SITOX
19° Congresso Nazionale
Società Italiana di Tossicologia
Paracelso nel XXI secolo:
«Dosis sola facit, ut venenum non fit»
BOLOGNA
11-12 Febbraio 2020
Savoia Regency Hotel

IN SILICO TOXICITY PREDICTIONS FOR DATA-POOR CHEMICALS
APPLICATIONS IN THE PHARMACEUTICAL AREA

DR. CARLA LANDOLFI, ERT
European Registered Toxicology

carla.landolfi@toxhub-consulting.com

Toxicological Risk Assessment

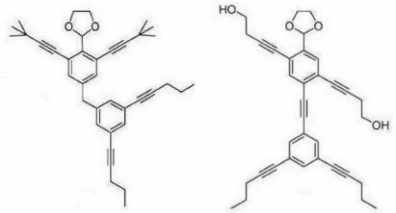
Safety Limits Calculation

Gathering of toxicological information by litterature search to select relevant data:

- *Mutagenicity*
- *PoD from repeated toxicity studies*

Unfortunately in the most of cases no toxicological data are available

Data-poor chemicals



KEEP CALM AND ASK A CHEMOINFORMATIC

DATA-POOR CHEMICALS IN PHARMA AREA

Active Pharmaceutical Ingredient Synthesis

Potential Genotoxic Impurities

Clining Validation Procedures

Cross-contamination by Isolated Process Intermediates

Workers' protection procedures

Exposure to Isolated Process Intermediates

Formulation Development

Degradation products

Packaging Quality

Extractables & Leachables characterization

DATA-POOR CHEMICALS CAN BE:

- ✓ *Potential Genotoxic Impurities in Human and Veterinary drugs*
- ✓ *Degradation products in Human and Veterinary drugs*
- ✓ *Extractables & Leachables*
- ✓ *Isolated Process Intermediates to manage according to the cleaning procedures*
- ✓ *Isolated Process Intermediates to manage protecting worker health*

DATA-POOR CHEMICALS CAN BE:

- ✓ *Potential Genotoxic Impurities in Human and Veterinary drugs*
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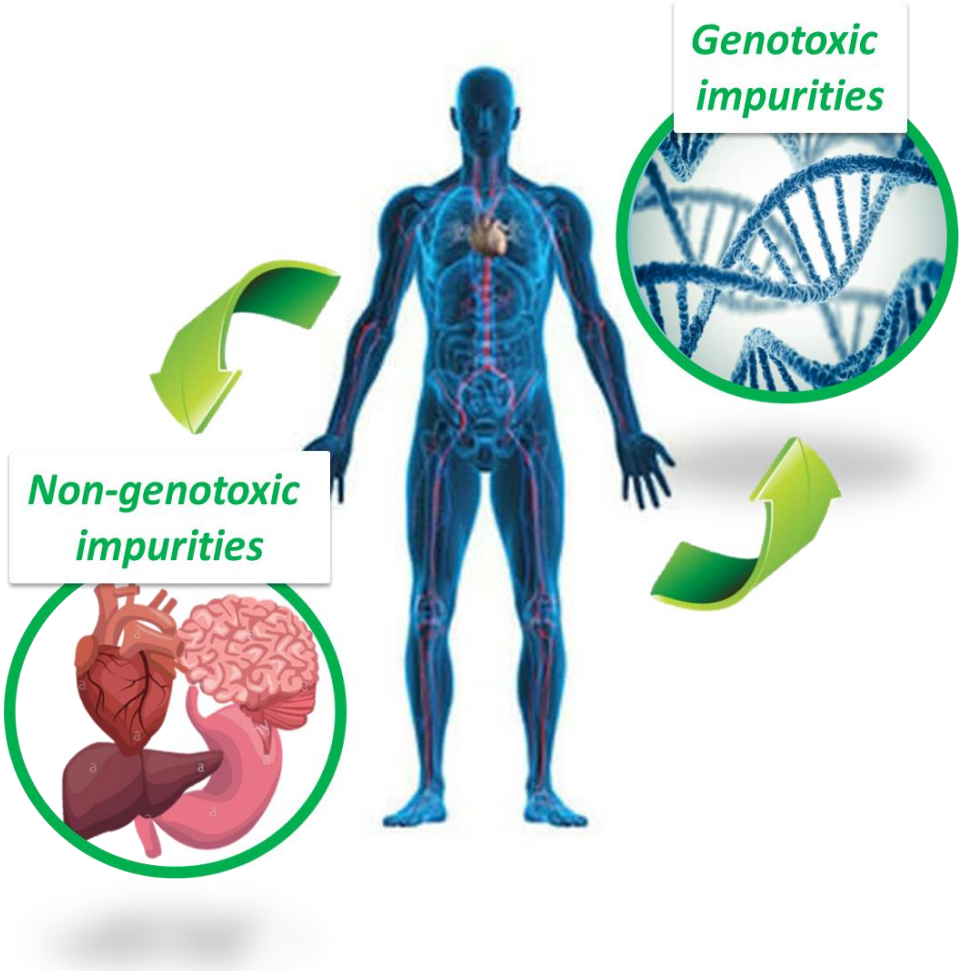
Pharmaceutical Impurities

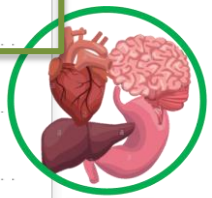


The presence of impurities, even in trace amount, may influence the efficacy and safety of pharmaceutical product.

"The control of impurities is currently a critical issue to the pharmaceutical industry"

Q3A - Q3D Impurities

Code	Document Title	Previously coded
Q3A(R2)	Impurities in New Drug Substances	
Q3B(R2)	Impurities in New Drug Products	
Q3C(R6)	Impurities: Guideline for Residual Solvents	Q3C, Q3C(M)
Q3C(R7)	Impurities: Guideline for Residual Solvents	
Q3D	Guideline for Elemental Impurities	
Q3D training	Implementation of Guideline for Elemental Impurities	

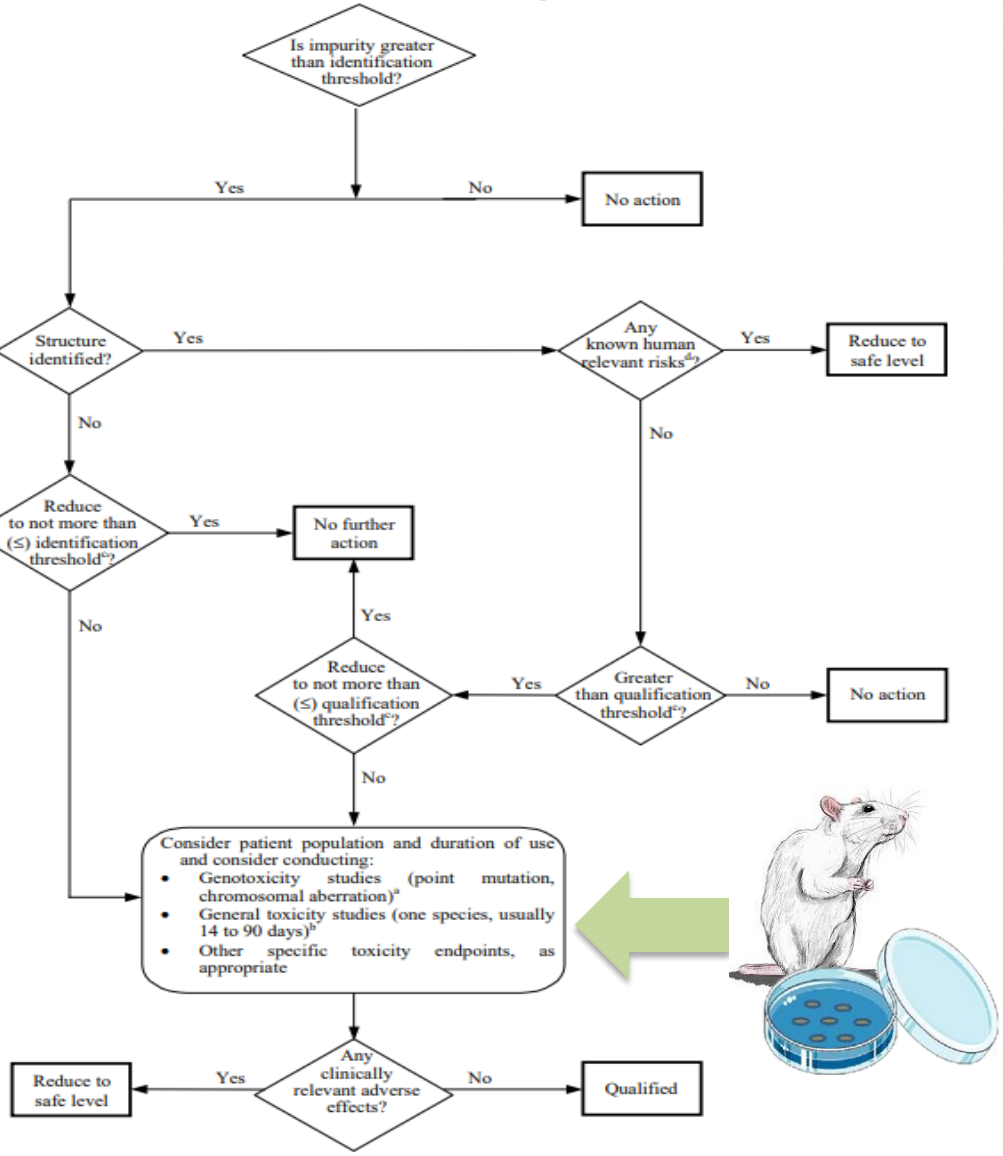


M7 Genotoxic Impurities

Code	Document Title	Previously coded
M7(R1)	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	
M7(R2)	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	

Non Genotoxic Impurities - ICH Q3A/B

Attachment 3: Decision Tree for Identification and Qualification



"Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified."

Attachment 1: Thresholds

Maximum Daily Dose[1]	Reporting Threshold[2,3]	Identification Threshold[3]	Qualification Threshold[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Attachment 1: Thresholds for Degradation Products in New Drug Products

Reporting Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
≤ 1 g	0.1%
> 1 g	0.05%

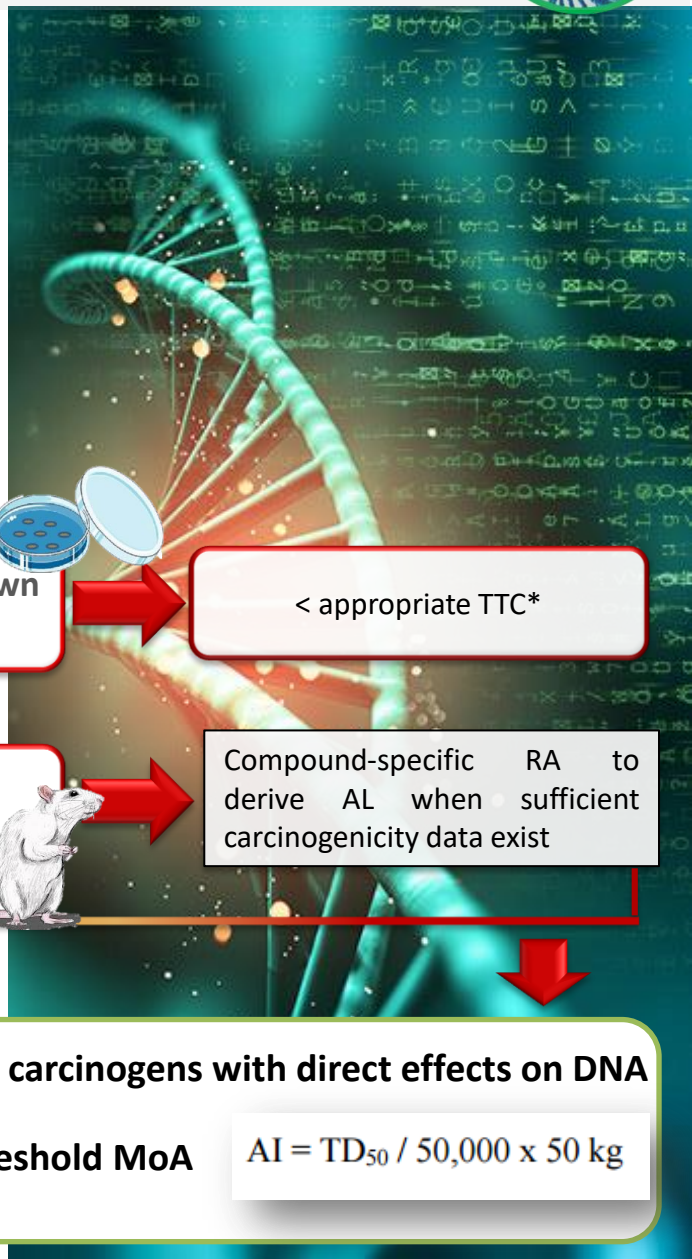
Identification Thresholds

Maximum Daily Dose[1]	Threshold[2, 3]
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

Maximum Daily Dose[1]	Threshold[2,3]
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

Potential Genotoxic Impurities - ICH M7



Drug substance and drug product impurity identification

↓

Hazard assessment

↓

Are genotoxicity experimental data available?

↓

Is the impurity mutagenic?

Yes → **Category 2** — Known mutagens with unknown carcinogenic potential → < appropriate TTC*

No ↓

Is the impurity carcinogenic?

Yes → **Category 1** — Known carcinogens → Compound-specific RA to derive AL when sufficient carcinogenicity data exist

Mutagens and carcinogens with indirect effects on DNA

Threshold MoA

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

Genotoxic carcinogens with direct effects on DNA

Non-threshold MoA

$$AI = TD_{50} / 50{,}000 \times 50\ kg$$

Potential Genotoxic Impurities - ICH M7

Drug substance and drug product impurity identification

↓

Hazard assessment

↓

Are genotoxicity experimental data available?

↓ **No**

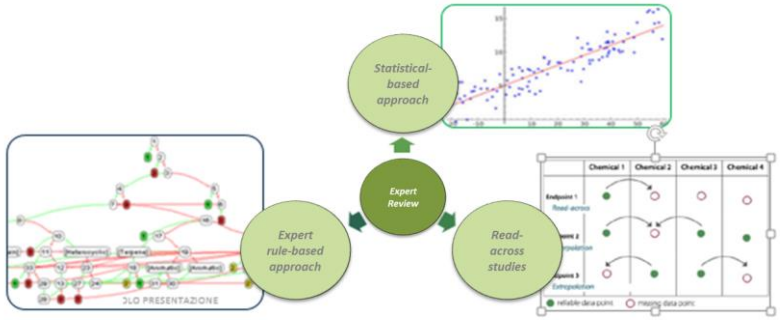
Is the impurity mutagenic?

Data-poor chemical

QSAR

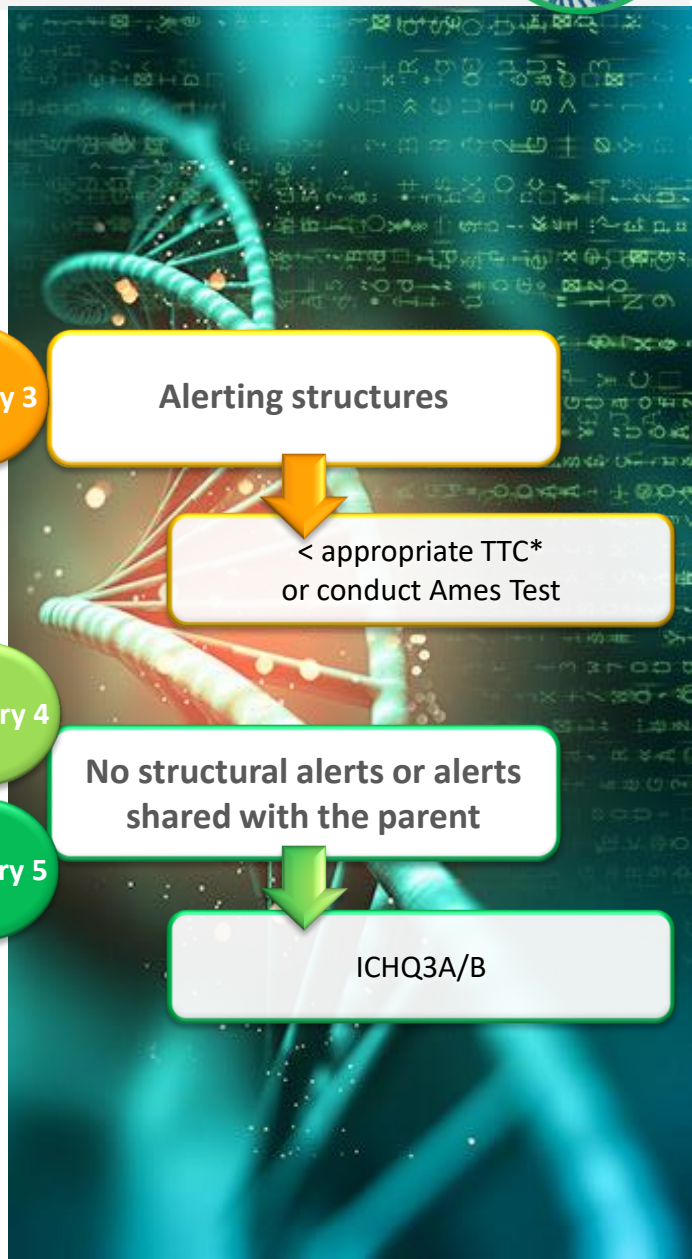
- Mutagenicity potential

The computational toxicology assessment should be performed using two different (Q)SAR methodologies to predict bacterial mutagenicity



It is well known that a single model does not work well
More accurate predictions can be achieved using **multiple models** and **multiple approaches** to have improvement in accuracy, specificity and reliability of the predictions following a step-by-step procedure

Potential Genotoxic Impurities - ICH M7



Drug substance and drug product impurity identification

↓

Hazard assessment

↓

Are genotoxicity experimental data available?

↓ **No**

Is the impurity mutagenic?

Data-poor chemical

QSAR
- Mutagenicity potential

(+)ve

(-)ve

Category 3

Alerting structures

< appropriate TTC*
or conduct Ames Test

Category 4

No structural alerts or alerts shared with the parent

Category 5

ICHQ3A/B

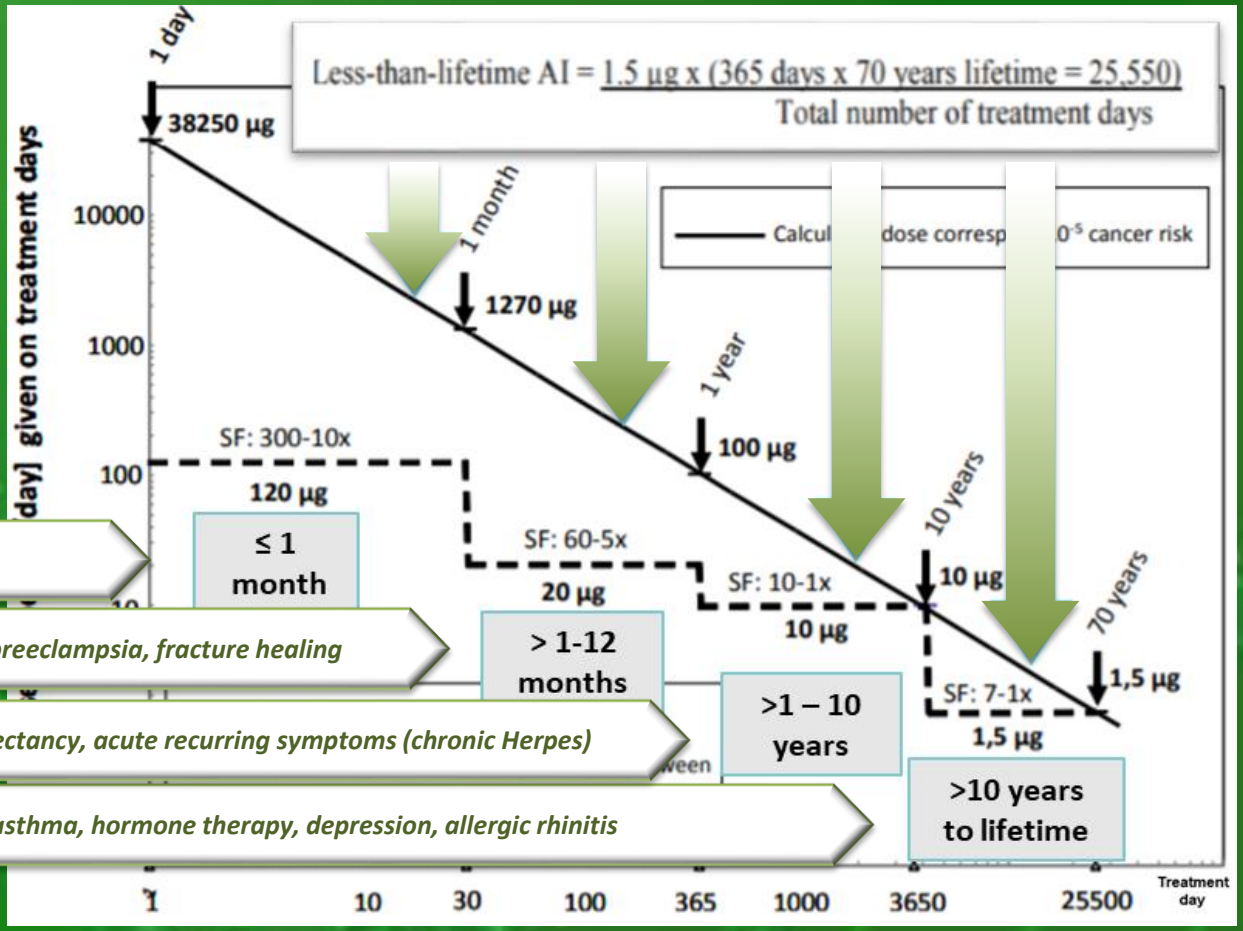
DEFINITION OF ACCEPTABLE SAFETY LIMITS

Threshold of toxicological concern (TTC)

A generic TTC value of 1.5 µg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals, below which there is a very low probability of an appreciable risk to human health

The limit of 1.5 µg/day is considered **very conservative**. It was obtained:

- by linear extrapolation from rodent carcinogenic dose and
- calculated using most sensitive species, sex and site of tumor
- including high potency compounds
- assuming a lifetime exposure (70 years) and most of the drugs are not given for a lifetime



Drugs used in emergency procedures

Drugs occasionally used : anti-infective, peptic ulcer, preeclampsia, fracture healing

Drugs intermittently used : disease with short life expectancy, acute recurring symptoms (chronic Herpes)

Drugs chronically used: hypertension, dyslipidaemia, asthma, hormone therapy, depression, allergic rhinitis

DATA-POOR CHEMICALS CAN BE:

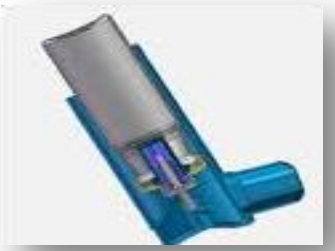
- ✓ *Potential Genotoxic Impurities in Human and Veterinary drugs*
- ✓ *Degradation products in Human and Veterinary drugs*
- ✓ ***Extractables & Leachables***
- ✓ *Isolated Process Intermediates to manage according to the cleaning procedures*
- ✓ *Isolated Process Intermediates to managed protecting worker health*

EXTRACTABLES & LEACHABLES - DEFINITIONS

EXTRACTABLES

*"Compounds which can be **extracted** from individual components of the container/closure system (CCS) under appropriate solvent and temperature conditions simulating a 'worst case' leachable situation"*

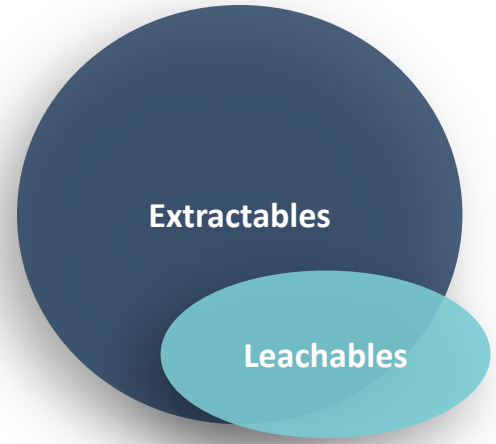
- ✓ *Possible impact*
- ✓ *Test the material*



LEACHABLES

*"Compounds that **migrate** from the container/closure system of the drug product under normal in-use storage conditions and to which a patient can be exposed during intake of the drug"*

- ✓ *Actual impact*
- ✓ *Test the final product*



"Leachables are typically a subset of extractables"

REGULATIONS

No harmonized guidances for E&L in pharmaceutical products are available

ICH Q3A/B → not applicable!

- ✓ ICH Q3A/B thresholds are for DS-/DP-related impurities
- ✓ E&L are contaminants and not drug- or process-related impurities
- ✓ They have different hazard profiles than the API
- ✓ They cannot be qualified as a % of API in the DP

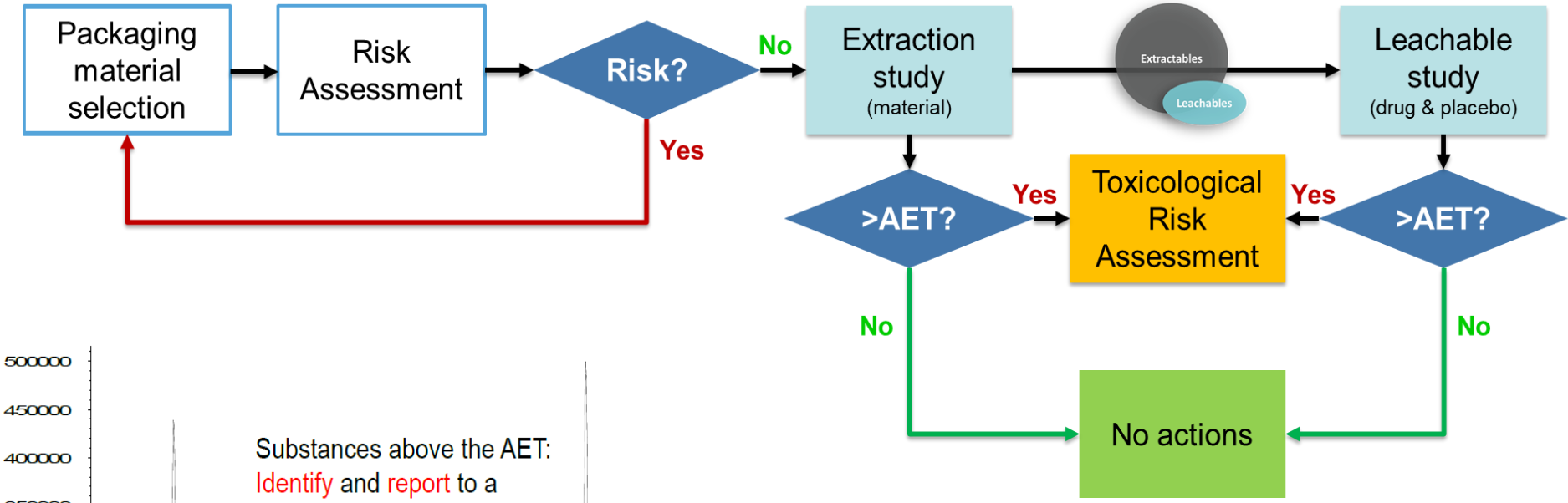
ICH M7

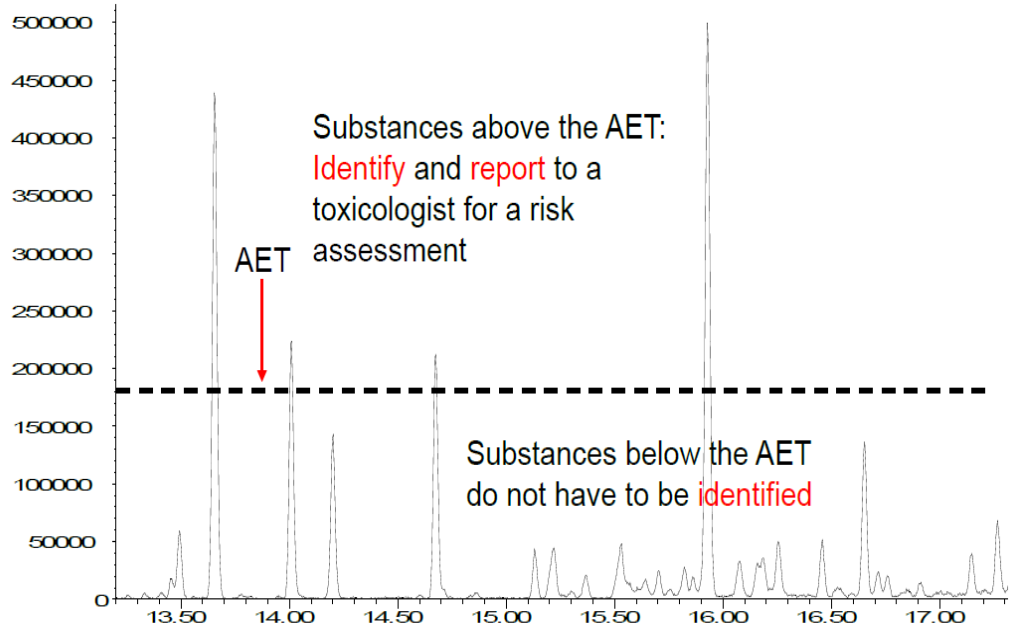
"Application of this guideline to leachables associated with drug product packaging is not intended, but the safety risk assessment principles outlined in this guideline for limiting potential carcinogenic risk can be used if warranted"

It is a Working Group on Leachables and Extractables currently in operation

- ➢ Orally Inhaled and Nasal Drug Products (OINDP)
- ➢ Parenteral and Ophthalmic Drug Products (PODP)

KEY PRINCIPLES OF E&L RISK ASSESSMENT



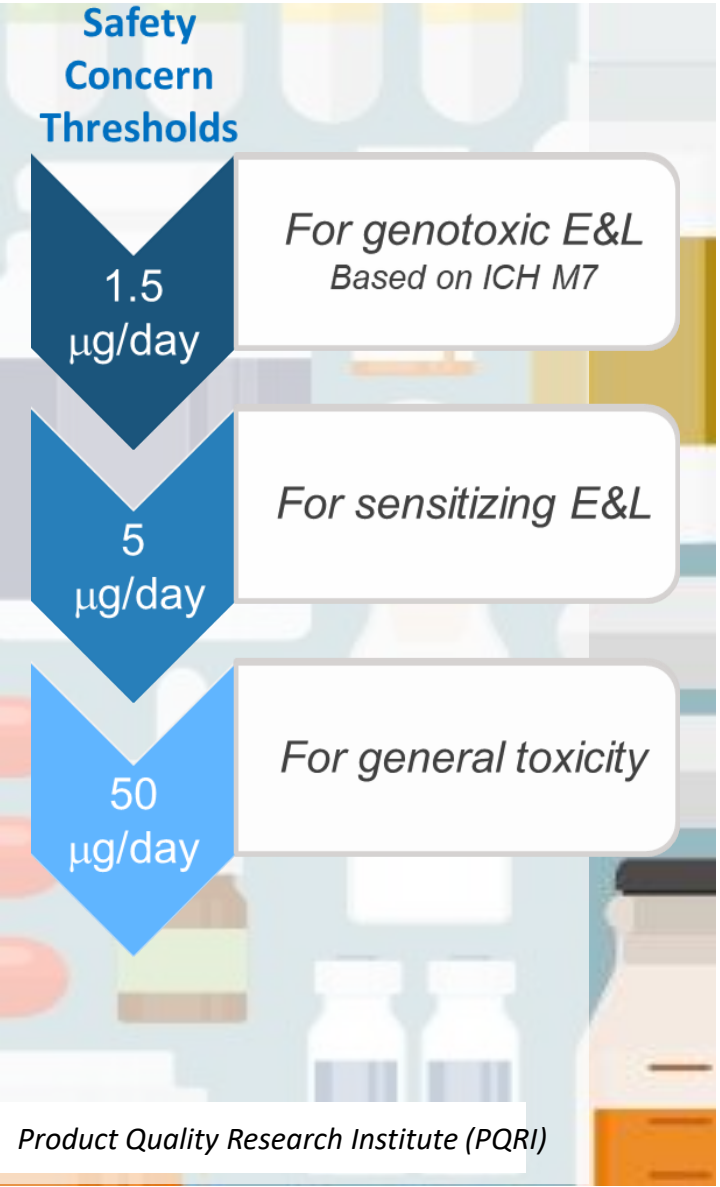


AET: analitical evaluation threshold

AET is derived by Safety Concern Threshold (SCT) considering route of administration, frequency and duration of drug product administration, posology, dosages

AET = SCT / MDI

KEY PRINCIPLES OF E&L RISK ASSESSMENT



Product Quality Research Institute (PQRI)

KEY PRINCIPLES OF E&L RISK ASSESSMENT

Safety Concern Thresholds

1.5 µg/day — *For genotoxic E&L* — *Based on ICH M7*

5 µg/day — For sensitizing E&L

50 µg/day — For gene

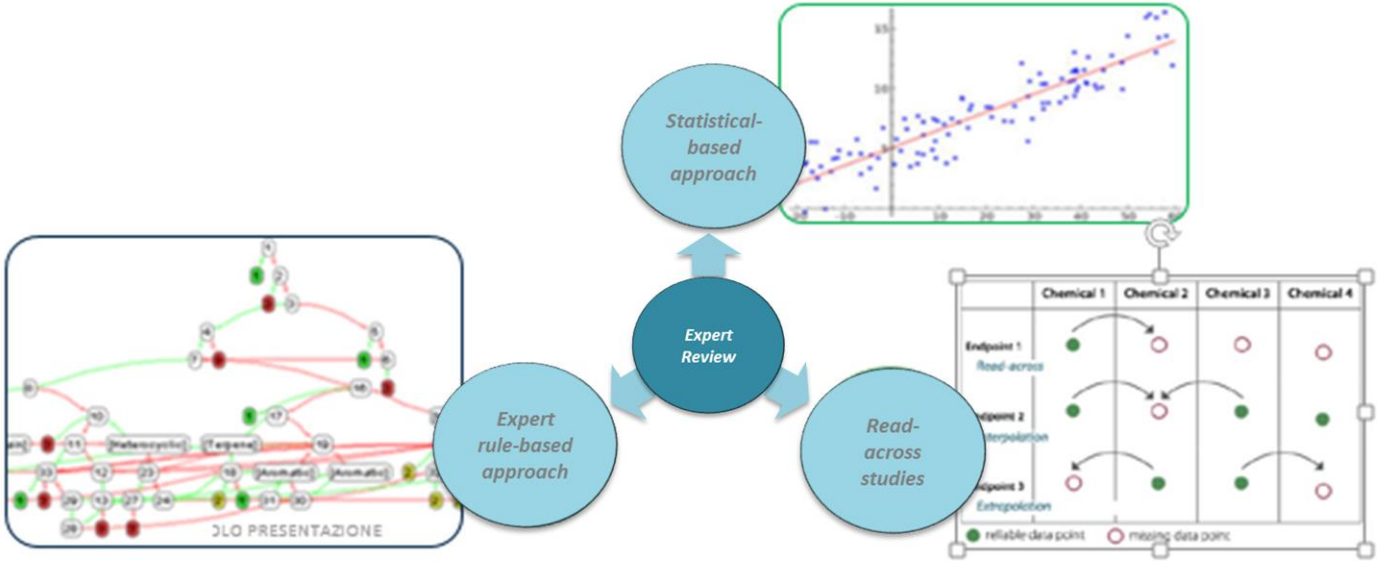
Exposure ≤ SCT — No action

Exposure ≥ SCT → Assess the genotoxic potential

- Experimental data
- QSAR

+ve → Setting safety limits according to ICH M7

-ve → No action



KEY PRINCIPLES OF E&L RISK ASSESSMENT

Safety Concern Thresholds

- 1.5 µg/day — *For genotoxic E&L* — *Based on ICH M7*
- 5 µg/day — *For sensitizing E&L*
- 50 µg/day — *For general toxicity*

Exposure ≤ SCT
No action

Exposure ≥ SCT → Assess the genotoxic potential
- Experimental data
- QSAR

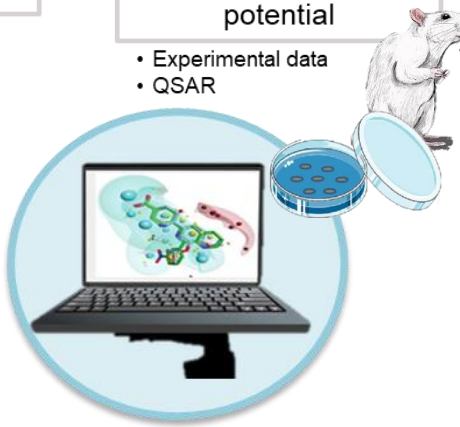
+ve → Setting safety limits according to ICH M7

-ve → No action

Exposure ≥ SCT → Assess the sensitizing/irritant potential
- Experimental data
- QSAR

+ve → Setting safety limits according to the results

-ve → No action



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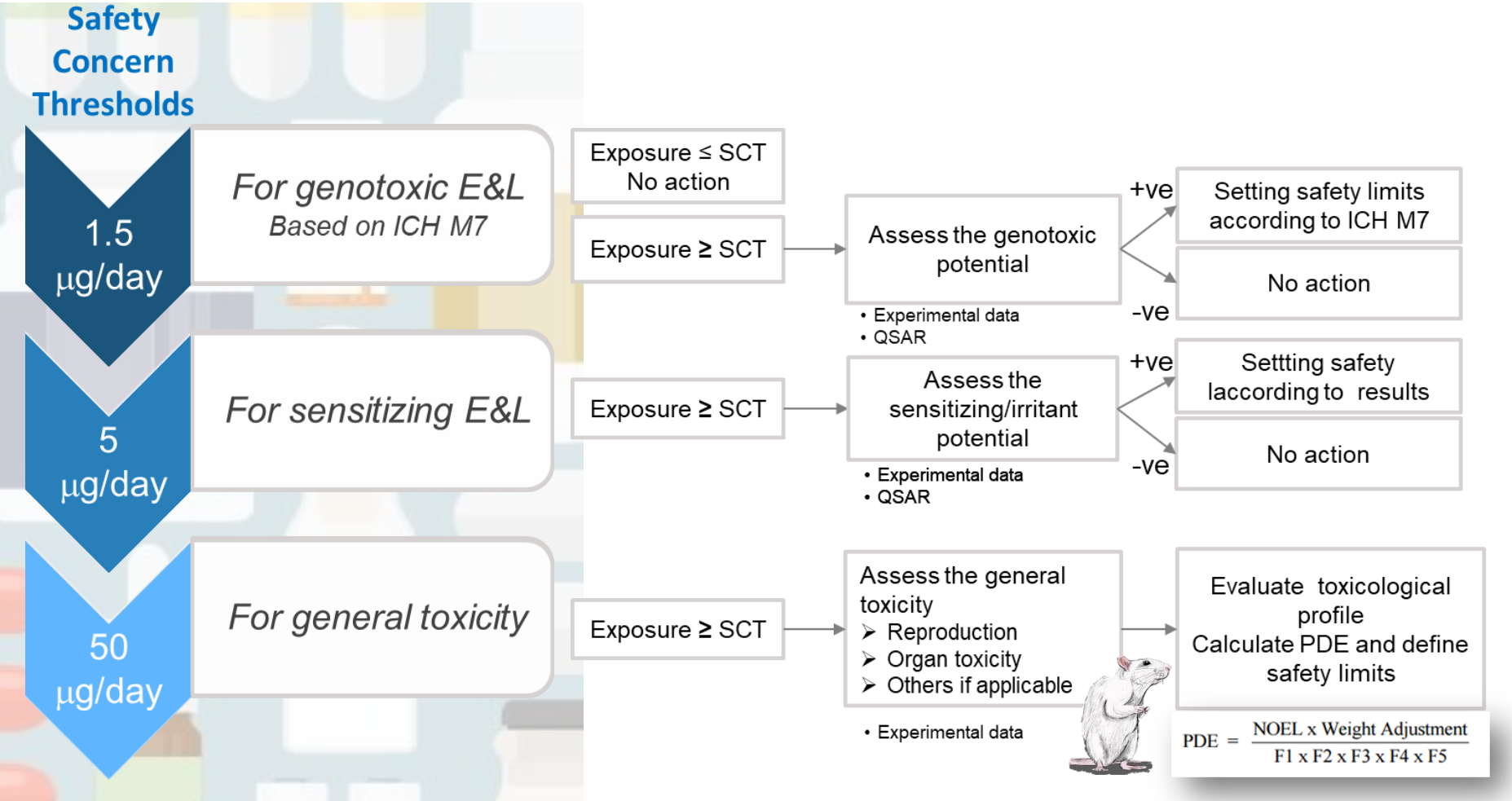

KEY PRINCIPLES OF E&L RISK ASSESSMENT

Safety Concern Thresholds

- 1.5 µg/day — *For genotoxic E&L* — *Based on ICH M7*
- 5 µg/day — *For sensitizing E&L*
- 50 µg/day — *For general toxicity*

*Cramer classes**

Concept	Value [µg/person/day]
Cramer Class I	1800
Cramer Class II	540
Cramer Class III	90

Class I = Substances with simple chemical structures and for which efficient modes of metabolism exist, suggesting a low order of oral toxicity

Class II = Substances which possess structures that are less innocuous than Class I substances, but do not contain structural features suggestive of toxicity like those substances in Class III

Class III = Substances with chemical structures that permit no strong initial presumption of safety or may even suggest significant toxicity or have reactive functional groups

*QSAR ToolBox/ToxTree

Exposure ≥ SCT → Assess the general toxicity
- Reproduction
- Organ toxicity
- Others if applicable

- Experimental data
- QSAR

→ Evaluate toxicological profile
Calculate PDE and define safety limits

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

DATA-POOR CHEMICALS CAN BE:

- ✓ *Potential Genotoxic Impurities in Human and Veterinary drugs*
- ✓ *Degradation products in Human and Veterinary drugs*
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- ✓ ***Isolated Process Intermediates to manage according to the cleaning procedures***
- ✓ *Isolated Process Intermediates to managed protecting worker health*

CROSS CONTAMINATION

When different medicinal products are produced in shared facilities, the potential for cross contamination is a major concern for the pharmaceutical industry

The cleaning procedures have to cover all the range of substances produced in the facility including APIs, intermediates and industrial chemicals

REGULATIONS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/CHMP/ CVMP/ SWP/169430/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

Draft Agreed by Safety Working Party	December 2012
Adoption by CVMP for release for consultation	November 2012
Adoption by CHMP for release for consultation	13 December 2012
End of consultation (deadline for comments)	30 June 2013
Adoption by CVMP	11 September 2014
Adopted by Safety Working Party	October 2014
Adoption by CHMP	20 November 2014
Date for coming into effect	01 June 2015

- ICH guideline Q3C (R6) on impurities: guideline for residual solvents
- ICH guideline Q3D (R1) on elemental impurities
- ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 August 2019
EMA/CHMP/ICH/82260/2006
Committee for Human Medicinal Products

ICH guideline Q3C (R6) on impurities: guideline for residual solvents
Step 5


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 March 2019
EMA/CHMP/ICH/353369/2013
Committee for Human Medicinal Products

ICH guideline Q3D (R1) on elemental impurities


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 August 2015
EMA/CHMP/ICH/83812/2013
Committee for Human Medicinal Products

ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
Step 5

Procedure to determine Health-Based Exposure Limits

Chemical categorization in shared facilities

Toxicological characterization

Is the chemical highly sensitizing?

NO

Is the chemical a CMR?

NO

- Experimental data

Identification of *"critical effects"*

Hazards Identified

	YES	NO	UNKNOWN
Genotoxicant	☐	☐	☐
Reproductive developmental toxicant	☐	☐	☐
Carcinogen	☐	☐	☐
Highly sensitizing potential	☐	☐	☐

PoD identification:

- No-Observed-(Adverse)-Effect-Level (NO(A)EL)
- Lowest-Observed-Adverse-Effect-Level (LOAEL)
- Lowest Therapeutic Dose (LTD)

- Experimental data

PDE Calculation

$$\text{PDE (mg/kg bw/day)} = \frac{\text{PoD (mg/kg bw/day) x Mass Adjustment (kg) x } \alpha}{F1 \times F2 \times F3 \times F4 \times F5}$$

Procedure to determine Health-Based Exposure Limits

There is no effective guidance regarding how to address intermediates used within the manufacture of an active

Generally no toxicological information is available

Chemical categorization in shared facilities

Toxicological characterization

Is the chemical highly sensitizing?

Is the chemical a CMR?

Is the chemical a highly toxic compound?

Hazards Identified

	YES	NO	UNKNOWN
Genotoxicant			✓
Reproductive developmental toxicant			✓
Carcinogen			✓
Highly sensitizing potential			✓

Data-poor chemical

QSAR

- Genotoxicity potential
- Sensitizing potential
- General toxicity

As per E&L Safety Concern Thresholds can be applied

1.5 µg/day	*For genotoxic E&L* *Based on ICH M7*
5 µg/day	*For sensitizing E&L*
50 µg/day	*For general toxicity*

DATA-POOR CHEMICALS CAN BE:

- ✓ *Potential Genotoxic Impurities in Human and Veterinary drugs*
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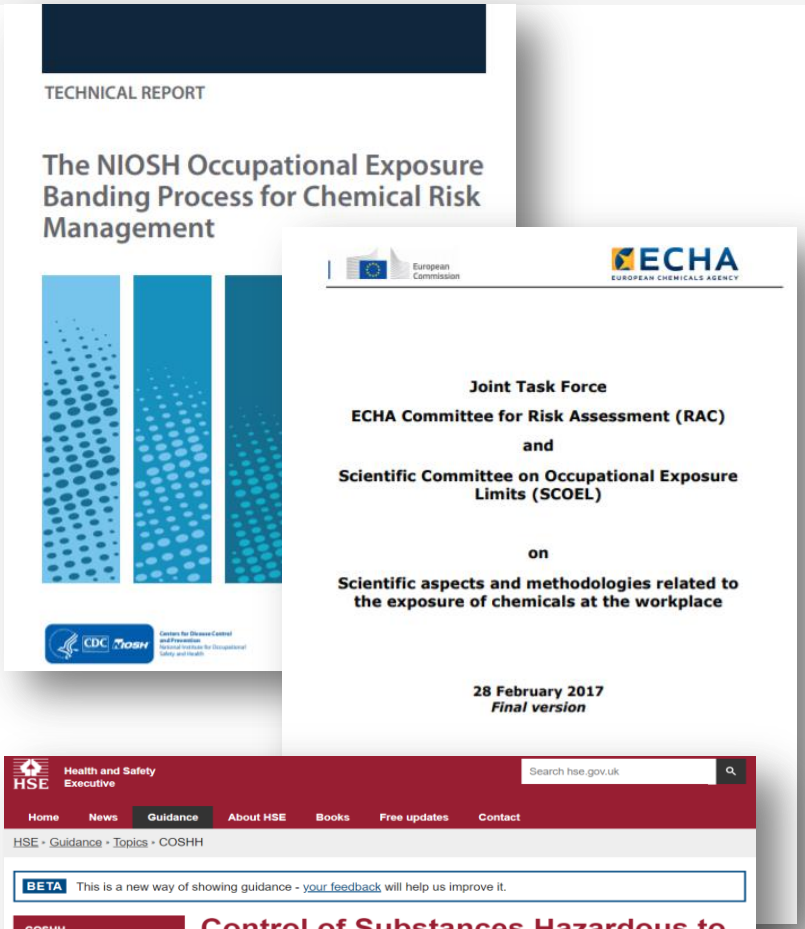
- ✓ *Isolated Process Intermediates to manage according to the cleaning procedures*
- ✓ ***Isolated Process Intermediates to manage protecting worker health***

Occupational Exposure Limits

We need to know how much of a hazardous substance a worker can breathe without harm

Occupational Exposure Limit (OEL) is the concentration in the air to which nearly all workers may be repeatedly exposed, day after day, without adverse health effects to themselves or their children

REGULATIONS

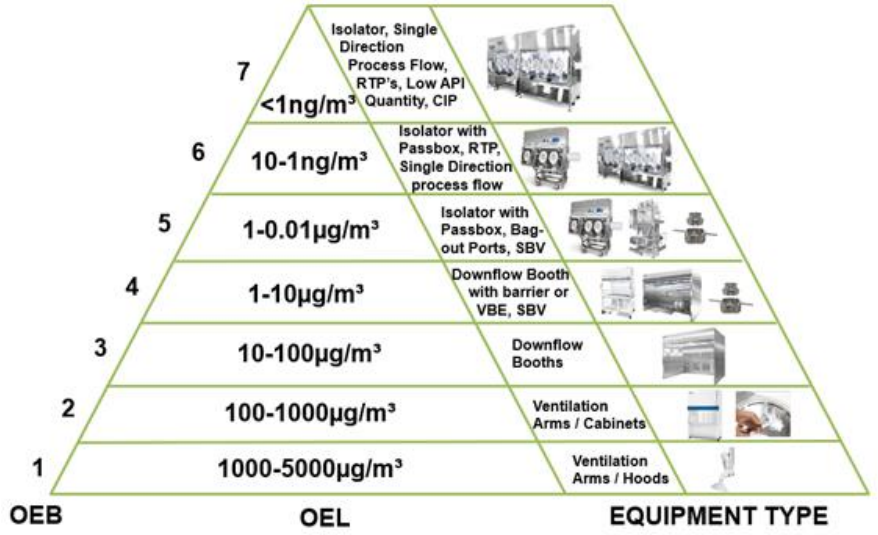


No harmonized guidances are available for OEL determination

Calculate an OEL on a health-based procedure

Assign an Occupational Exposure Banding

Select the appropriate equipment type



PROCEDURES TO DETERMINE HEALTH-BASED OCCUPATIONAL EXPOSURE LIMITS

Identify the chemical

Select physical state of the chemical

Range of bands depends on the physical state: either dust/particle or gas/vapor

Collect all the available data

- Existing OELs
- Toxicological information (in vitro and in vivo)
- Human data
- GHS hazard statement

Is an OEL available? — *Yes* → **Calculate the OEL**

No

Is toxicological information available? — *Yes* → Are they sufficient for an OEL calculation? — *Yes* → **Calculate the OEL**

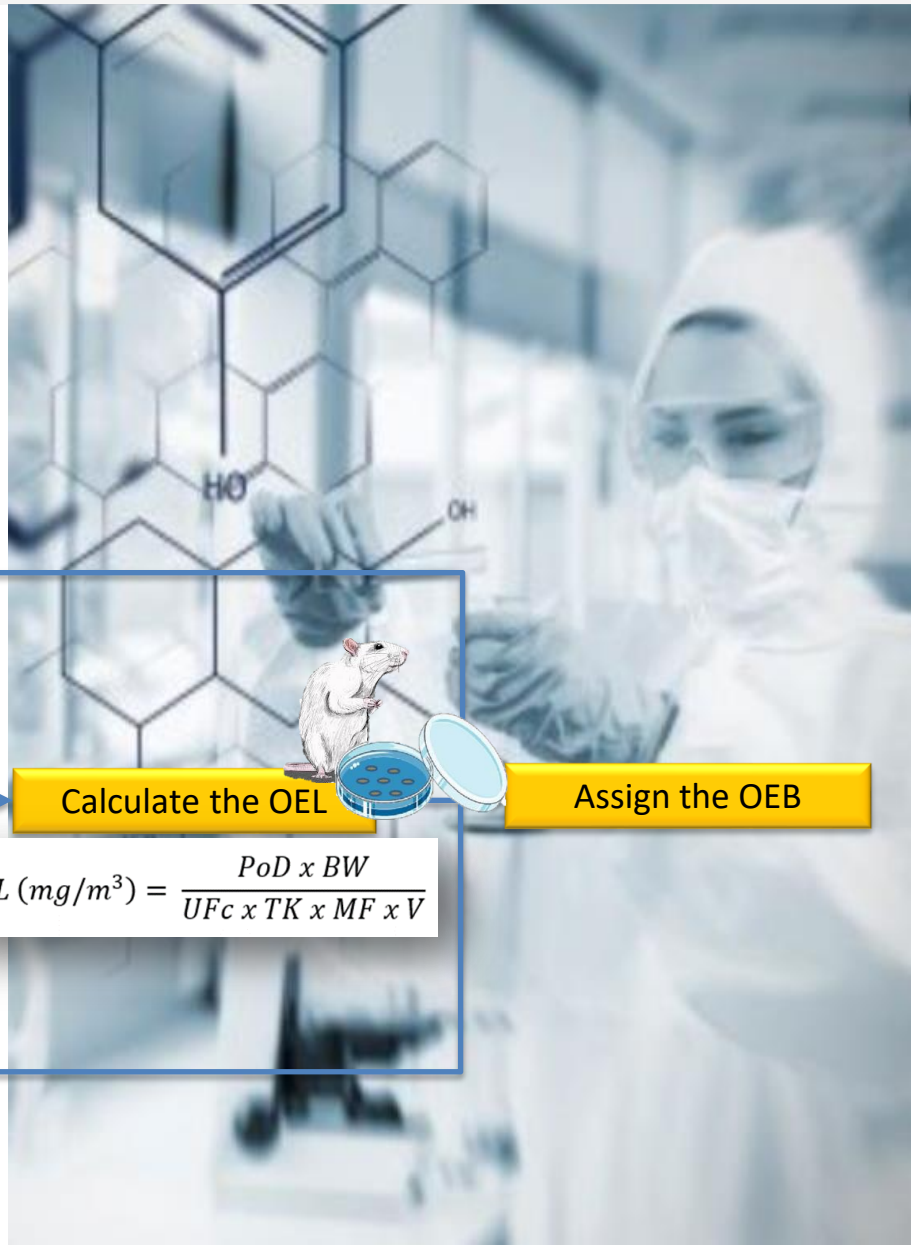
No

- Experimental data:
  - Mutagenicity
  - Sensibilization
  - Repeated toxicity

Are GHS hazard statements available? — *Yes* → **Calculate the OEL**

$$OEL\ (mg/m^3) = \frac{PoD\ x\ BW}{UFc\ x\ TK\ x\ MF\ x\ V}$$

Calculate the OEL → **Assign the OEB**



Procedures to determine Health-Based Occupational Exposure Limits

Identify the chemical

↓

Select physical state of the chemical

Range of bands depends on the physical state: either dust/particle or gas/vapor

↓

Collect all the available data

- Existing OELs
- Toxicological information (in vitro and in vivo)
- Human data
- GHS hazard statement

↓

Is an OEL available?

↓ *No*

Are toxicological information available?

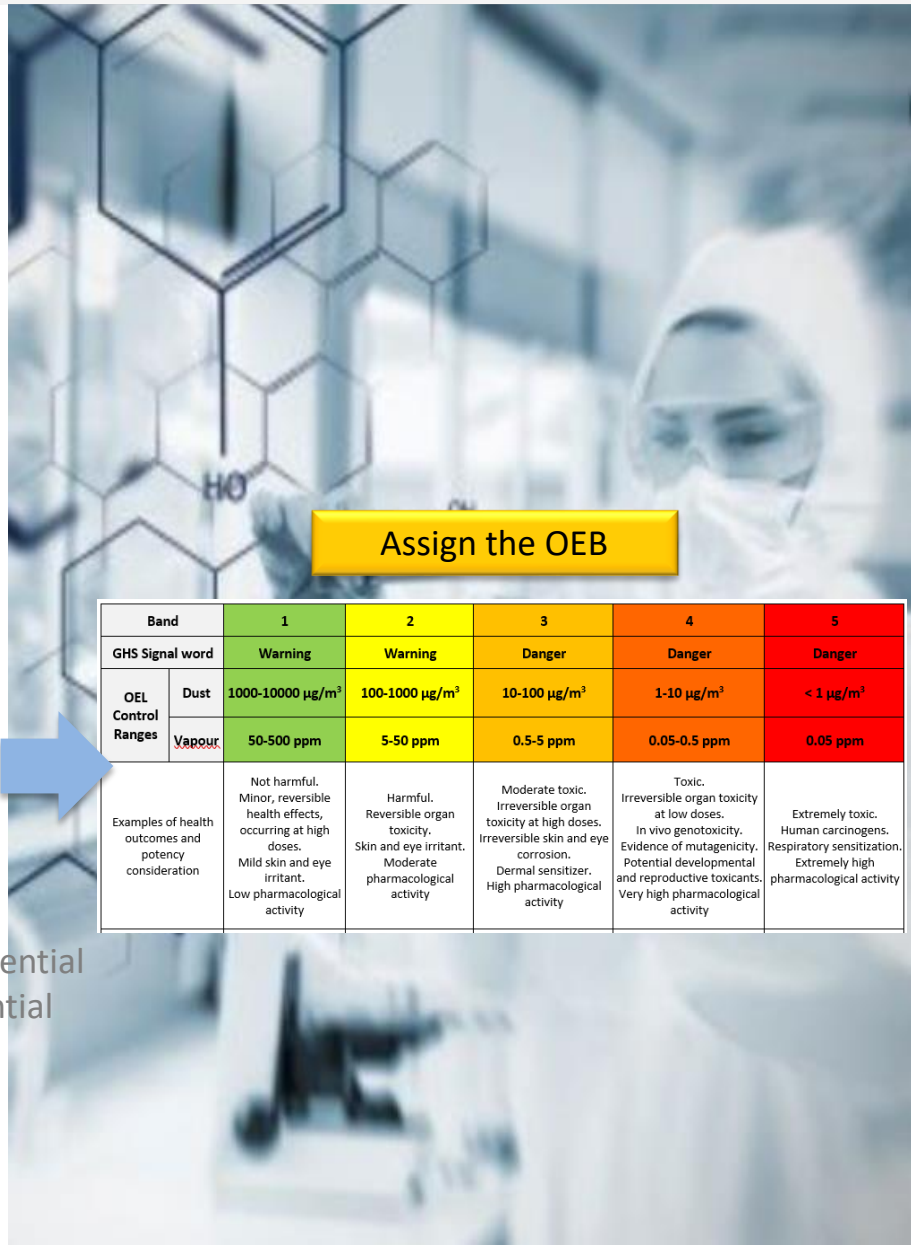
↓ *No*

Are GHS hazard statements available?

Data-poor chemical

QSAR

- Genotoxicity potential
- Sensitizing potential
- General toxicity



Assign the OEB

Band		1	2	3	4	5
GHS Signal word		Warning	Warning	Danger	Danger	Danger
OEL Control Ranges	Dust	1000-10000 µg/m³	100-1000 µg/m³	10-100 µg/m³	1-10 µg/m³	< 1 µg/m³
	Vapour	50-500 ppm	5-50 ppm	0.5-5 ppm	0.05-0.5 ppm	0.05 ppm
Examples of health outcomes and potency consideration		Not harmful. Minor, reversible health effects, occurring at high doses. Mild skin and eye irritant. Low pharmacological activity	Harmful. Reversible organ toxicity. Skin and eye irritant. Moderate pharmacological activity	Moderate toxic. Irreversible organ toxicity at high doses. Irreversible skin and eye corrosion. Dermal sensitizer. High pharmacological activity	Toxic. Irreversible organ toxicity at low doses. In vivo genotoxicity. Evidence of mutagenicity. Potential developmental and reproductive toxicants. Very high pharmacological activity	Extremely toxic. Human carcinogens. Respiratory sensitization. Extremely high pharmacological activity


Thank you
for your attention
H2O
H2O