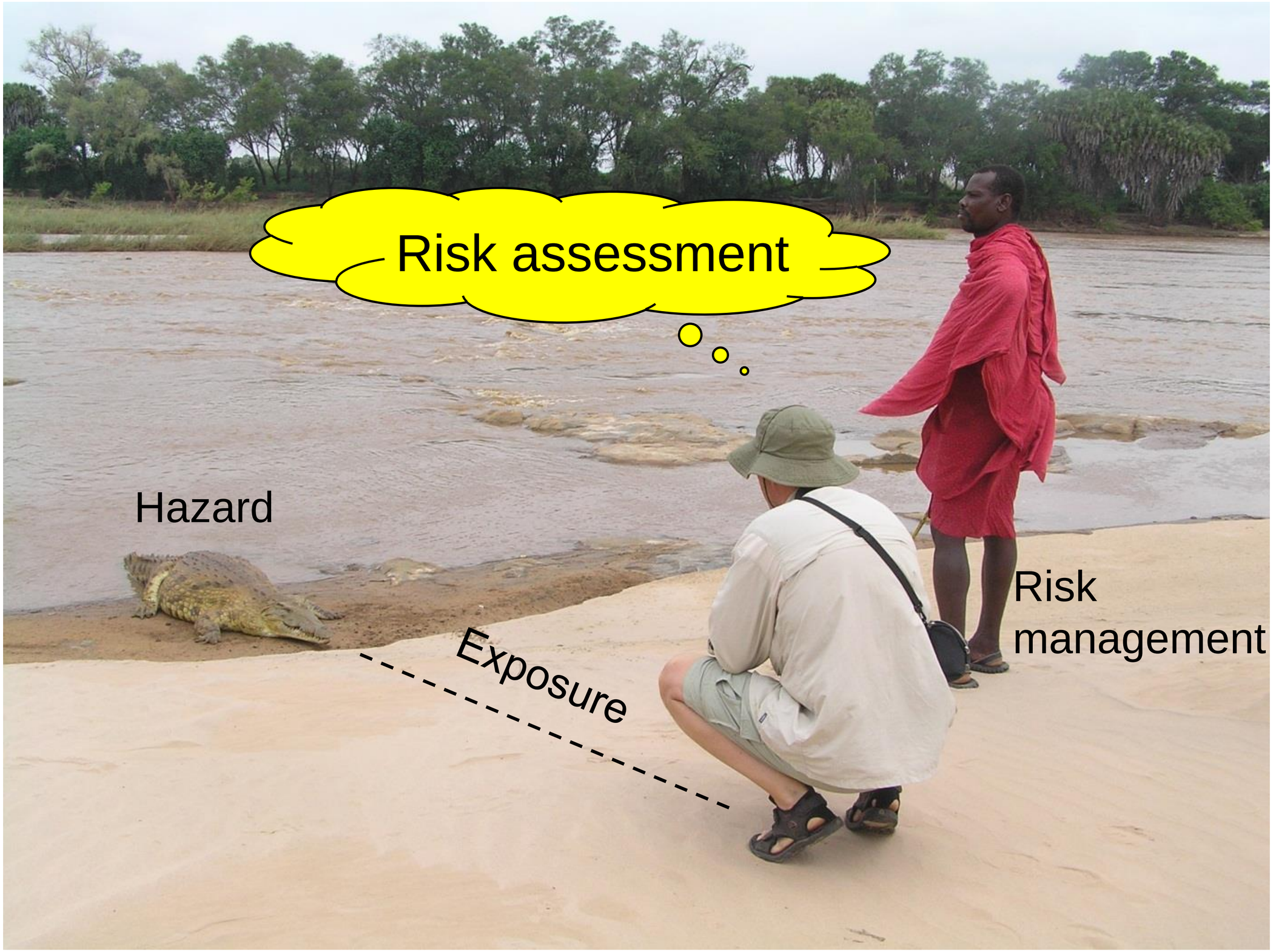
Risk Assessment

Lennart Dock, Ph.D.
Swedish Chemicals Agency

17-18 October 2017

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency


Risk assessment
Hazard
Exposure
Risk
management

- Hazard: Ability to cause damage or harm

(Intrinsic hazardous properties)

- Risk: Probability for damage or harm to occur

Risk = Hazard x Exposure

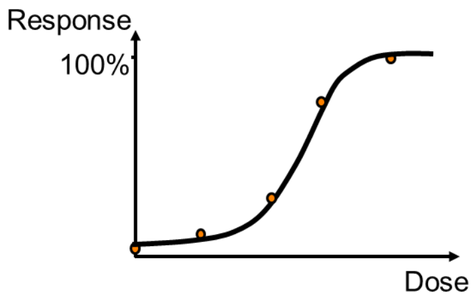
Why risk assessment?

- A tool for decision-making

Framing the issue

- What is the chemical(s) of concern?
- Why is it of concern (intrinsic hazardous properties)?
- Who/What/Where is at risk?
  - Individual persons
  - General population
  - Population subgroups
    - Children
    - Elderly
    - Pregnant/nursing women (the unborn child and infants)
    - Highly susceptible persons (e.g. asthmatics)
    - Highly exposed (based on e.g. geographic area, gender, racial or ethnic group, or economic status)

Risk assessment



Hazard identification

- *Is the identity of the chemical known?*
- *Is the chemical potentially hazardous to humans?*

Classification and Labelling

Hazard characterization and guidance/guideline value identification

- *What properties of the chemical have the potential to cause adverse health effects?*
- *Do guidance or guideline values from international organizations exist for the chemical?*
- *What assumptions about exposure and dose are incorporated into guidance/guideline values for the chemical?*
- *Do those assumptions reflect conditions specific to the local population?*

Exposure assessment

- *In what ways could people come into contact with the chemical?*
- *How much exposure is likely to occur?*
- *For how long is exposure likely to occur?*
- *What metric of exposure is appropriate for characterizing health risks?*

Risk characterization

- *How does the estimated exposure compare with guidance/guideline values for the chemical?*

Adapted from: WHO Human Health Risk Assessment Toolkit

Questions	Outputs
Hazard identification	
Is the identity of the chemical known?	➔Clear identification of chemical in question e.g. through CAS no.
Is the chemical potentially hazardous to humans?	➔Description of health hazards obtained from internationally available information
Hazard characterization	
What properties of the chemical have the potential to cause adverse health effects?	➔Qualitative and quantitative description of the inherent properties of the agent having the potential to cause adverse health effects
Do guidance values from international organizations exist for the chemical?	➔List of guidance values for the chemical obtained from internationally available resources
What assumptions about exposure and dose are incorporated into guidance values for the chemical?	➔List of assumptions about contact rates, absorption and other factors incorporated into the guidance values
Do those assumptions reflect conditions specific to the local population?	➔A reference value that refelects exposure and dose parameters specific to the local culture and demographics
Exposure assessment	
In what ways could people come into contact with the chemical?	➔Qualitative description of the relevant media and exposure routes
What metric of exposure is appropriate for characterizing health risks?	➔Determination from the guidance value of whether an exposure concentration or exposure rate is needed to perform the risk characterization
Risk characterization	
How does the estimated exposure compare with guidance values for the chemical?	➔A quantitative or qualitative statement of non-cancer or cancer risk

Adapted from: WHO Human Health Risk Assessment Toolkit

A tiered approach to risk assessment

Increased resource demand

Tier	Description	Hazard identification	Hazard characterization	Exposure assessment
1	Existing hazard and exposure data from international sources	Identify the chemical; obtain hazard information from international resources	Apply appropriate existing guidance values from international organizations	Existing qualitative or quantitative estimates; local exposure conditions
2	Existing hazard data from international sources reflecting local conditions; existing local exposure data		Adjust guidance values from international organizations for local conditions	Existing quantitative estimates; local exposure conditions
3	Existing hazard data from international sources; new local exposure data			Conduct measurement or modelling campaign
4	Locally conducted hazard and exposure assessments	Independent review of original hazard data or controlled experimental trials, gather local observations	Establish new guidance value	Estimate from measurements or models

Adapted from: WHO Human Health Risk Assessment Toolkit

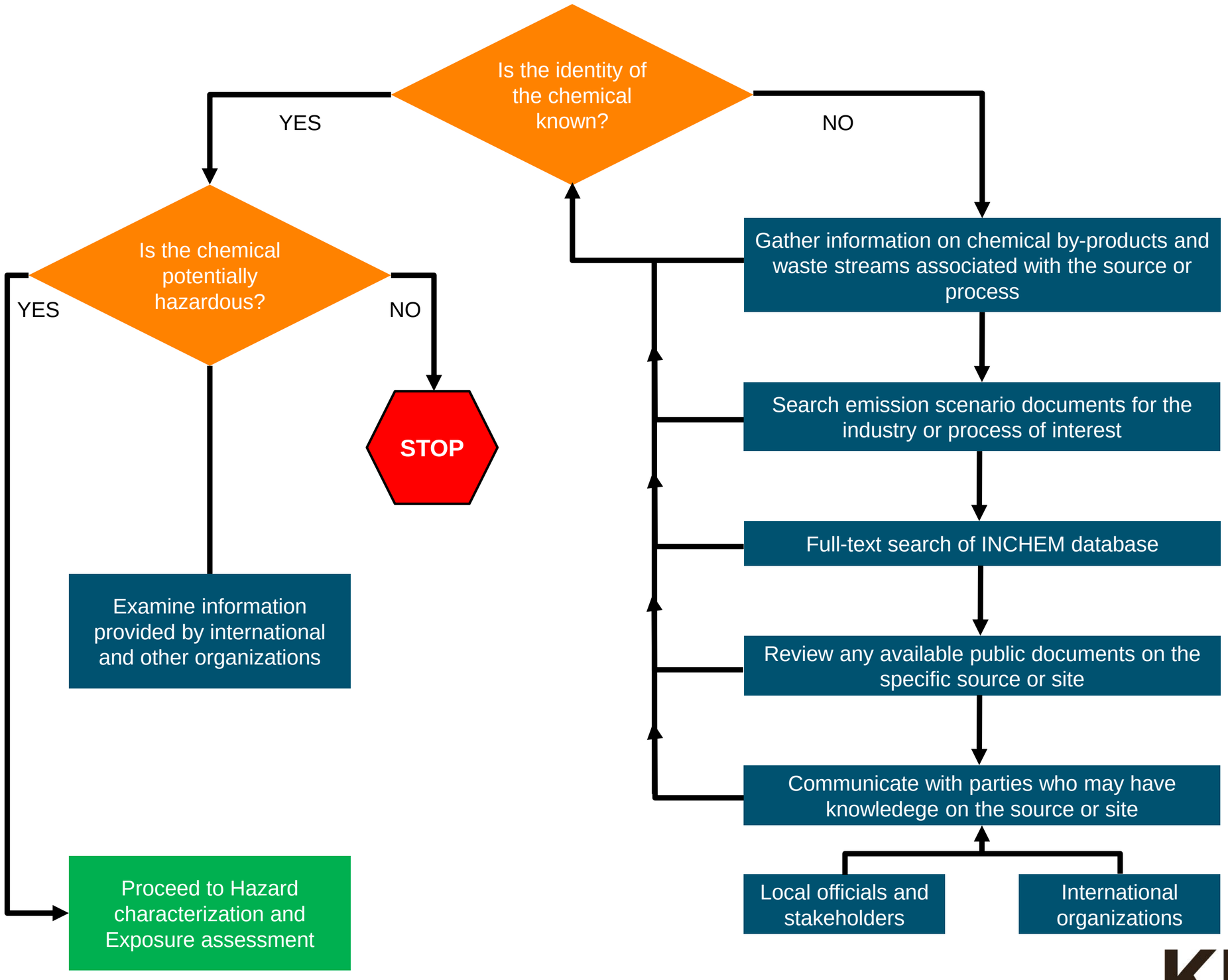
A bridging approach between existing data and the local situation

Risk in existing assessment considered acceptable	Local exposure level compared to exposure level in existing assessment		
	Higher	**Similar**	**Lower**
Yes	Carry out a local assessment	Risk for the situation under review acceptable	Risk for the situation under review acceptable
No	Risk for the situation under review not acceptable	Risk for the situation under review not acceptable	Carry out a local assessment

Hazard Identification

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

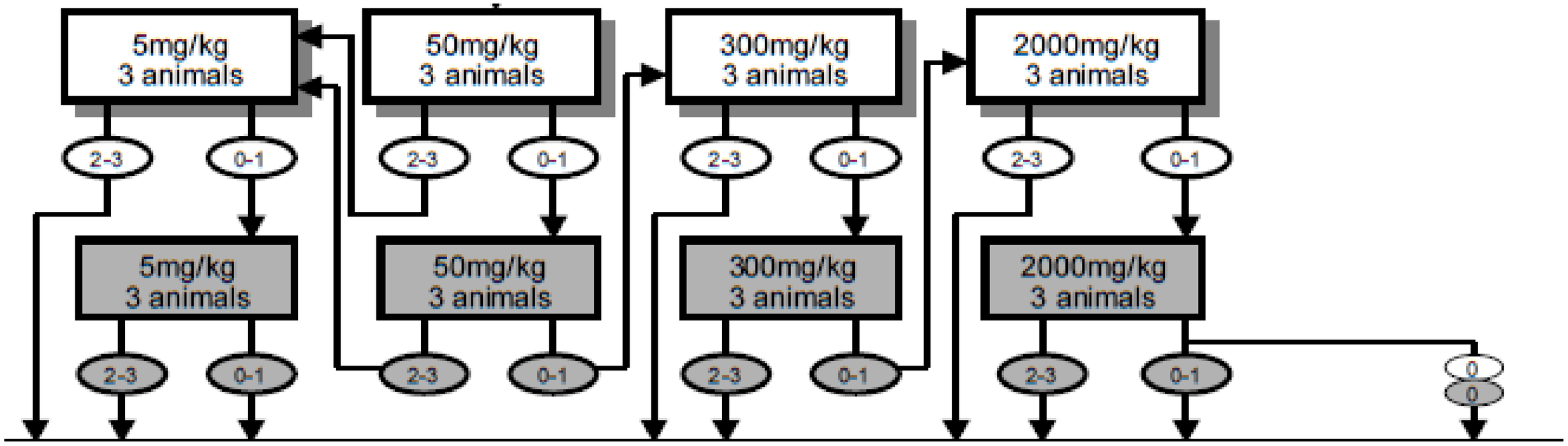
Hazard identification road map



Modified from WHO Human Health Risk Assessment Toolkit

Acute Toxic Class Method (OECD TG 423)

Recommended starting dose



GHS Cat.1 >0-5	GHS Cat.2 >5-50	GHS Cat.3 >50-300	GHS Cat.4 >300-2000	GHS Cat.5 >2000-5000	Category 5 or Unclassified

Klimisch scoring system

Category	Details
1: Reliable without restriction	Studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method
2: Reliable with restriction	Studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.
3: Not reliable	Studies or data from the literature/reports in which there are interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert judgment.
4: Not assignable	Studies or data from the literature, which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.).

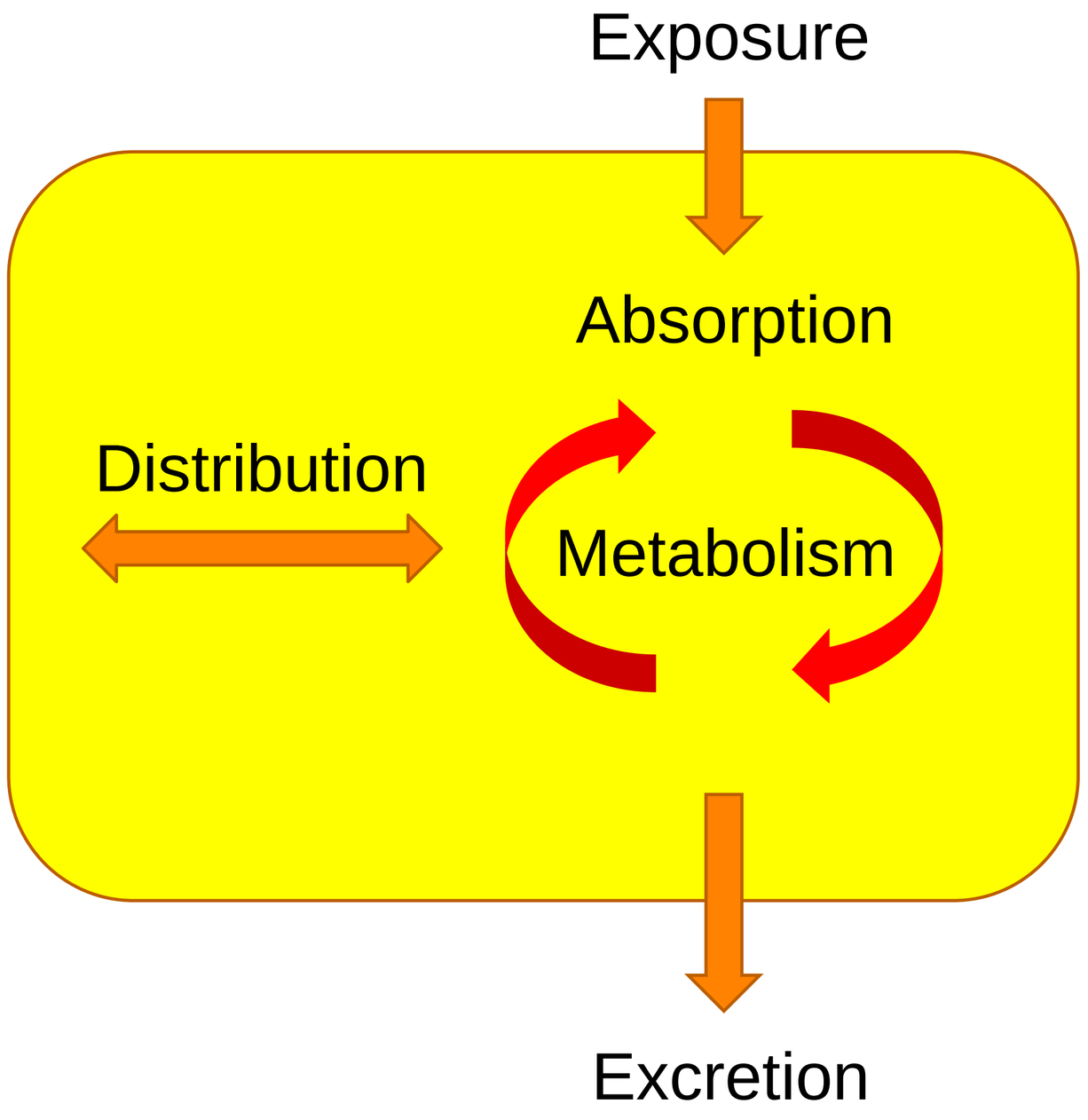
H.J. Klimisch, M. Andreae and U. Tillmann (1997): A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data, Regulatory Toxicology and Pharmacology Vol 25, pp 1–5

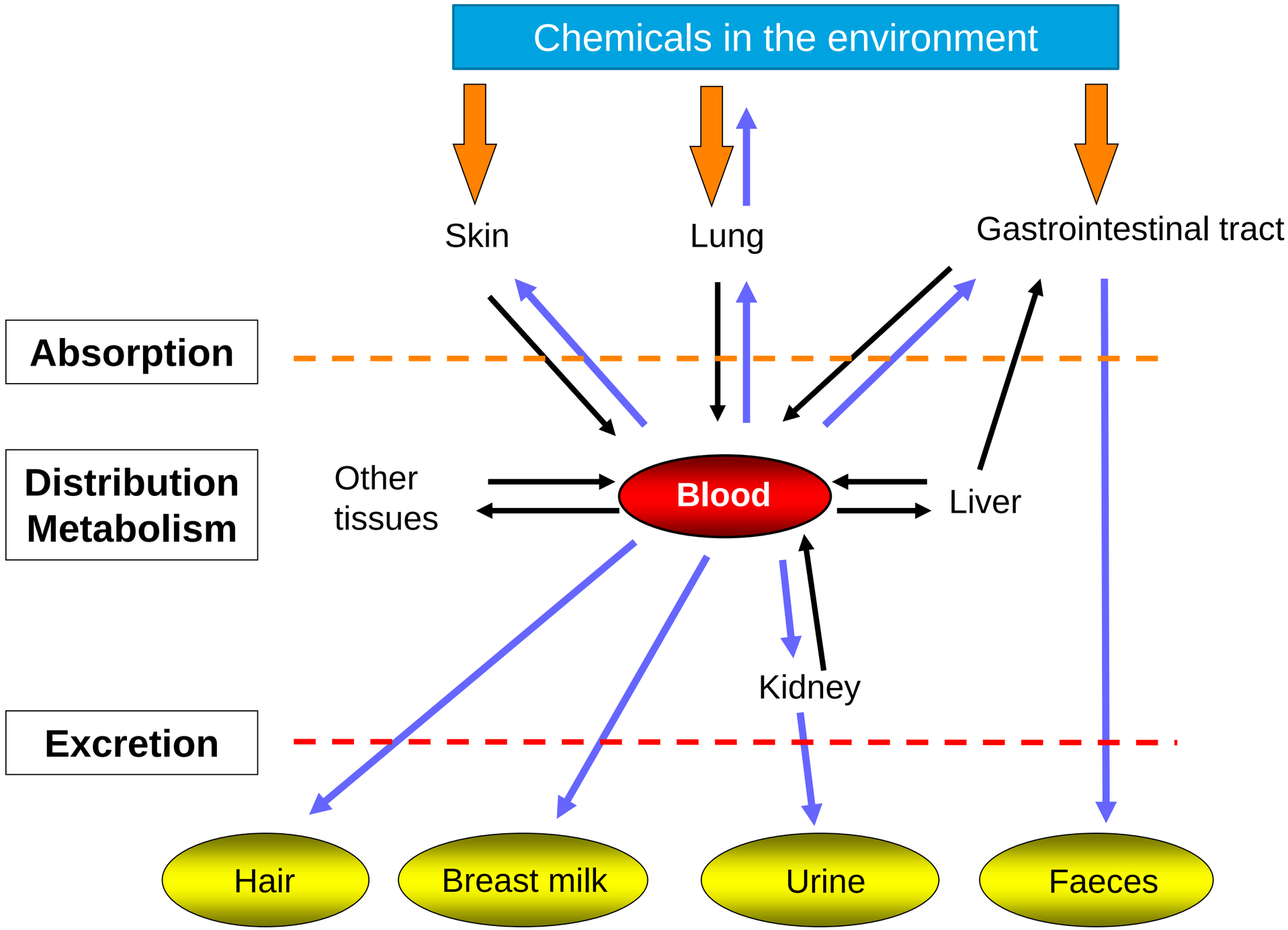
https://eurl-ecvam.jrc.ec.europa.eu/about-ecvam/archive-publications/toxrtool/toxrtool-toxicological-data-reliability-assessment-tool

Toxicokinetics

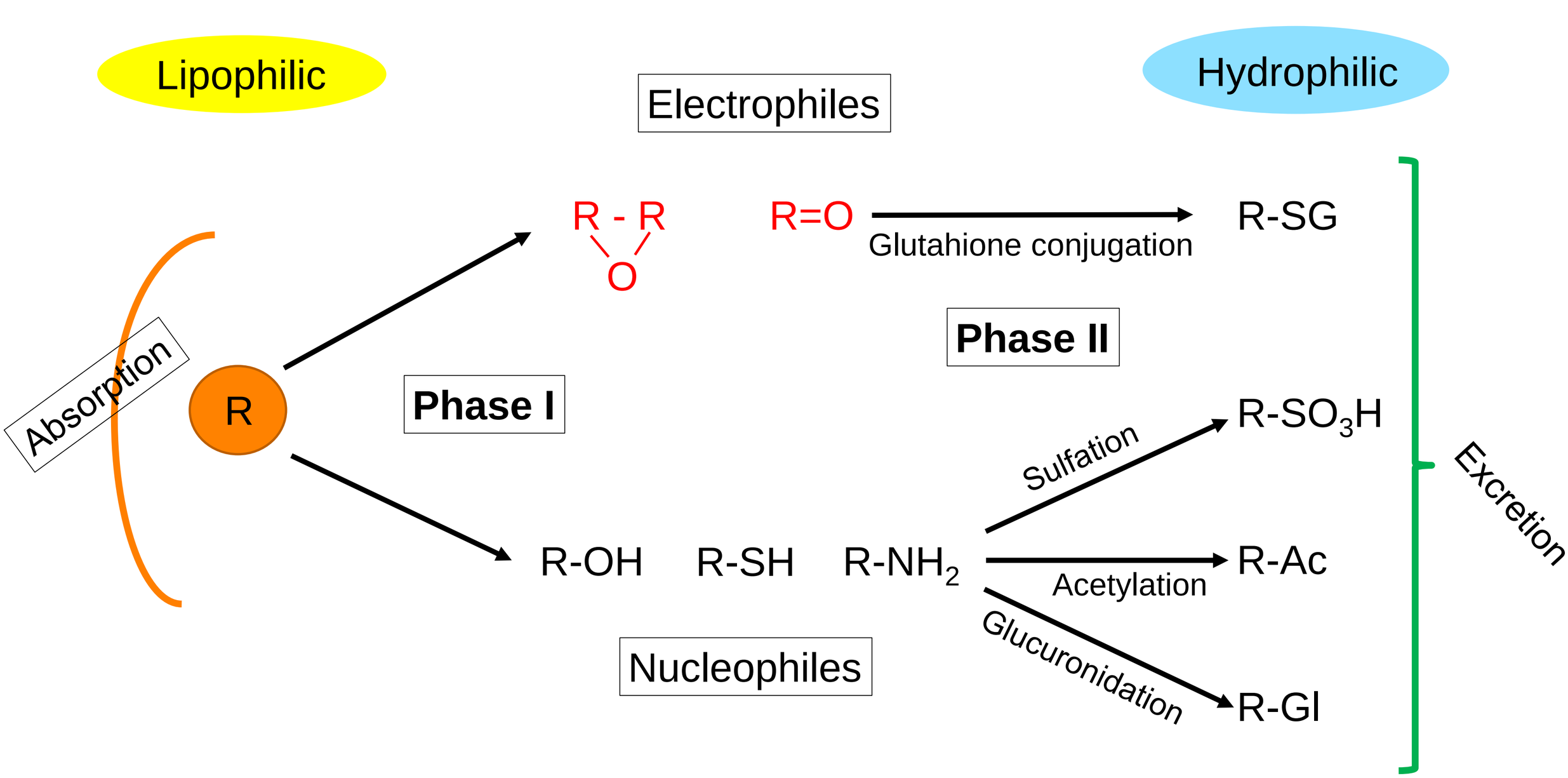
Physicochemical properties of chemical, e.g.:

- Molecular weight
- Water solubility
- Log Pow (n-Octanol/Water partition coefficient)


Exposure
Absorption
Distribution
Metabolism
Excretion


Chemicals in the environment
Skin
Lung
Gastrointestinal tract
Absorption
Distribution
Metabolism
Other
tissues
Blood
Liver
Kidney
Excretion
Hair
Breast milk
Urine
Faeces

Biotransformation



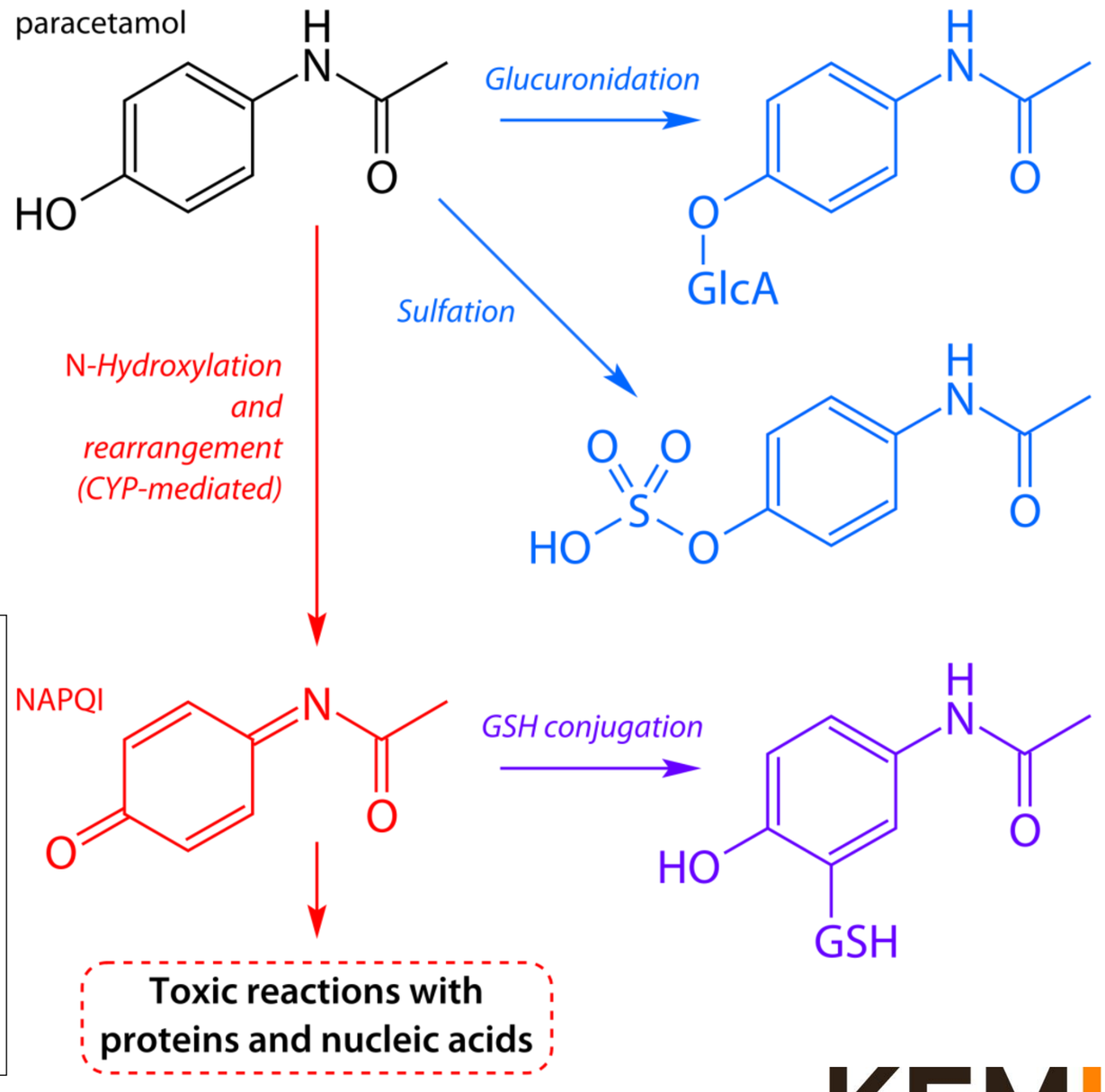
KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Biotransformation of paracetamol

Lethal dose 10-15 g - or even less
Within hours: nausea, vomiting, pallor, sweating

Between 24 and 72 hours: signs of increasing liver damage, possibly kidney failure

At 3 to 5 days: massive hepatic necrosis, kidney failure, multiple organ failure, and death.



KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

The ECHA Classification and Labelling Inventory

A data base of all C&L information submitted to ECHA

- Harmonized (legally binding) classifications (=CLP Annex VI)
- Notified classifications (“self-classification”)
- Over 120,000 substances
- Over 5.7 million notifications

Available at www.echa.eu

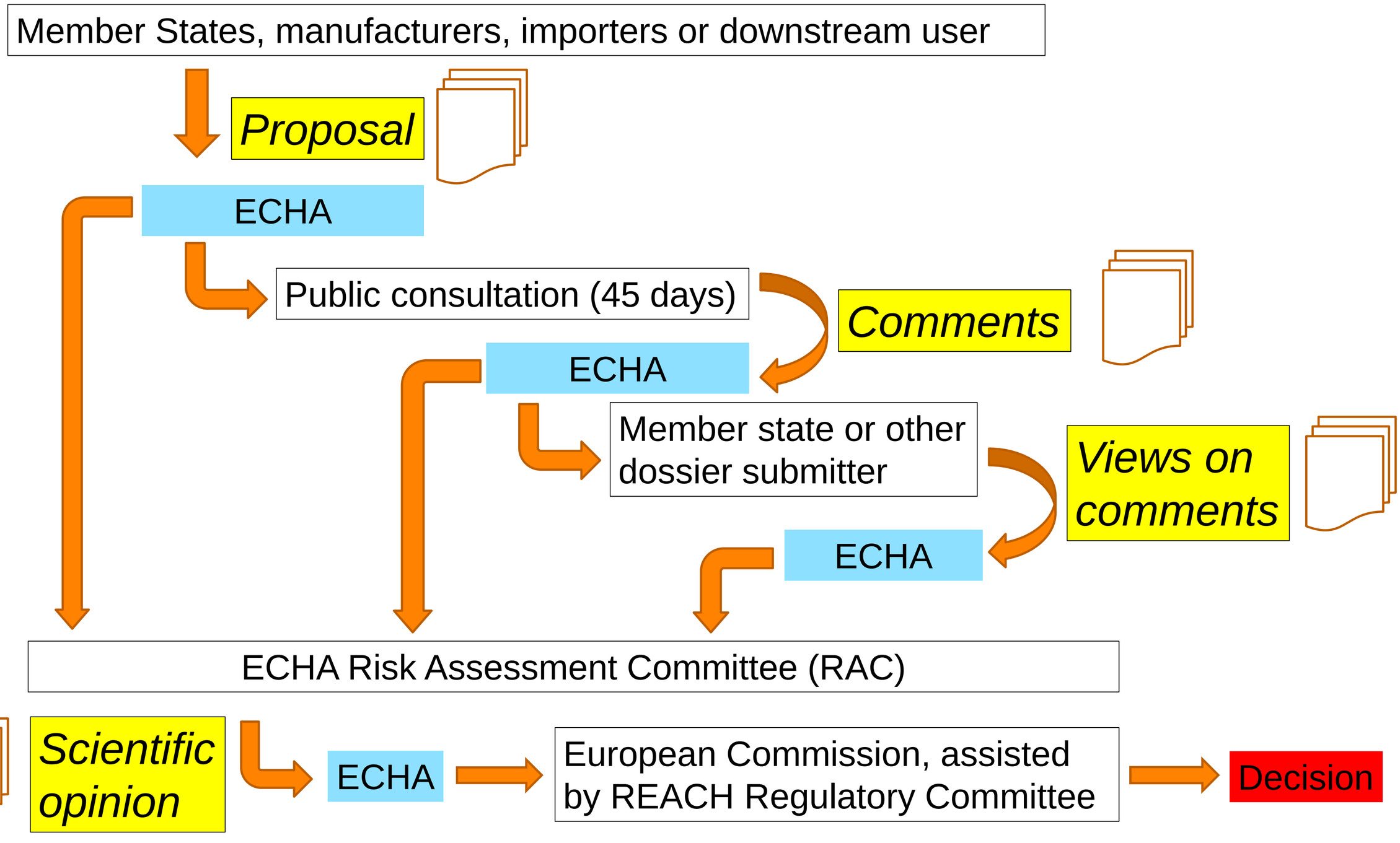
EU-harmonised and legally binding classification and labelling

- Shall normally be done for all effects/hazard classes of active substances in:
  - –plant protection products
  - –biocidal products.

- Shall for other substances normally be done for substances that may be
  - –Carcinogenic, Mutagenic or Toxic for Reproduction (CMR);
  - –Respiratory sensitisers

  ➢Other effects may be considered on a case-by-case basis

Harmonized classification and labelling



CLP annex VI (example)

Table 3.1 (GHS-format)

Index No	Intern. Chemical Identific.	EG No	Cas No	Classification Hazard Class and Category code(s)	Haz. Statem. Code(s)	Labelling Hazard pictogram, Signal word code(s)	Hazard Statement code(s)
603-004-00-6	n-butanol	200-751-6	71-36-3	Flam. Liq. 3 Acute Tox. 4 (*) STOT SE 3 Skin Irrit. 2 Eye Dam. 1 STOT SE 3	H226 H302 H335 H315 H318 H336	GHS02 GHS05 GHS07 Dgr	H226 H302 H335 H315 H318 H336

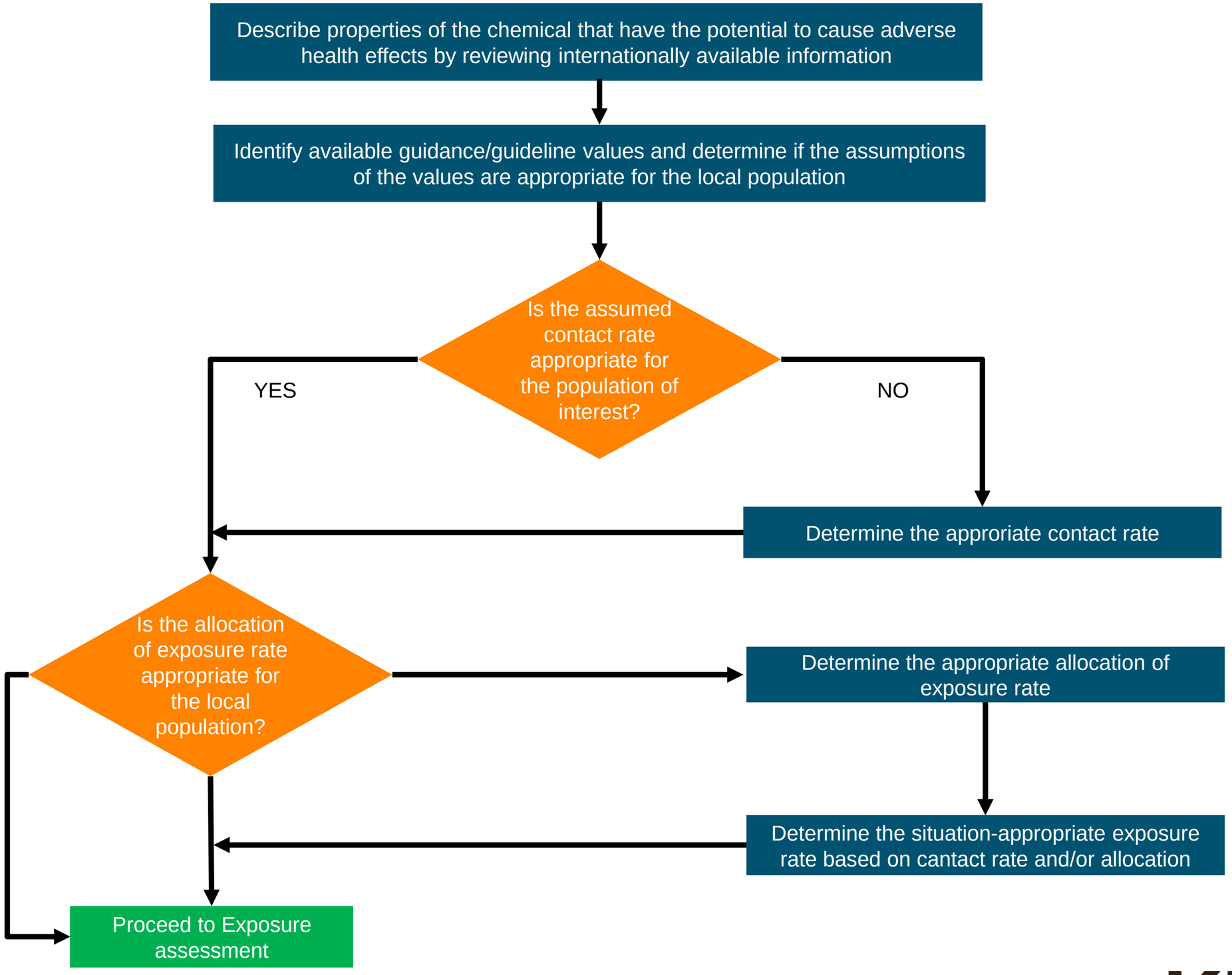
Danger

Causes serious eye damage

Hazard Characterisation

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Hazard characterization road map

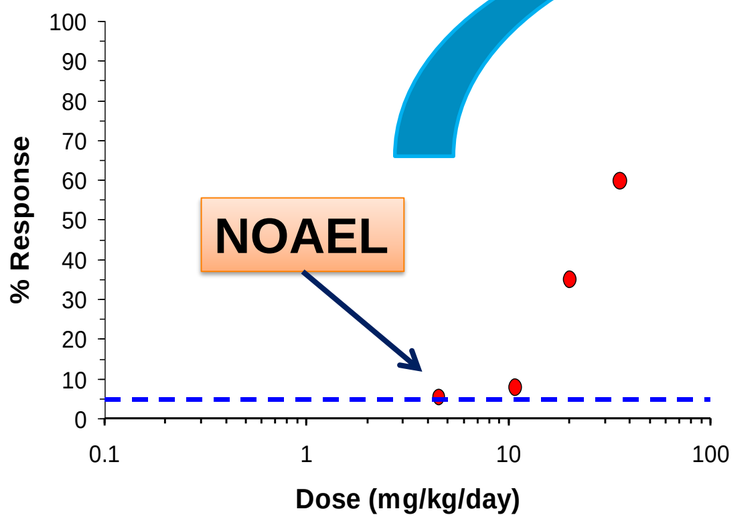


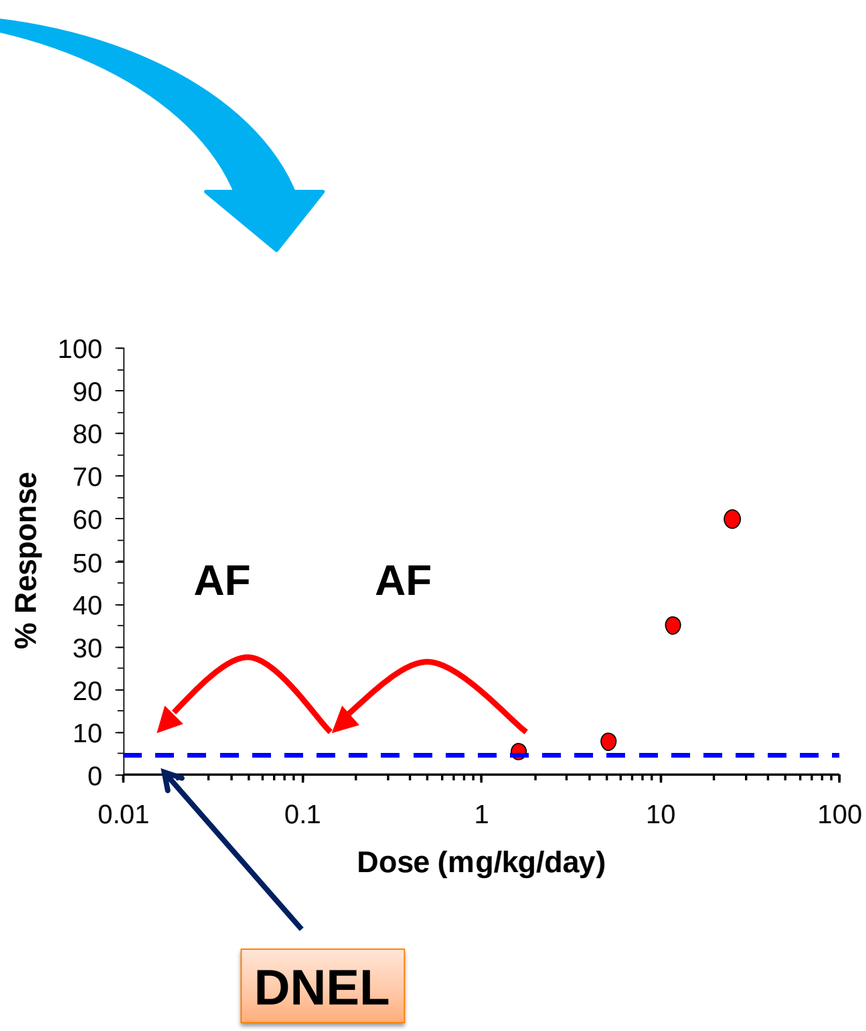
Modified from WHO Human Health Risk Assessment Toolkit

Derived No Effect Level (DNEL)

the level of exposure to the substance below which no adverse effects are expected to occur.

➔the level of exposure to the substance above which humans should not be exposed





AF = Assessment Factor

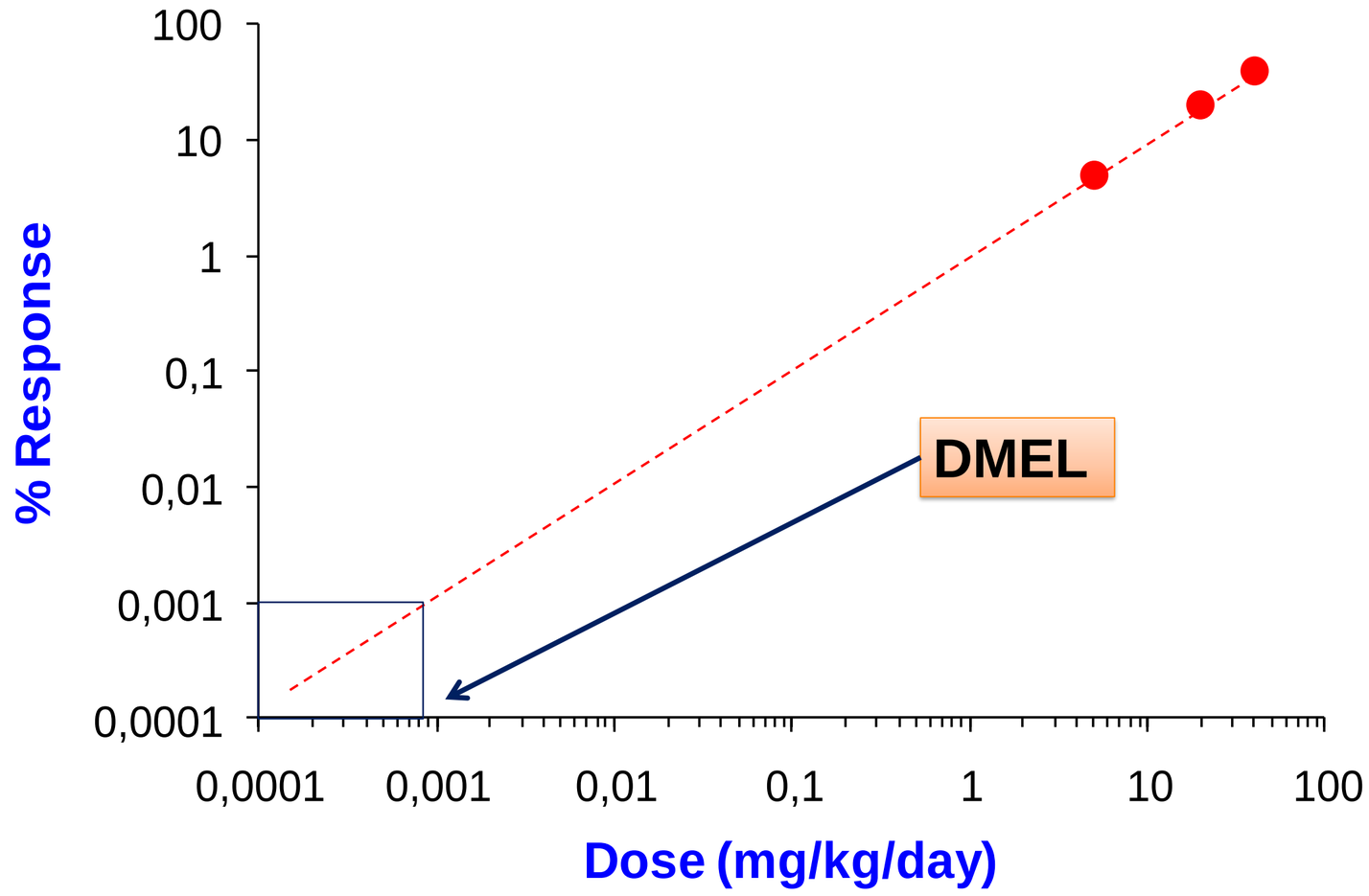
$$DNEL = \frac{NOAEL}{AF \times AF}$$

Assessment Factors

Assessment factor (AF) accounting for:		Default value
Interspecies differences	e.g. rat to man	10
Intraspecies differences	*Worker* *General population* *Children*	5 10 10-100
Exposure duration	*Subacute to sub-chronic* *Sub-chronic to chronic* *Subacute to chronic*	3 2 6
Dose-response	*e.g. LOAEL to NOAEL*	3-10
Quality of whole database		1-10

Derived Minimum Effect Level (DMEL)

- A reference risk level which is considered to be of very low concern (e.g. a lifetime cancer risk of 10^{-5})
- A DMEL should be seen as a **tolerable level of effects** and it should be noted that it is ***not*** a level where no potential effects can be foreseen.



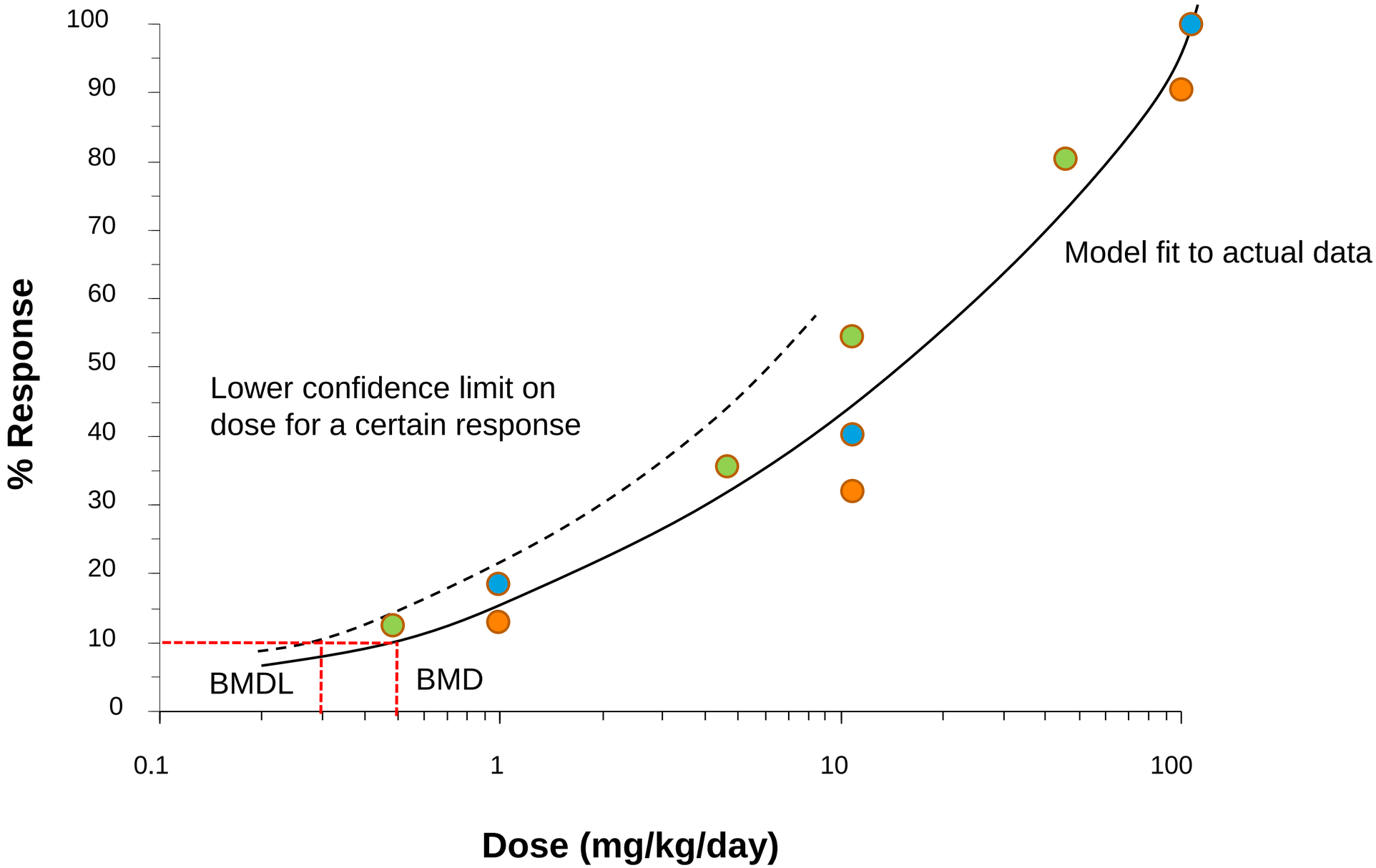
Benchmark dose

For contaminants that are both genotoxic and carcinogenic, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) also recommends the use of the *benchmark dose* (BMD) approach for hazard characterization, mostly using data derived from studies in rodents given daily doses many orders of magnitude greater than the estimated exposure in humans.
Dose–response data from epidemiological studies may also be used for hazard characterization and would avoid interspecies comparisons and extrapolation over many orders of magnitude.

The benchmark dose (BMD) is the dose for a predetermined level of response, called the *benchmark response* (BMR), such as a 5% or 10% cancer incidence. BMDs or their lower confidence limits (BMDLs) are used to determine the margin of exposure (MOE) at the risk characterization stage in the risk assessment process.

JECFA establishes BMDs or BMDLs only for food contaminants; it does not use this approach for substances intentionally added (directly or indirectly) to food, such as food additives, veterinary drugs or pesticides, because it is considered to be inappropriate to intentionally add compounds with genotoxic and carcinogenic properties to food (FAO/WHO, 2006).

Benchmark dose



Guidance/guideline values developed by FAO/WHO

Guidance value	Abbreviation	Unit
Tolerable daily intake	TDI	mg/kg body weight per day
Provisional tolerable weekly intake	PTWI	mg/kg body weight per week
Acceptable daily intake	ADI	mg/kg body weight per day
Reference dose	RfD	mg/kg body weight per day
Acute reference dose	ARfD	mg/kg body weight per day

Guidelines	Abbreviation	Unit
Drinking-water quality guidelines		mg/l
Air quality guidelines		$\mu g/m^3$
Maximum residue limits of pesticides in food	MRL	mg/kg
Maximum limits of contaminats in food	ML	mg/kg

Adapted from: WHO Human Health Risk Assessment Toolkit

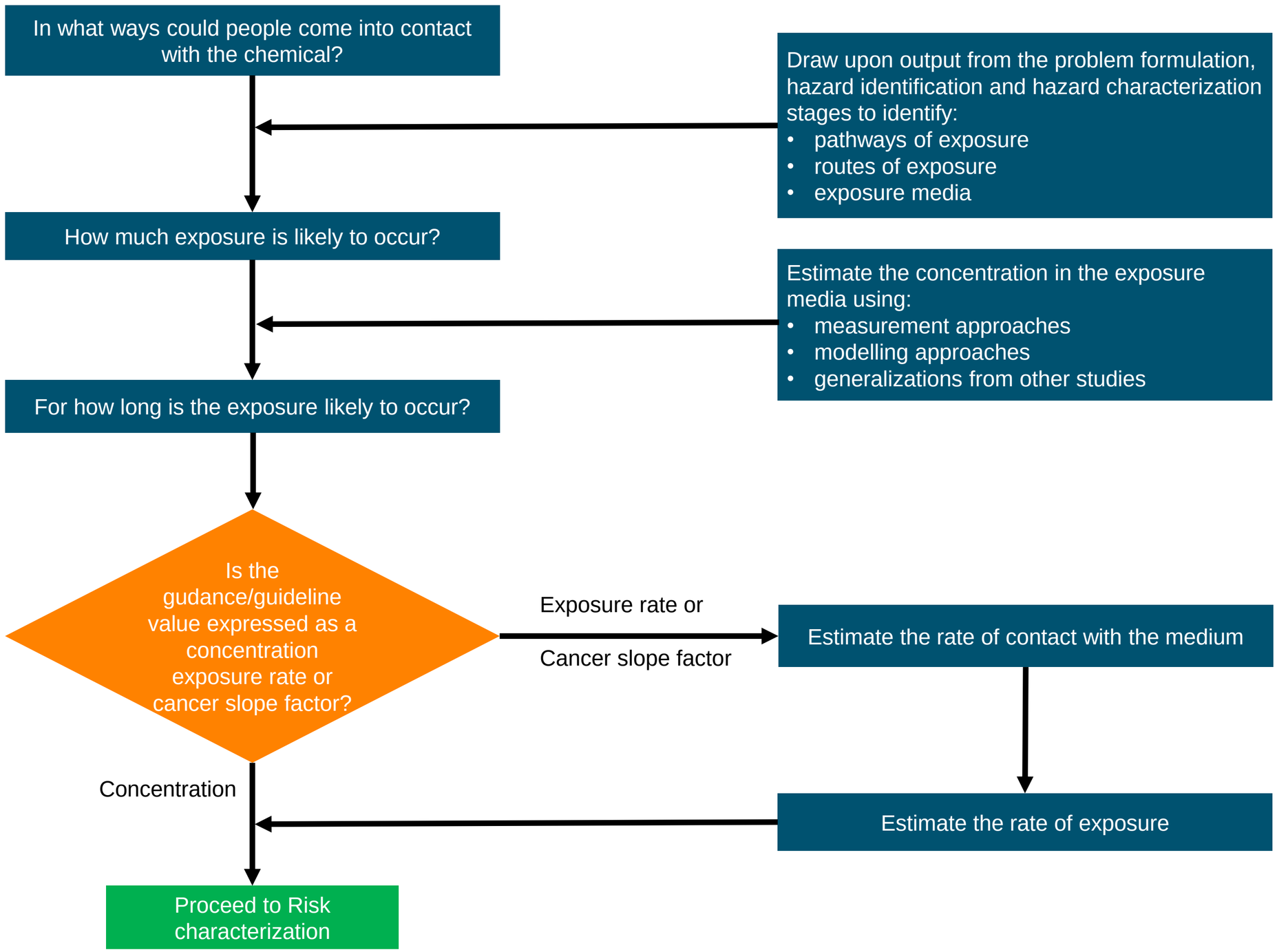
Type of outcome	Term	Unit	Definition
Non-cancer, including laboratory animal carcinogens not relevant to humans	Tolerable Daily Intake (PTWI)	mg/kg bw per day	An estimate of the amount of a chemical in air, food, soil or drinking water that can be taken daily or weekly per unit body weight (bw) over a lifetime without appreciable health risk
	Provisional Tolerable Weekly Intake (PTWI)	mg/kg bw per week	
	Acceptable Daily Intake (ADI)	mg/kg bw per day	
	Reference dose (RfD)	mg/kg bw per day	
	Acute reference dose (ARfD)	mg/kg bw per day	Amount of a chemical, normally in food or drinking water, that can be ingested in a period of 24 h or less per unit body weight (bw) without appreciable health risk
Cancer potentially relevant to humans	Slope factor (SF) - Oral	$[mg/kg\ bw\ per\ day]^{-1}$	An estimate of the cancer risk associaed with a unit dose of a chemical through ingestion or inhalation per unit body weight over a lifetime
	Slope factor (SF) - in relation to a concentration of a chemical in air	$[\mu g/m^3]^{-1}$	An estimate of cancer risk associated with a unit concentration of a chemical in air
	Slope factor (SF) - in relation to a concentration of a chemical in water ($[\mu g/l]^{-1}$)	$[\mu g/l]^{-1}$	An estimate of cancer risk associated with a unit concentration of a chemical in water
Cancer highly relevant to humans	Benchmark dose (BMD)	mg/kg bw per day	Amount of chemical derived from studies in which experimental animals are given daily doses that produce a predefined cancer incidence (e.g. 5% or 10%)

Adapted from: WHO Human Health Risk Assessment Toolkit

Exposure Assessment

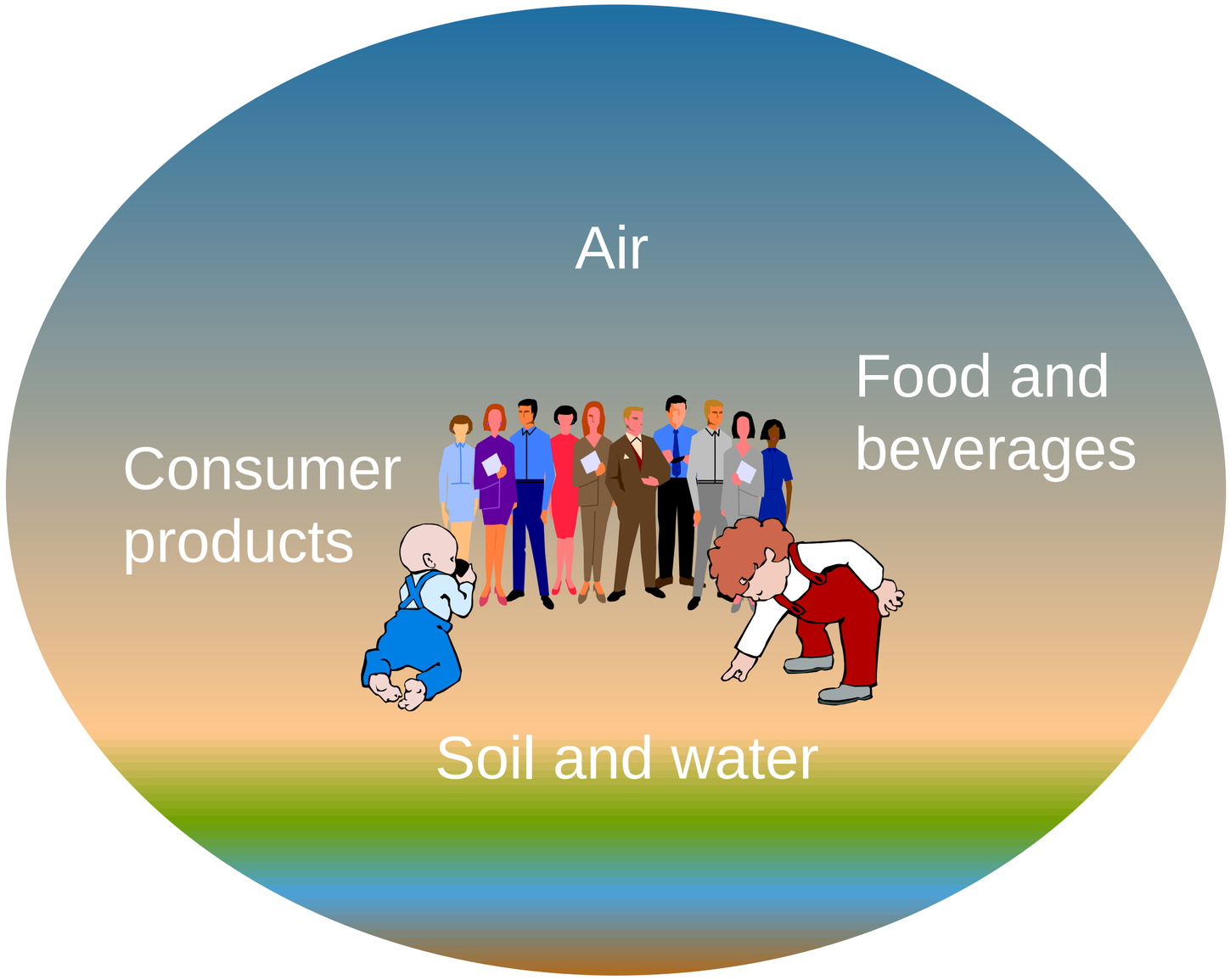
KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Exposure assessment road map



Modified from WHO Human Health Risk Assessment Toolkit

Exposure media



Exposure

What is the source(s) of exposure?

- Point sources (e.g. industrial emission or discharge, contaminated site)
- Non-point sources (e.g. automobile exhaust, agricultural runoff)
- Natural sources (e.g. arsenic in groundwater)
- Use-related sources

Routes of exposure

Environmental sources

- Air
- Surface Water
- Groundwater
- Soil
- Solid Waste
- Food
- Non-food consumer products, pharmaceuticals

What route(s) of exposure are relevant?

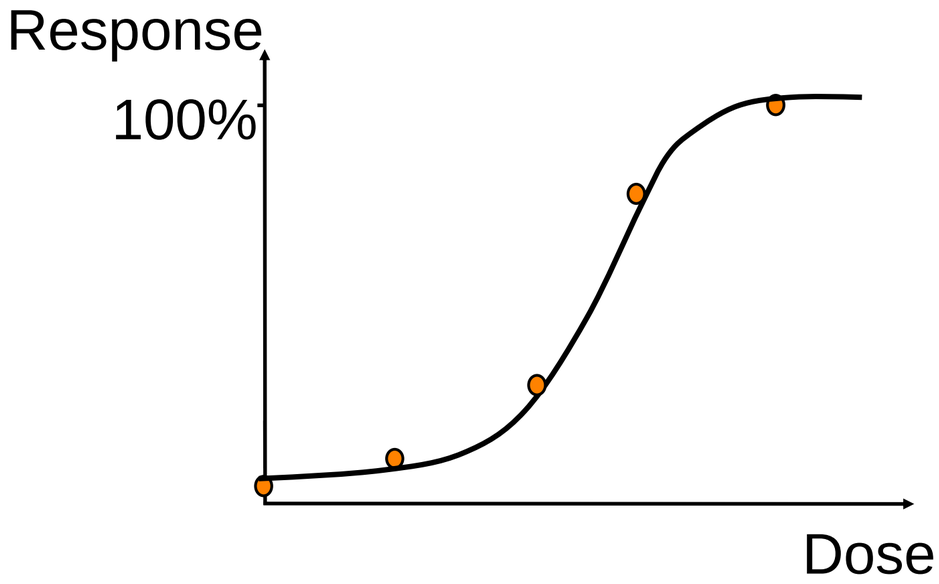
- Ingestion (via food/water)
- Contact with skin
- Inhalation
- Non-dietary ingestion (e.g. soil and dust)

Exposure and dose

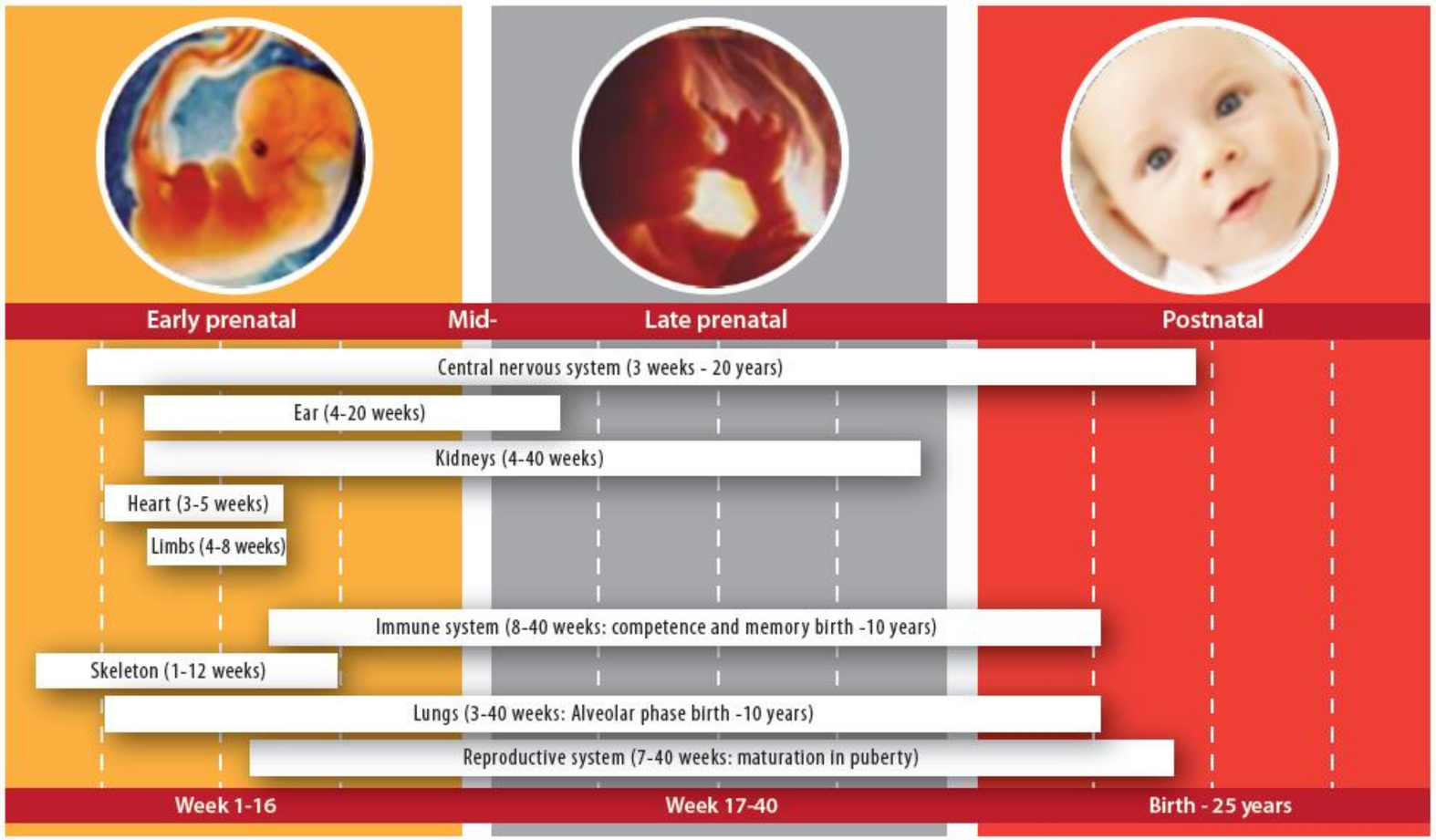
How long does it take for the chemical to exert its toxic effects?

Does it matter when in a lifetime exposure occurs?

- Magnitude of exposure
- Duration of exposure
  - Acute – immediate effects or within a few hours to a day
  - Subchronic - weeks or months
  - Chronic – lifelong or a significant part of a lifetime
  - Intermittent (e.g. workplace exposure)
- Timing of exposure
  - Critical lifestage (e.g., fetal development, childhood, aging)



”The dose makes the poison”



”The timing makes the poison”

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Dose and effects

How does the body deals with the chemical and how is this impacted by factors such as age, race, sex, genetics, etc.?

- Absorption - does the body take up the chemical?
- Distribution – is the chemical dispersed throughout the body or concentrated in one organ?
- Metabolism – is the chemical transformed within the body?
- Excretion - how and at what rate is the chemical and its metabolites removed from the body?

What health effects are associated with exposure to the chemical?

e.g. cancer, developmental disturbances, liver dysfunction

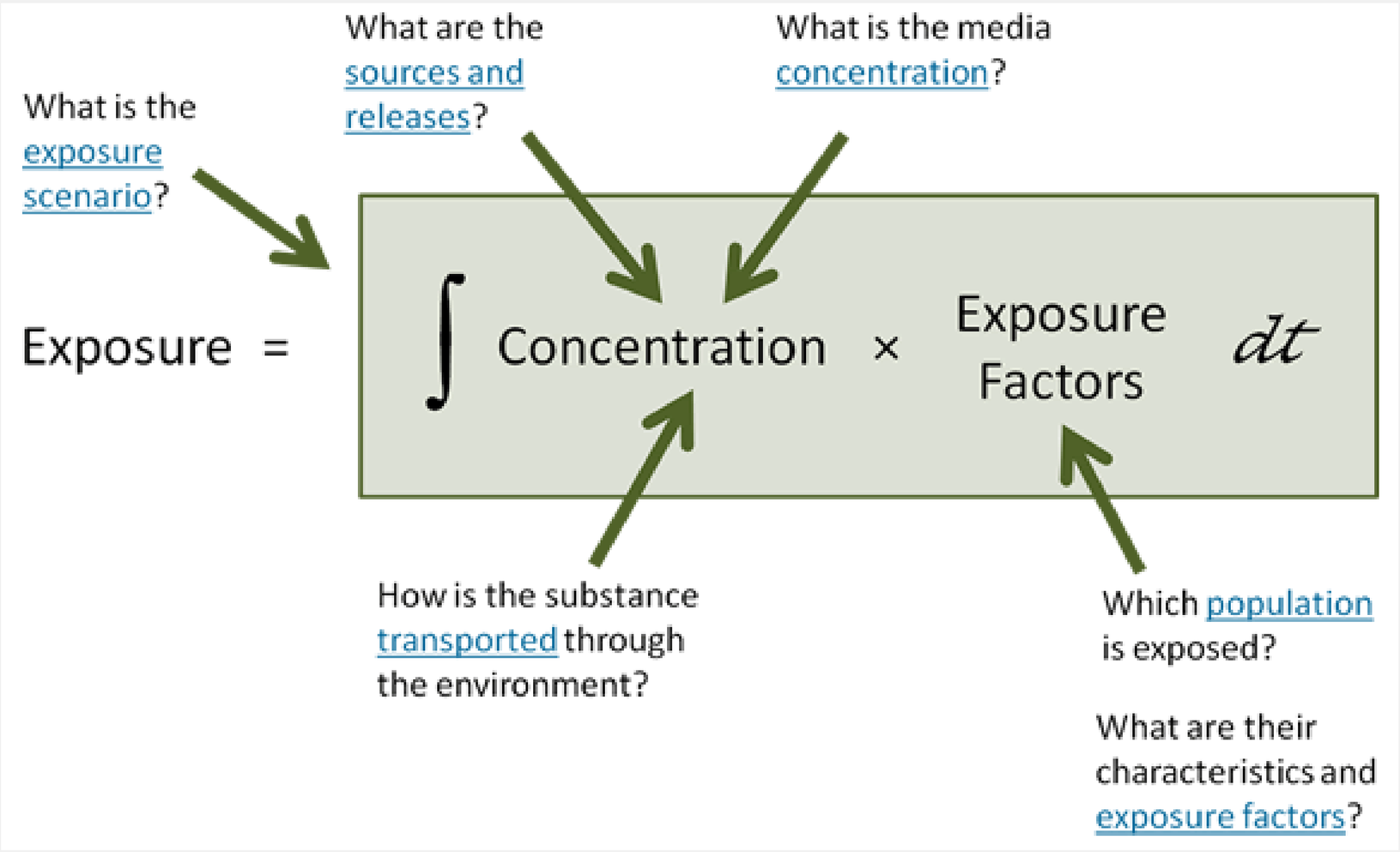
Exposure considerations

- Routes
- Magnitude
  - Modelling
  - Measurements
- Duration
  - Short-term/single
  - Medium-term/intermediate
  - Long-term/cumulative

Exposure estimation

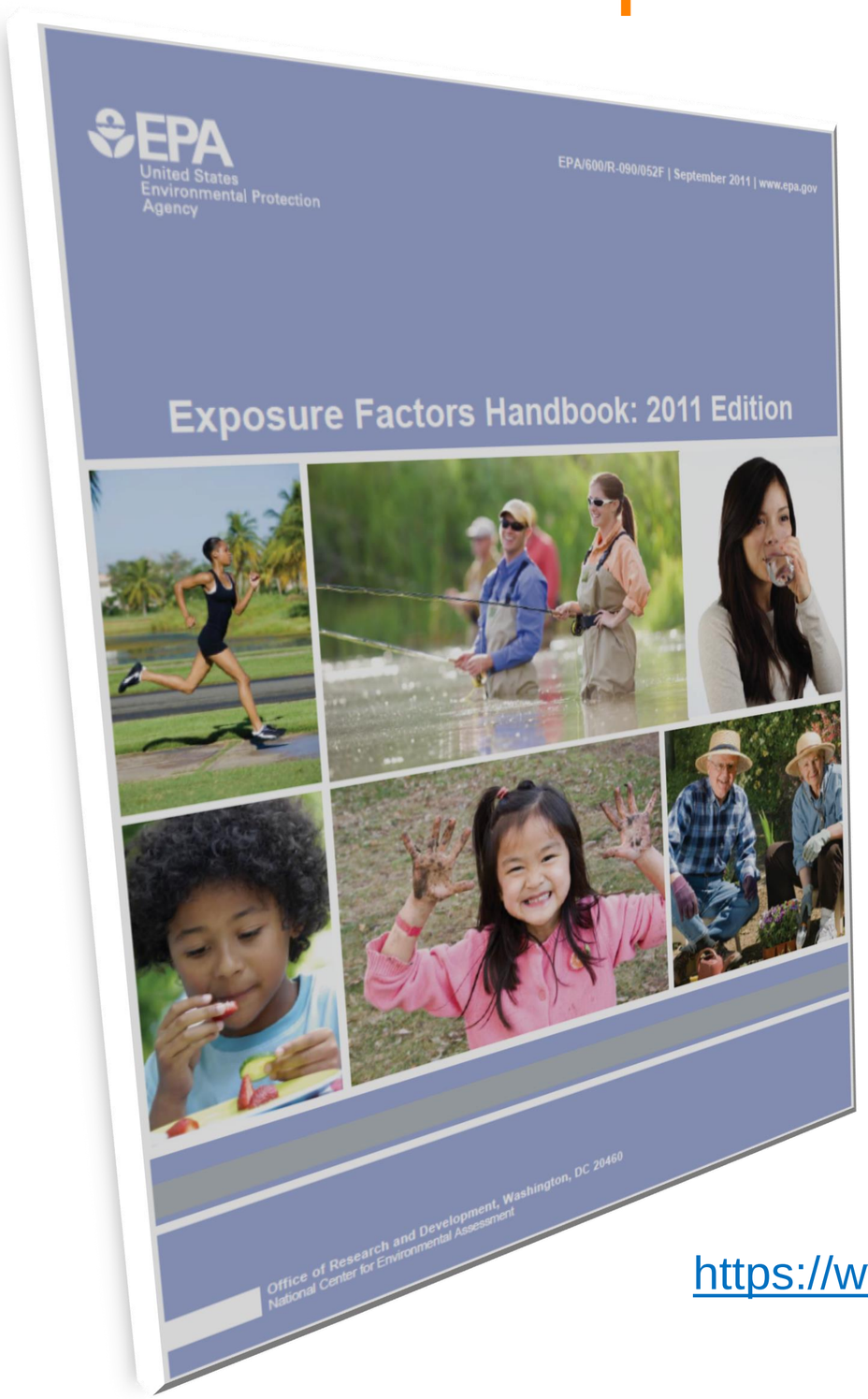
- Direct approach (measurements at point-of-contact)
- Indirect appoach (modelling)
- Reconstruction approach (biomonitoring and reverse dosimetry)

Indirect approach



https://www.epa.gov/expobox

US EPA Exposure Factors Handbook



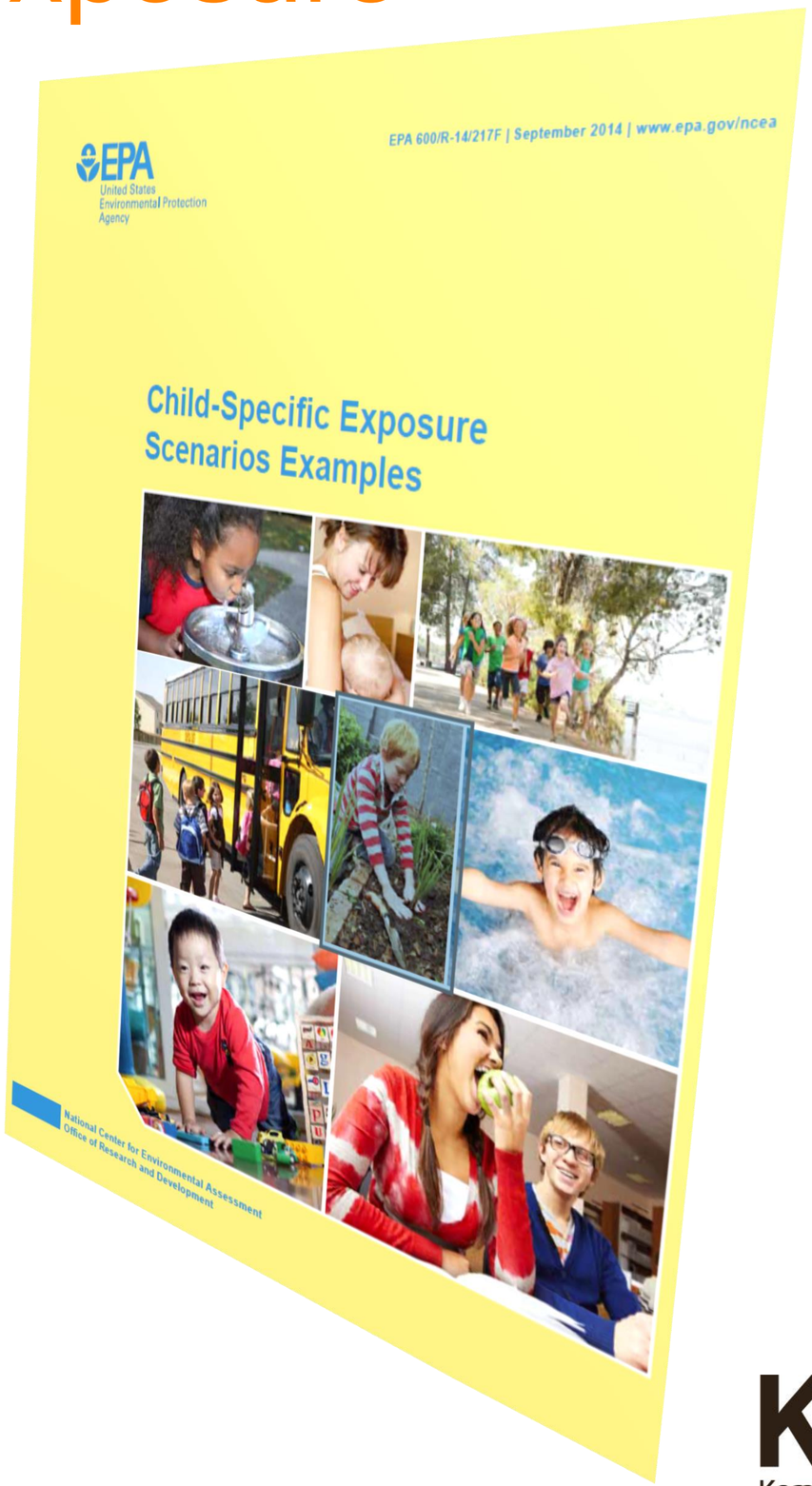
- Intake of water and selected liquids
- Non-dietary ingestion factors
- Ingestion of soil and dust
- Inhalation rates
- Dermal exposure factors
- Ingestion of fruits, vegetables, meats, dairy products, fats, fish, shellfish, grains, home-produced foods, total dietary intake, and human milk
- Activity factors
- Consumer products
- Building characteristics

Search the Exposure Factor Handbook Tables

https://www.epa.gov/expobox/about-exposure-factors-handbook

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Childhood exposure



www.kemikalieinspektionen.se

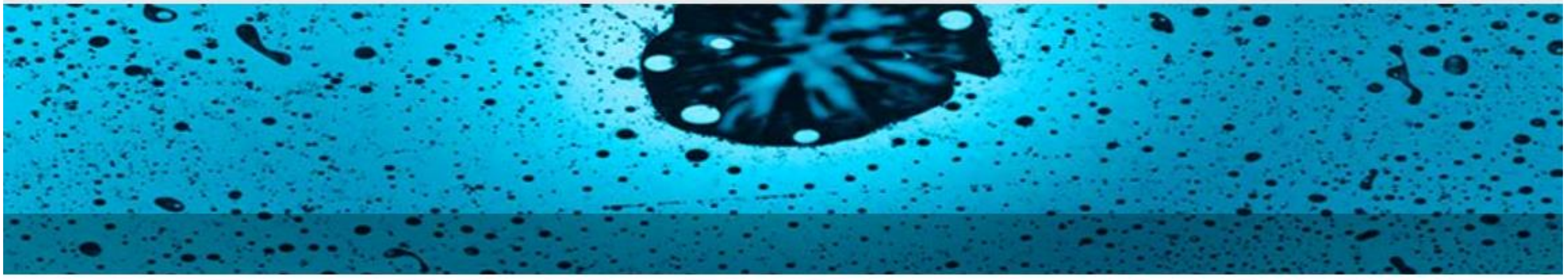
KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

ecetoc

EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS

MEMBER'S LOGIN | Search | HOME

ABOUT ECETOC | ECETOC MEMBERSHIP | SCIENCE PROGRAMME | **TOOLS** | TOPICS | PUBLICATIONS | NEWS | EVENTS | LINKS



Targeted Risk Assessment (TRA)

› **History**

ECETOC Human Exposure Assessment Tools Database (heatDB)

hSSD Tool

LRI Toolbox

TARGETED RISK ASSESSMENT (TRA)

ECETOC's Targeted Risk Assessment (TRA) tool calculates the risk of exposure from chemicals to workers, consumers and the environment. It has been identified by the European Commission's Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as a preferred approach for evaluating consumer and worker health risks (ECHA, 2010 a,b).

In response to feedback received from users of the TRA, ECETOC further improved the consumer portion of the model by the inclusion of the ability to account for infrequent uses of consumer products. The changes which were developed in cooperation with ECHA are found in the current version 3.1 of the TRA and are also to be found within version 2.3 of Chesar (https://chesar.echa.europa.eu).

http://www.ecetoc.org/tools/targeted-risk-assessment-tra/

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Targeted Risk Assessment (TRA)

ECETOC Human Exposure Assessment Tools Database (heatDB)

hSSD Tool

LRI Toolbox

ECETOC HUMAN EXPOSURE ASSESSMENT TOOLS DATABASE (HEATDB)

ecetoc heatDB

heatdb is a public directory of exposure data sources as well as available tools for exposure

The Human Exposure Assessment Tools Database (heatDB) is a resource for risk assessors to use to quickly search and locate human exposure tools and data available in the public domain. Available sources of exposure data have been gathered, structured and categorised into a harmonised system. Additionally, available tools for exposure assessment were gathered and categorised into the same system. This allows risk assessors to quickly review what data sources and tools are available for given purposes and to have guidance on their appropriate use using a tiering system. In parallel with this database, a report was developed providing analysis, discussion and case studies demonstrating different uses of some the different tools and data sources (available on the main ECETOC website). There are hundreds of identified sources of human exposure data and tools in heatDB. Users can register for free, login and use the database as required. There is a quick and very responsive search box which searches on all fields and provides results instantaneously. Additionally, there is a message board where users can leave suggestions for improvements to the database or identify new data sources and tools to include in future versions.

http://www.ecetoc.org/tools/ecetoc-heat-db/

Human Exposure Assessment Tools Database

heatdb is a public directory of exposure data sources as well as available tools for exposure

LOGIN REGISTER FOR FREE

About ECETOC heatDB

The Human Exposure Assessment Tools Database (heatDB) is a resource for risk assessors to use to quickly search and locate human exposure tools and data available in the public domain. Available sources of exposure data have been gathered, structured and categorised into a harmonised system. Additionally, available tools for exposure assessment were gathered and categorised into the same system. This allows risk assessors to quickly review what data sources and tools are available for given purposes and to have guidance on their appropriate use using a tiering system. In parallel with this database, a report was developed providing analysis, discussion and case studies demonstrating different uses of some the different tools and data sources (available on the main ECETOC website). There are hundreds of identified sources of human exposure data and tools in heatDB. Users can register for free, login and use the database as required. There is a quick and very responsive search box which searches on all fields and provides results instantaneously. Additionally, there is a message board where users can leave suggestions for improvements to the database or identify new data sources and tools to include in future versions. Enjoy!

https://heatdb.cremeglobal.com/

Exposure rate

$$\frac{concentration\ x\ contact\ rate\ x\ exposure\ duration}{body\ weight\ x\ averaging\ time}$$

Concentration = the amount of chemical in the exposure medium
Contact ratio = amount of medium in contact with the human body
Exposure duration = time during which the person is in contact with the chemical
Body weight = body weight over the averaging time
Averaging time = period of time of exposure relevant for the health risk characterization

The *ADR* via inhalation of contaminated indoor air is calculated as follows:

$$ADR_{indoor\ air\ inh} = \frac{C_{indoor\ air} \times ET \times IR \times ED}{AT}$$

where:

$ADR_{indoor\ air\ inh}$ = acute dose rate of contaminated indoor air (mg/kg-d);

$C_{indoor\ air}$ = concentration of contaminants in the indoor air (mg/m^3);

ET = exposure time (min/d);

IR = inhalation rate (m^3/min-kg);

ED = exposure duration (d); and

AT = averaging time (d).

$$ADR_{indoor\ air\ inh} = \frac{1 \times 10^{-3}\,\frac{\text{mg}}{\text{m}^3} \times 1{,}305\,\frac{\text{min}}{\text{d}} \times 3.7 \times 10^{-4}\,\frac{\text{m}^3}{\text{min-kg}} \times 1\,\text{d}}{1\,\text{d}}$$

$$ADR_{indoor\ air\ inh} = 4.8 \times 10^{-4}\,\frac{\text{mg}}{\text{kg-d}}$$

Example: Ingestion of soil and dust

$$LADD_{soil+dust\ ing} = \frac{C_{soil+dust} \times CF \times IR_{soil+dust} \times EF \times ED}{BW \times LT}$$

$LADD_{soil + dust\ ing}$ = potential lifetime average daily dose from ingestion of soil and dust (mg/kg-d);
$C_{soil + dust}$ = concentration of contaminant in soil and dust (mg/g);
CF = conversion factor of 0.001 g/mg;
$IR_{soil + dust}$ = intake rate of soil and dust (mg/d);
EF = exposure frequency (d/yr);
ED = exposure duration (yr);
BW = average body weight (kg);
LT = lifetime (d).

US EPA Child-Specific Exposure Factors Handbook

Childhood exposure to lead in soil and dust

$$ADD_{soil+dust\ ing} = \frac{C_{soil+dust} \times CF \times IR_{soil+dust} \times EF \times ED}{BW \times T}$$

$$ADD_{soil+dust\ ing} = \frac{1 \times 0.001 \times 100 \times 365 \times 4}{15.6 \times 1{,}460}$$

$$ADD_{soil+dust\ ing} = 0.0064 \text{ mg/kg per day}$$

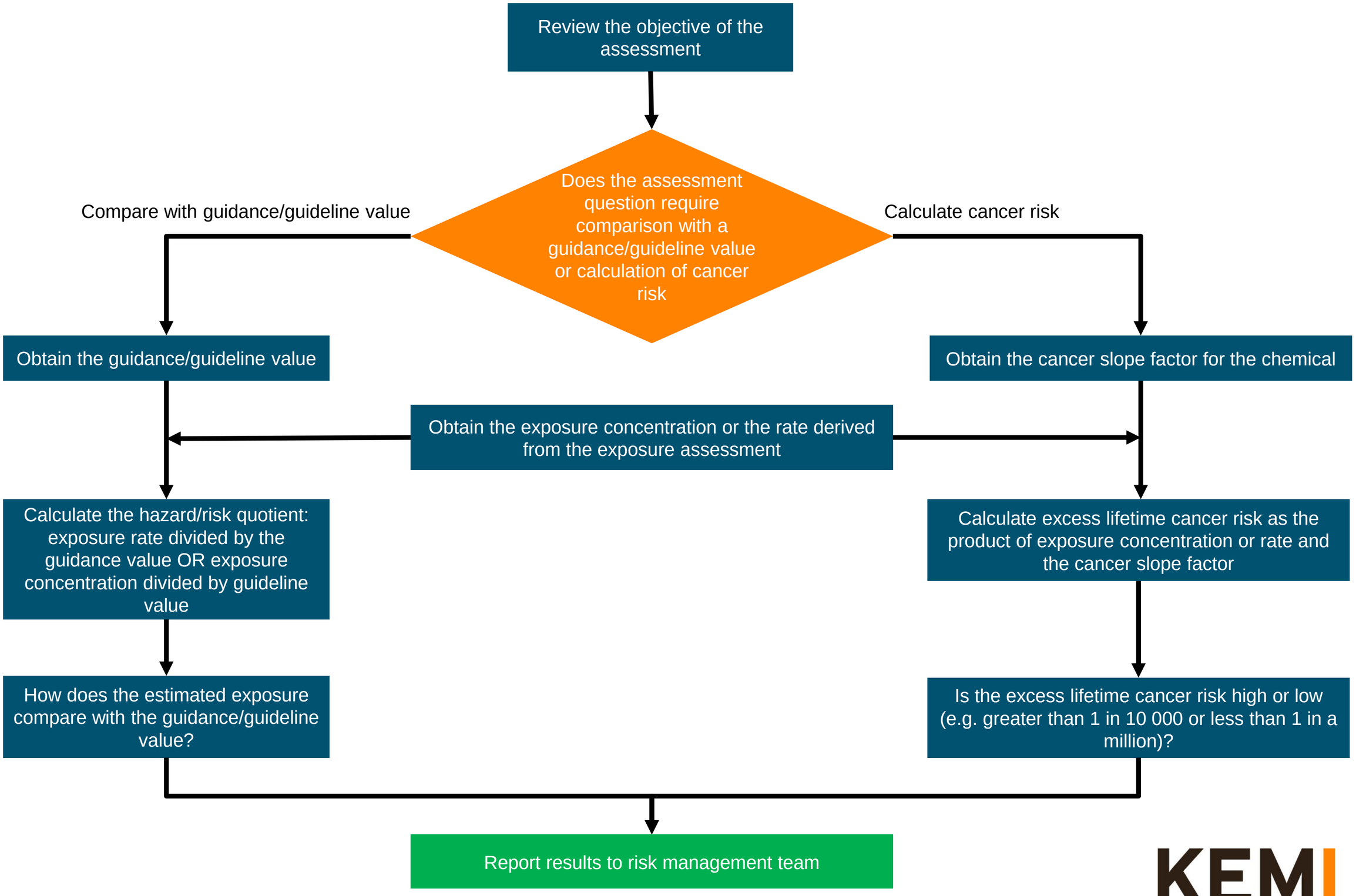
$ADD_{soil + dust\ ing}$ = Early childhood average daily dose from ingestion of soil and dust (mg/kg per d);
$C_{soil + dust}$ = concentration of contaminant in soil and dust (1 mg/g);
CF = conversion factor of 0.001 g/mg;
$IR_{soil + dust}$ = intake rate of soil and dust (100 mg/d);
EF = exposure frequency (365 d/yr);
ED = exposure duration (4 years);
BW = average body weight (kg);
T = Time (4 years, in days).

Adapted from
US EPA Child-Specific Exposure Factors Handbook

Risk Characterization

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Risk characterization road map



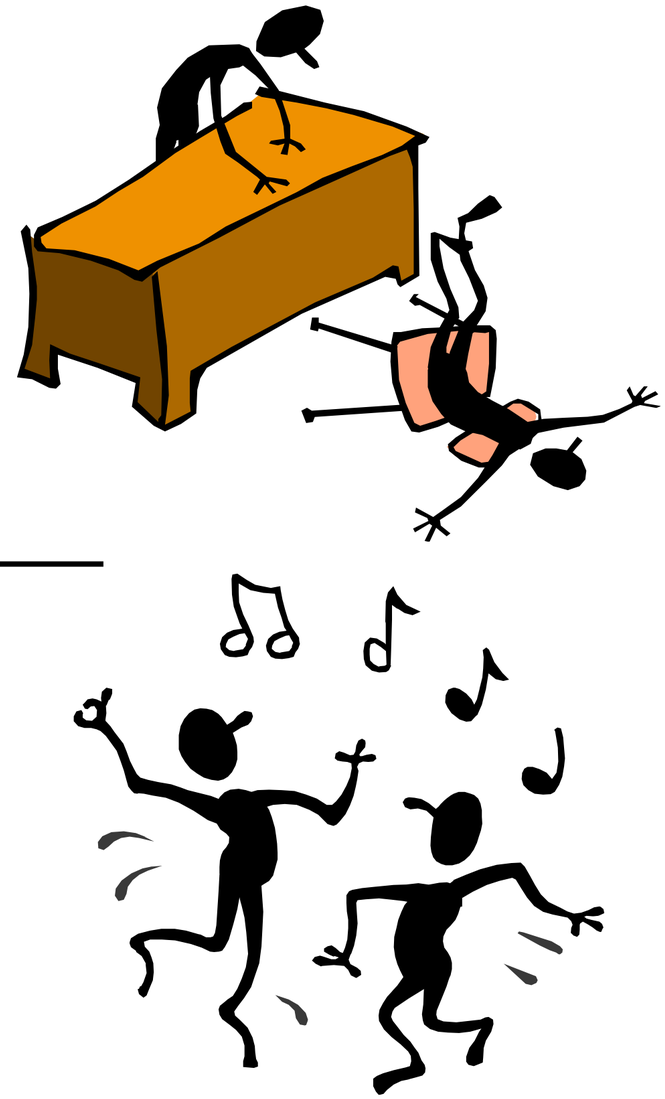
Modified from WHO Human Health Risk Assessment Toolkit

Risk charcterisation

Guideline value

Risk

No risk



KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Chemical Safety Assessment (CSA)

- The goal of the CSA is to identify and describe the conditions under which the risks are controlled (“safe use”).
- Risks are regarded as controlled when the estimated exposure levels do not exceed the derived no effect levels (DNEL)
- The CSA needs to document the relevant data, judgements, justifications and conclusions in a chemicals safety report (CSR)

Elements of the EU REACH process

Substance information: Available ←→Required/needed
- *Intrinsic properties*
- *Manufacture, use, tonnage, exposure, risk management*

Hazard assessment
- *Hazard identification*
- *Classification and Labelling*
- *Derivation of threshold lelevs*
- *PBT/vPvB assessment*

Exposure assessment
- *Exposure scenarios*
- *Exposure estimation*

STOP

NO

Hazardous or PBT/vPvB

YES

Risk characterization

Risk controlled?

YES

NO

Iteration

Chemical Safety Report

SDS

Exposure Scenario

www.kemikalieinspektionen.se

Risk characterisation - Stepwise procedure

Step	Action
1	Risk characterisation for physical hazards
2	Collect the predicted or derived no-effect levels or minimal effect levels (PNECs, DNELs or DMELs if appropriate) for the relevant time scales, environmental ecosystems, human populations, health effects, and routes of exposure. For endpoints where no DNEL can be derived, collect other information on potency of the substance.
3	For each exposure scenario collect the exposure values, measured or estimated, for the relevant time scales and spatial scales, environmental compartments, human populations and human routes of exposure.
4	Compare matching exposure and predicted or derived no-effect levels or minimal effect levels for all relevant matching combinations.
5	If no predicted or derived no-effect level or minimal effect level could be derived for a substance for a certain environmental compartment or human effect, carry out a qualitative risk characterisation for that compartment/effect.
6	Calculate the sum of risk characterisation ratios of combined exposure, e.g. for each human population and for the general population (combined worker and consumer exposure).
7	Decide on possible iterations of the assessment, taking uncertainties into account. The risk characterisation should demonstrate control of risks, based on a sufficiently robust hazard and exposure assessment.
8	Finalise the risk characterisation.

Risk characterisation ratios (RCRs)

When the leading health effect is a threshold effect with a DNEL:

RCR = Exposure/DNEL

RCR < 1 ➔ Risk is ***adequately controlled (Safe use)***

RCR > 1 ➔ Risk is NOT controlled

If the risk characterisation shows that **risk is not controlled**, an **iteration** of the CSA is needed

Derived Minimum Effect Level (DMEL)

Exposure **<** DMEL ➔ Exposure is controlled to a ***risk level of low concern***

Exposure **>** DMEL ➔ Risk is NOT controlled

If the risk characterisation shows that **risk is not controlled**, an **iteration** of the CSA is needed

Human Health Hazard Assessment
- Human and non-human information -

- Toxicokinetics
- Acute toxicity
  - Oral
  - Inhalation
  - Dermal
  - Other routes
- Irritation
  - Skin
  - Eye
  - Respiratory tract
- Corrosivity
- Sensitisation
  - Skin
  - Respiratory
- Repeated dose toxicity
  - Oral
  - Inhalation
  - Dermal
  - Other routes
- Mutagenicity
  - In vitro
  - In vivo
- Carcinogenicity
  - Oral
  - Inhalation
  - Dermal
  - Other routes
- Toxicity for reproduction
  - Effects on fertility
  - Developmental toxicity
- Other effects
  - Neurotoxicity
  - Immunotoxicity
  - Specific investigations – other studies

Human Health Hazard Assesment of Physicochemical Properties

- Explosivity
- Flammability
- Oxidising potential

Environmental Hazard Assessment

- Aquatic compartment (including sediment)
- Terrestrial compartment
- Atmospheric compartment

PBT and vPvB Assessment

- Persistence assessment
- Bioaccumulation assessment
- Toxicity assessment

REACH Exposure assessment

1. Development of Exposure scenarios

2. Exposure estimation

Exposure scenarios

The conditions under which a substance is manufactured and used

The purpose is to describe the conditions under which a substance can be used safely (= risks are controlled).

- The **initial** ES describes the conditions of use as known at the beginning of the assessment process.
- The **final** ES describes the conditions ensuring control of risk as a conclusion of the assessment process.

- Manufacture
- Transfer
- Cleaning and maintenance
- Formulation and repackaging (closed/open systems)
- Receiving and charging
- Mixing/blending
- Use at industrial sites
- Professional use
- Consumer use

Exposure Assessment and Related Risk Characterization

- Environment
  - Man via the environment
- Workers
- Consumers

Exposure estimation

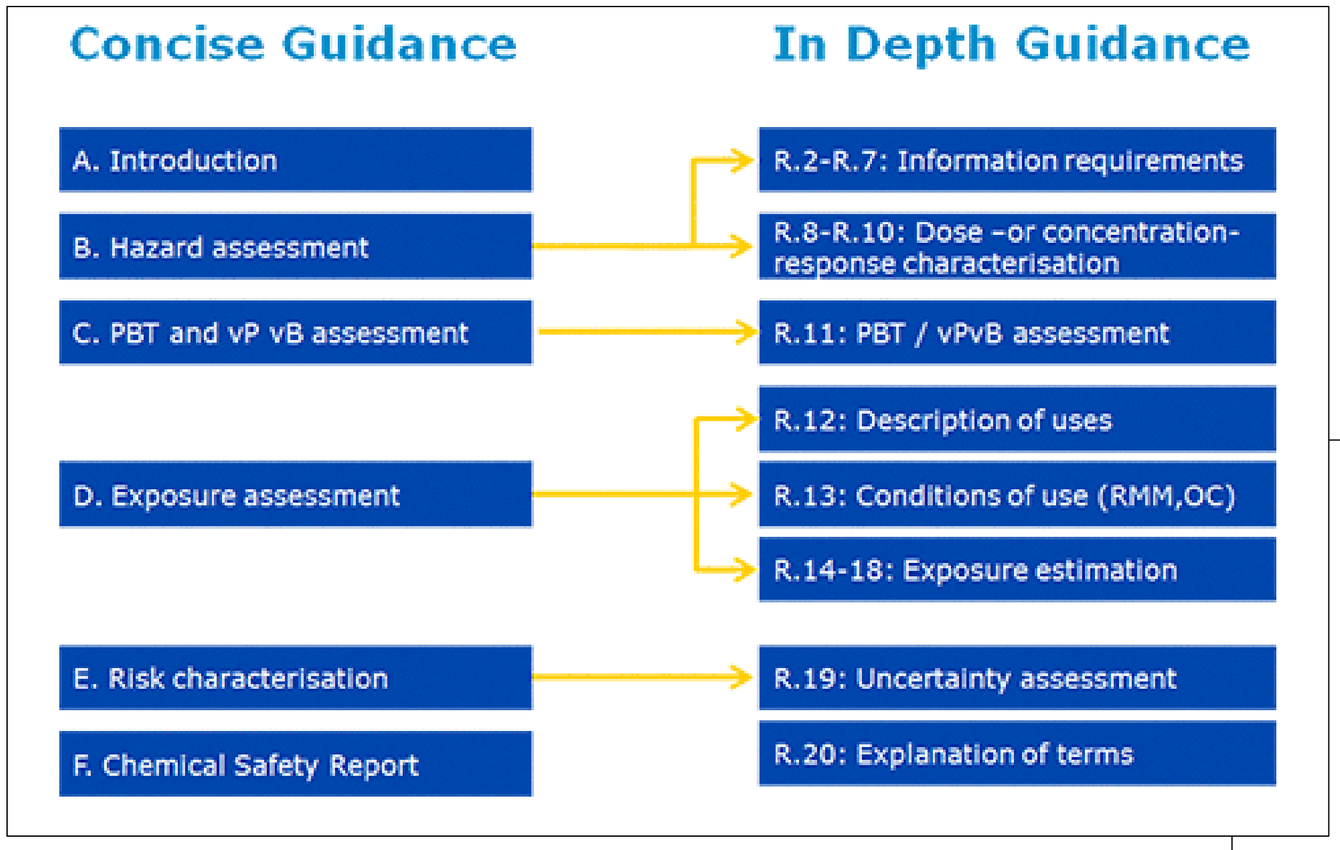
- The assessment needs to cover the *manufacturing* and *all identified uses* of the substance and the *life cycle stages* resulting from these identified uses. This includes the *waste* stage and, where relevant, the service-life of *articles* containing the substance.
- The estimation can be based on modeling or on measured data, if available.
- The estimation can be carried out in a tiered process starting with conservative assumptions on emissions and exposure.

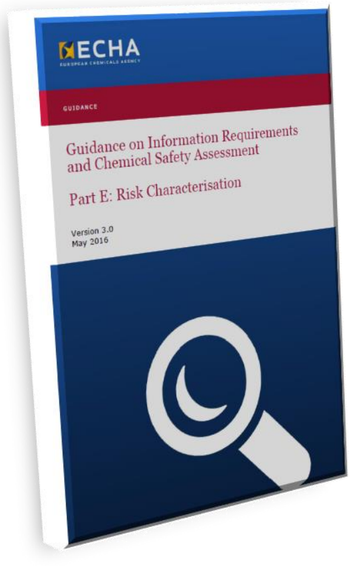
Chemical Safety Report

- Documents the chemical safety assessment undertaken as part of the REACH registration process
- Provides registrant information to all users of chemicals through the exposure scenarios.
- Forms a basis for e.g. substance evaluation, authorisation and restriction.
- Demonstrates that the risks from the exposure to a substance, during its manufacture and use, are controlled when specific operational conditions and risk management measures (exposure sceanarios) are applied.
- Should be readily understandable in all its parts as a stand-alone document
- Should include all the relevant information for the chemical safety assessment.
- The principles applied in the hazard and exposure assessments, the assumptions made and the conclusions drawn should be transparent and well documented. The key data should be easily identifiable without the need to revert to the underlying substance datasets (IUCLID substance dataset).

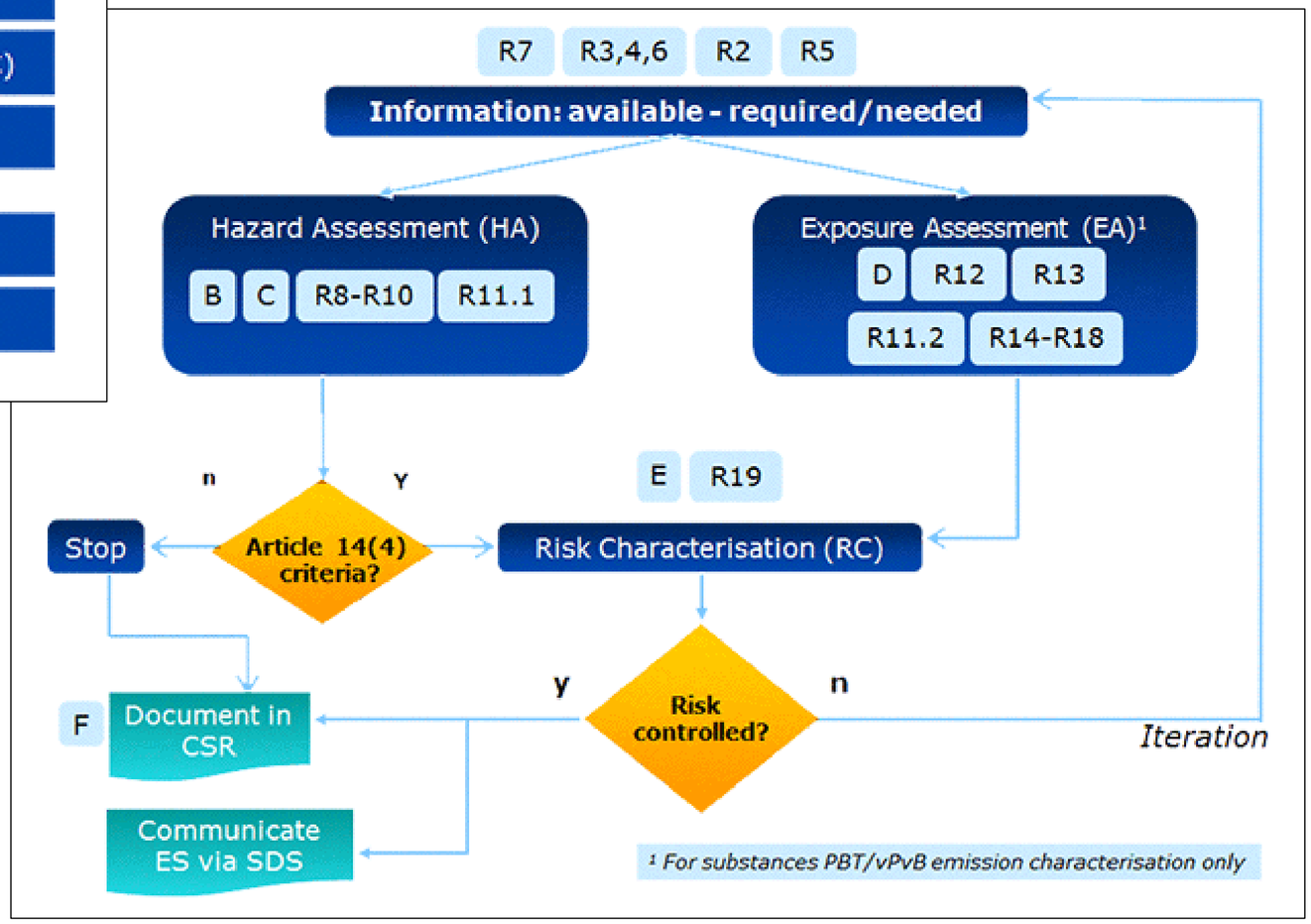
Ref.: REACH Annex I, Section 7

ECHA Guidance on Risk Assessment





The overall process and how a particular guidance element is related to it



KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Risk Management Measures

- Measures that **control the emission** of a substance **and/or exposure** to it.
  - ➢ Any action, use of tool, change of parameter state that is introduced during manufacture or use of a substance in order to **prevent, control, or reduce exposure**
    - containment of process (closed system),
    - waste water treatment,
    - local exhaust ventilation,
    - exhaust air filters,
    - personal protective equipment (gloves etc.),
    - etc.

Risk Characterisation

If “hazardous” or PBT/vPvB:

- **Exposure assessment** – taking into account risk reducing measures applied or recommended (per exposure scenario)
- **Risk characterisation (for each exposure scenario)**
  1. Compare exposure data with DNEL
  2. Is exposure for each identified use (Exposure Scenario) ”adequately controlled”? (Exposure< DNEL?)
  3. If not “adequately controlled”: Refine hazard and/or exposure assessment or enhance risk reducing measures

Options

- *Get more accurate effect data! ⇨ new data/test*
- *Get more/better exposure data! ⇨ new model/measurements*
- *Decrease exposure! ⇨ new/additional risk reducing measures*

Iteration until “adequately controlled”

Iterations of the CSA - Strategy

- **Improve the hazard information** - if a limited toxicity data set is available
- **Improve the exposure information** – Iterations on exposure data or on assumptions, refinement of data on substance properties, emission data, exposure assumptions, model definition or complexity, or replace model predictions by measured data.
- **Improve information on operational conditions** - The description of the operational conditions can be refined to get closer to reality
- **Improve information on risk management -** such as on-site waste water treatment, changing to a closed system or improved recirculation of processing chemicals

CSR Guidance

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Risk characterisation – Example 1

NOAEL	1 mg/kg x day
AF	100 (10x10)
DNEL	1/100 = 0.01 mg/kg x day
Exposure media	Drinking water
Concentration	0.15 mg/l
Media contact	2 l/day
Body weight	60 kg
Exposure	(0.15 x 2)/60 = 0.005 mg/kg x day
RCR	0.005/0.01 = 0.5

Exposure < DNEL➔ **risk is controlled**

Risk characterisation – Example 2

NOAEL	1 mg/kg x day
AF	500 (10x10x5)
DNEL	1/500 = 0.002 mg/kg x day
Exposure media	Drinking water
Concentration	0.15 mg/l
Media contact	1 l/day
Body weight	20 kg
Exposure	(0.15 x 1)/20 = 0.0075 mg/kg x day
RCR	0.0075/0.002 = 3.75

Exposure > DNEL➔ **risk is not controlled**

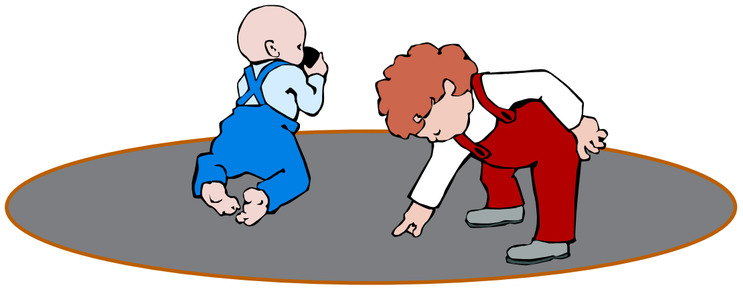
Risk characterisation – Example 3

NOAEL	1 mg/kg x day
AF	500 (10x10x5)
DNEL	1/500 = 0.002 mg/kg x day
Exposure media	Drinking water
Concentration	
Media contact	1 l/day
Body weight	20 kg
Exposure	
RCR	

Drinking water concentration for Exposure < DNEL???

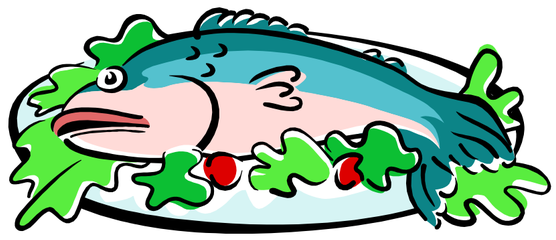
Three examples

- Lead in soil and dust



- Arsenic in drinking water

- Methyl mercury in food



Lead dietary exposure in the European population (EFSA, 2012)

The 2010 EFSA opinion identified a *95th percentile lower confidence limit of the benchmark dose of 1 % extra risk (BMDL01) of 0.50 µg/kg b.w. per day* for developmental neurotoxicity in young children. This corresponds to a blood lead level of 12 µg/l.

Exposure was highest for toddlers and other children with 1.32 and 1.03 µg/kg b.w. per day, respectively, while two infant surveys ranged between 0.83 and 0.91 µg/kg b.w. per day.

http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2831/epdf

Setting a guideline level för lead in soil

Pre-2010 PTWI: 25 µg/kg per week*

➔8.3 µg Pb/kg per day

Body weight (1-2 year): 10 kg

➔83 µg Pb/day

Exposure: daily

Fraction of daily lead exposure from soil and dust: max 10%

➔8.3 µg Pb

Soil + dust ingestion: 100 mg daily (excluding pica)

8.3/0.1 = 83 µg/g

**currently not considered protective following revised evaluation by JECFA*

EFSA 2010 opinion on lead: 1% extra risk level for neurotoxicity in children

➔0.5 µg Pb/kg per day

Body weight (1-2 year): 10 kg

➔5 µg Pb/day

Exposure: daily

Fraction of daily lead exposure from soil and dust: max 10%

➔0.5 µg Pb

Soil + dust ingestion: 100 mg daily (excluding pica)

0.5/0.1 = 5 µg/g

JECFA* evaluation (2011) of arsenic in drinking water

Critical effects: Lung cancer, bladder cancer, skin lesions (hyperkeratosis, hyperpigmentation and hypopigmentation)

Risk assessment: Based on data from an epidemiology study conducted on a highly-exposed population, *the inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer was calculated to be 3 µg/kg bw per day* (range: 2–7 µg/kg bw per day) using a range of assumptions to estimate total dietary exposure of the study population to inorganic arsenic from drinking water and food.

- What drinking water level corresponds to a daily intake of 3 µg As/kg bw per day?
- What drinking water level would correspond to a 10^{-5} risk level?
- What is the drinking water standard for As in Brazil?

*Joint FAO/WHO Expert Committee on Food Additives

http://apps.who.int/iris/bitstream/10665/44514/1/WHO_TRS_959_eng.pdf

JECFA evaluation (2011) of arsenic in drinking water

Based on data from an epidemiology study conducted on a highly-exposed population, *the inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer was calculated to be 3 µg/kg bw per day* (range: 2–7 µg/kg bw per day) using a range of assumptions to estimate total dietary exposure of the study population to inorganic arsenic from drinking water and food.

5 extra cases per 1000 exposed = 500 x 10^{-5}

Point of departure:
BMDL0.5

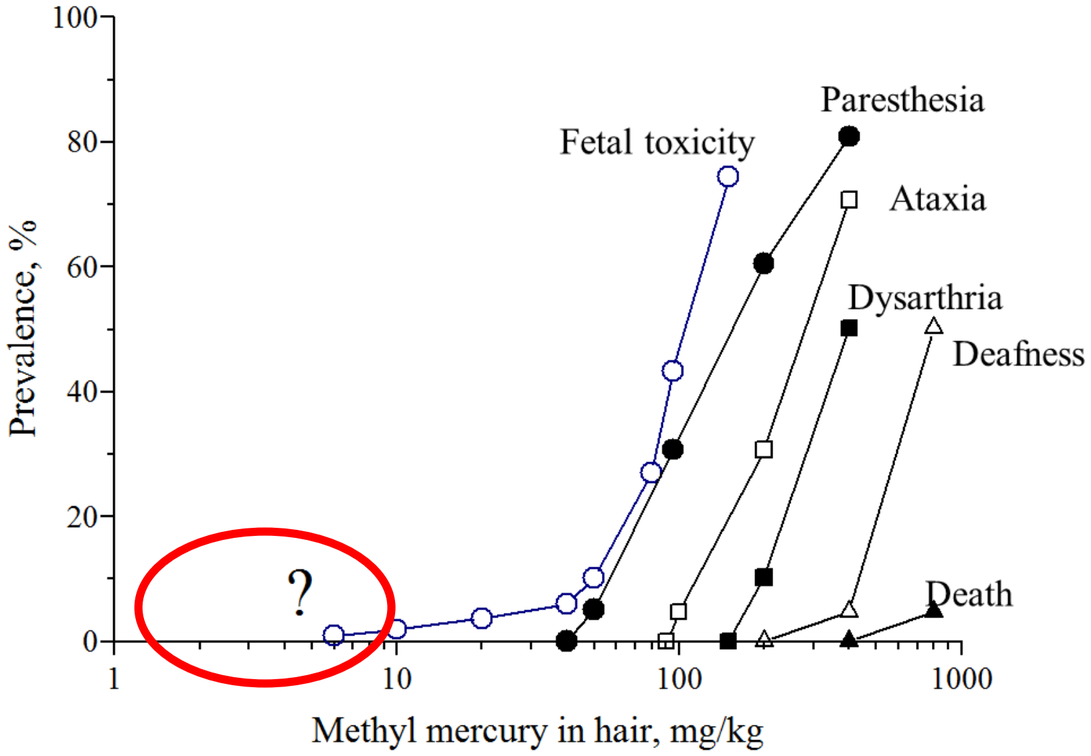
3 µg/kg bw/day (lung cancer);
5.2 µg/kg bw/day (bladder cancer);
5.4 µg/kg bw per day (skin lesions)

http://apps.who.int/iris/bitstream/10665/44514/1/WHO_TRS_959_eng.pdf

Methyl mercury

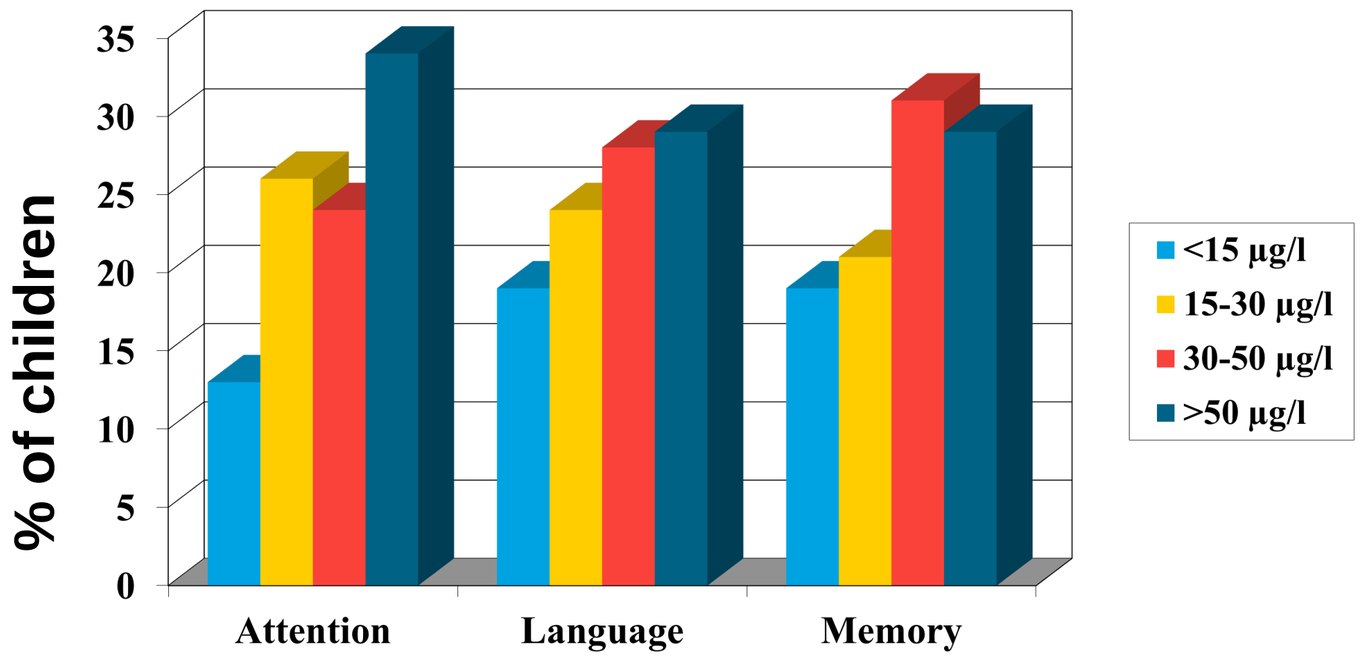
- In 2004 JECFA established a tolerable intake of 1.6 µg/kg bodyweight per week for methylmercury in order to protect the developing fetus from neurotoxic effects.
- For adults, up to about twice the tolerable intake per week would not pose any risk of neurotoxicity.
- Available data did not allow firm conclusions to be drawn for children (up to about 17 years), as they may be more sensitive than adults.
- Hence the tolerable intake established in 2004 applies also to children.

Neurodevelopmental effects of methyl mercury



WHO (1990), EHC 101

Faroe study (Grandjean et al, 1997):
Prenatal mercury exposure levels (cord blood concentrations) of children with test scores in the lowest quartile



15 µg/l cord blood = approx 2.3 µg/g hair

Risk assessment: JECFA

- The JECFA panel noted that 14 µg mercury/g maternal hair was not a NOAEL in the data from the Faroe Islands.
- The maternal hair concentration of 14 µg mercury/g was converted to a maternal blood concentration of 56 µg/l.
- This was converted into a daily intake of 1.5 µg/kg body weight using an equation which incorporated the rate of elimination.
- Assessment factors were introduced to allow for interindividual variability in the hair:blood ratio (2-fold) and in the rate of elimination ($10^{0.5}$ or 3.16-fold).
- Assessment factors for interindividual variability in (toxicodynamic) vulnerability or for incompleteness of the database were considered not to be necessary.
- The daily dose was calculated (1.5/6.32).
- The PTWI was estimated (7 x daily dose) as 1.6 µg/kg body weight per week.

http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/34.pdf

Risk assessment: US

- The US National Research Council used benchmark dose level from the Faroe Islands study (12 µg mercury/g maternal hair) and used a composite assessment factor of 10 (interindividual variability and incompleteness of the data base)
- The resulting exposure limit was 0.1 µg/kg body weight per day (0.7 µg/kg body weight per week).
- Additional probabilistic modelling including the results of the three prospective studies (Faroe Islands, New Zealand, and Seychelles Islands) led basically to the same outcome.

Obrigado!

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency