from the schema:

In the appendix B of OEHHA (page B-17),(http://oehha.ca.gov/air/hot_spots/2009/AppendixB.pdf)
the summary (II: health assessment values) mentions the human respiratory tract cancer incidence data from O'Berg (1980) as pivotal study, and the US EPA Relative risk model (1983), re-evaluated by CDHS/RCHAS (1988) as data and methods on which the OEHHA cancer slope factor is based.

The pivotal study from the primary source RV (US EPA IRIS) also dates from 1980 (Biodynamics, 1980a,b Quast et al., 1980a).

Therefore, the pivotal study of the OEHHA (2011) value is not more recent than the pivotal study of the US EPA IRIS RV (1987). Thus, the recentness of OEHHA (2011) is not a valid argumentation to prefer the OEHHA (2011) value over the US EPA IRIS RV (1987).
According to the default selection schema, the US EPA risk value of 5.4 per mg/kg bw/day is selected. The corresponding drinking water unit risk (1.5 10-5 per µg/l) is also taken forward.

RV selection according to 'default evaluation' for non-carcinogenic effects:

- **RV: slope factor 5.4 per mg/kg bw/day X (US EPA; 1987) and drinking water unit risk (1.5 10-5 per µg/l) (US EPA, 1987)**
- Critical effect on which is the RV is based: **Tumour site: nervous system, gastro-intestinal system**

→ ***Overall conclusion integrating carcinogenicity and non-carcinogenicity:***

Non -carcinogenic effects:
Chronic: 0.04 mg/kg/bw day (ATSDR, 1990)
Intermediate: 0.01 mg/kg/bw day (ATSDR, 1990)
Acute: 0.1 mg/kg/bw day (ATSDR, 1990)

Carcinogenicity : RV: slope factor 5.4 per mg/kg bw/day X (US EPA; 1987) and drinking water unit risk (1.5 10-5 per µg/l) (US EPA, 1987)

Most critical effect (CA vs non CA effects):

For cancer risk levels corresponding to $10^{-4}/10^{-5}/10^{-6}$, the drinking water concentrations are 6 µg/l, 0.6 µg/l and 0.06 µg/l.
Converting the non CA exposure RV for non-carc. To water equivalents (by assuming a body weight of 70 kg and drinking water intake of 2 L/day):

- Chronic: 0.04 mg/kg/bw/Day → 2 L/day and 70 kg bw → 1.4 mg/l drinking water
- Intermediate: 0.01 mg/kg/bw/Day → 2 L/day and 70 kg bw → 0.35 mg/l drinking water
- Acute 0.1 mg/kg/bw/Day → 2 L/day and 70 kg bw → 3.5 mg/l drinking water
-

- Comparing: CA vs non CA effects: CA effects are most critical ones

4.2.6. EVALUATION OF THE EXPOSURE CONCLUSION TIER 2 RV SELECTION:

Conclusion: use of well water containing 4mg/l acrylonitrile as drinking water is unsafe from health perspective:

- ➔ Exceeds strongly the risk on carcinogenicity (expected cancer risk lifelong water consumption: 6.7 per 10-3) and
- ➔ exceeds strongly the risk thresholds for non-cancer effects, both at chronic, intermediate and acute (1-14 days) of drinking water consumption at a rate of 2l /day.
- ➔

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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[5] approach. If possible, the BMDL[6] 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[7] is used, a higher MOE should be used.

In the case of non-threshold carcinogens, ECHA (2012) prescribes to derive a DMEL value. In the case of animal data, two approaches can be followed: the linearized approach and the Large Assessment Factor. Allometric scaling[8] 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.

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Ref Type: Report

EFSA. 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. The EFSA Journal 2005; 282: 1-31.

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

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

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

[8] 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) .