How to perform a Safety Evaluation – Risk Assessment on Extractables & Leachables

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Sevilla
29 – 30 Nov, 2018

Ir. John Iannone

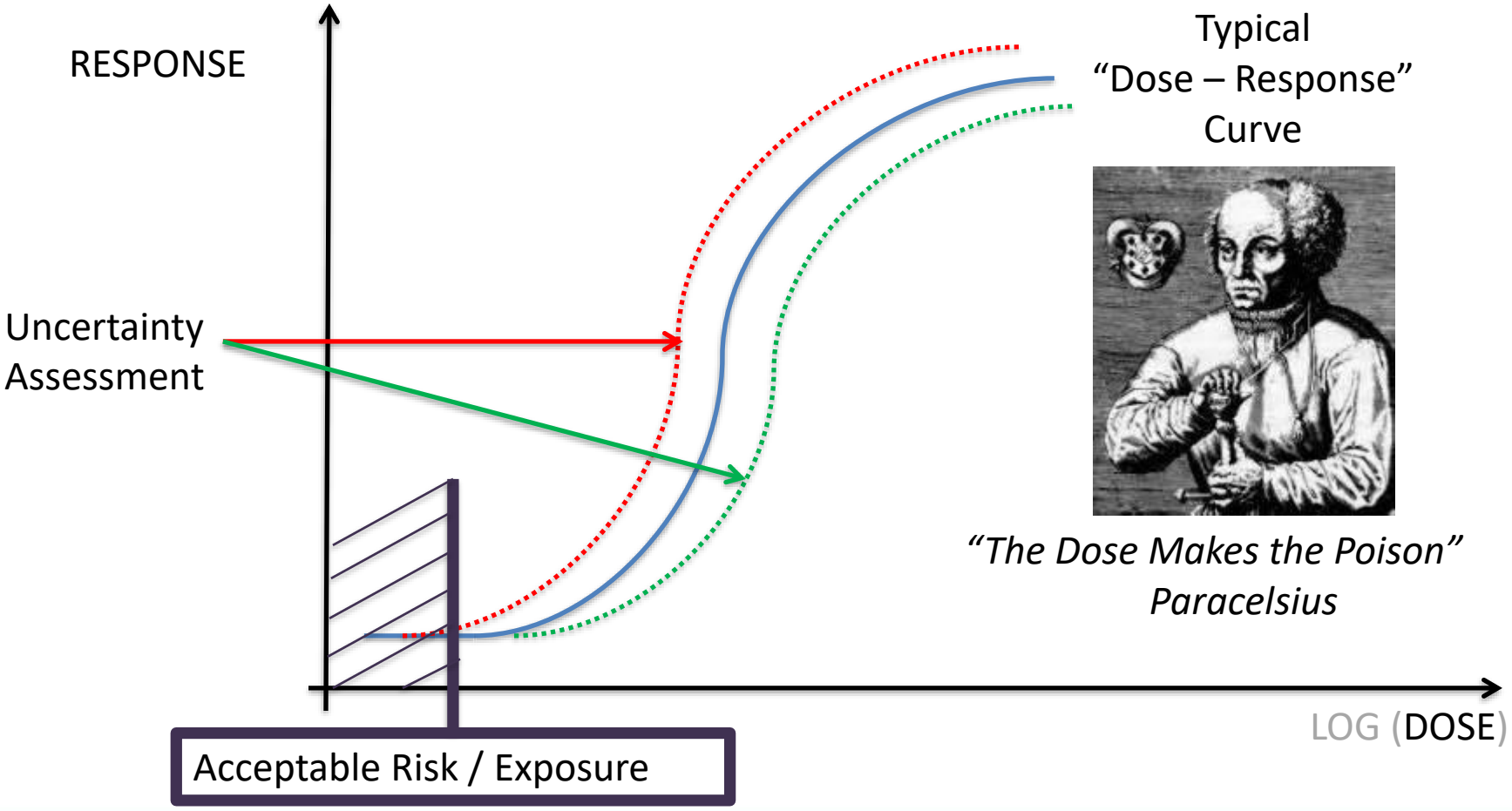
Topics Covered

- Basic Toxicological Principles dose response relationship
- Key Toxicological end-points
- General Impurity Qualification
- Solvents – Permissible Limits
- Mutagenic Impurities
- E&Ls
- Conclusions

THE DOSE-RESPONSE RELATIONSHIP

"The Dose Makes the Poison"
Paracelsius

THE DOSE-RESPONSE RELATIONSHIP

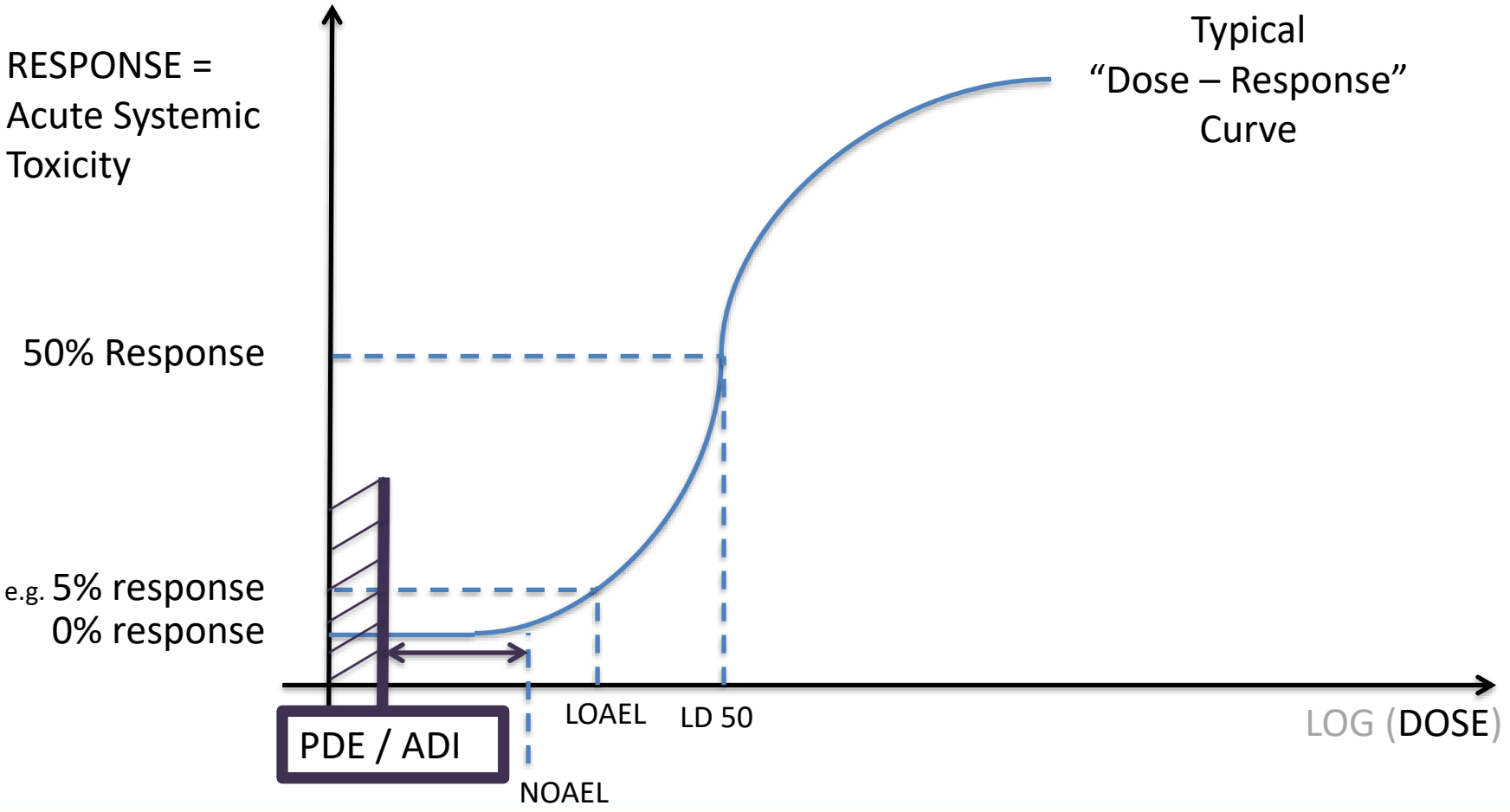


Typical "Dose – Response" Curve

"The Dose Makes the Poison"
Paracelsius

THE DOSE-RESPONSE RELATIONSHIP

EXAMPLE: ACCUTE SYSTEMIC TOXICITY



KEY ENDPOINTS

Toxicological endpoints to be considered (non – limitative):

Acute Systemic Toxicity → Often most readily available information

Genotoxicity

Irritation

Sensitization

Reproduction Toxicity

Carcinogenicity

} The "BIG FIVE"

Acute Systemic Toxicity

Definition:

Acute systemic toxicity testing is the **estimation** of the **human hazard potential** of a substance by determining its **systemic toxicity** in a test system (currently animals) following an **acute exposure**.

Source: alttox.org

Genotoxicity

Definition:

Genotoxicity is a broad term referring to **genetic damage**. This may be at a ***DNA level*** i.e. mutagenicity, or at a ***chromosomal level*** e.g. Clastogenicity / Aneugenicity.

This term has in the context of **ICH M7** been **replaced** by the more specific term mutagenicity that relates specifically to **DNA mutation**.

Carcinogenicity

Definition:

The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which **induce cancer** or **increase its incidence**".

An alternate definition is that carcinogenic substances are ones that "**induce tumors** (benign or malignant), **increase** their **incidence or malignancy**, or **shorten** the **time** to **tumor occurrence** when they are inhaled, injected, dermally applied, or ingested

Carcinogens are classified according to their mode of action as *genotoxic* or *non-genotoxic* carcinogens.

General Impurity Qualification

ICH Q3A / Q3B

Qualification

‘The process of **acquiring** & **evaluating** data
that establishes the **biological safety**
of an **individual impurity** *or* a **given impurity profile**
at the level(s) specified.’

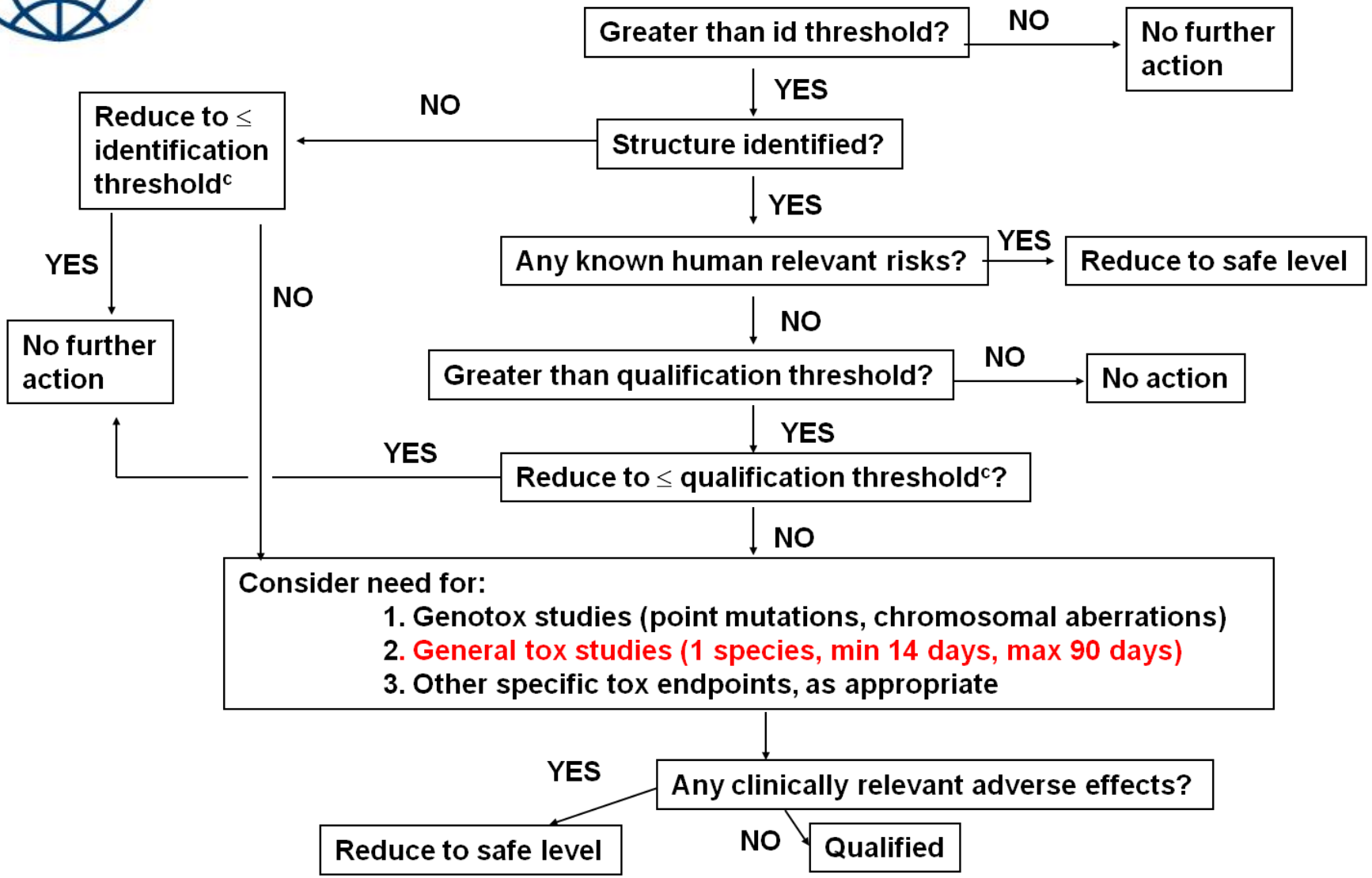
Qualification of Impurities – Basic points

- **Before** actives go into clinical trials the **impurities** present **must be qualified** in **preclinical** studies.
  - Typically includes a 14 -28 day study in rodents *(amongst others)*

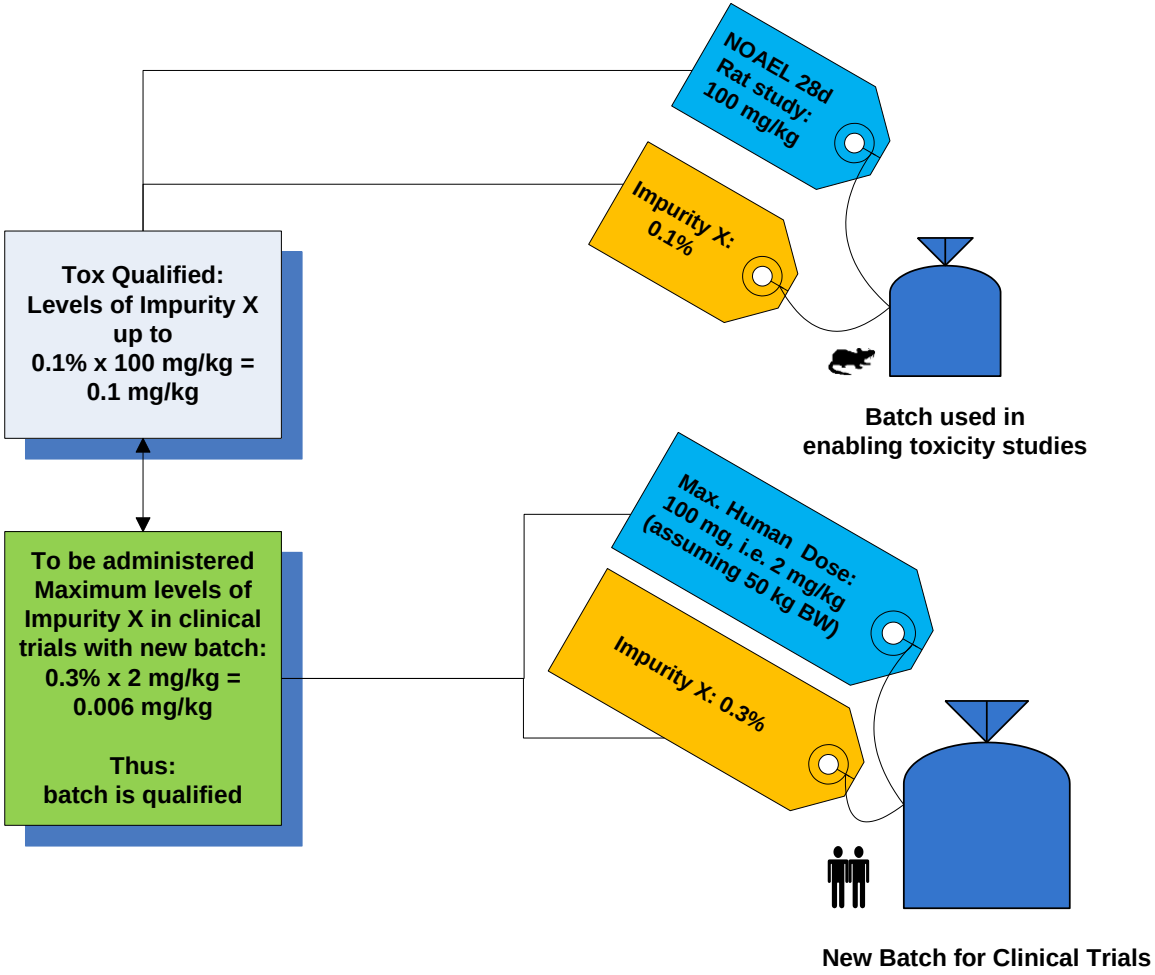
- Qualification of Impurities is described in ICH Q3A (API) & ICH Q3B (drug product)
  - **Process** described & illustrated through **Decision tree**
  - Defines thresholds for reporting, identification & qualification of impurities for Marketing Authorisation Applications
    - *E.g. For a drug dosed at up to 2g/day, the threshold for qualification for impurities is 0.15% or 1.0mg/day, whichever is lower*

- Important to note that ICH limits are not appropriate during drug development; guidance is likely to be company-specific

ICH decision tree for qualification studies

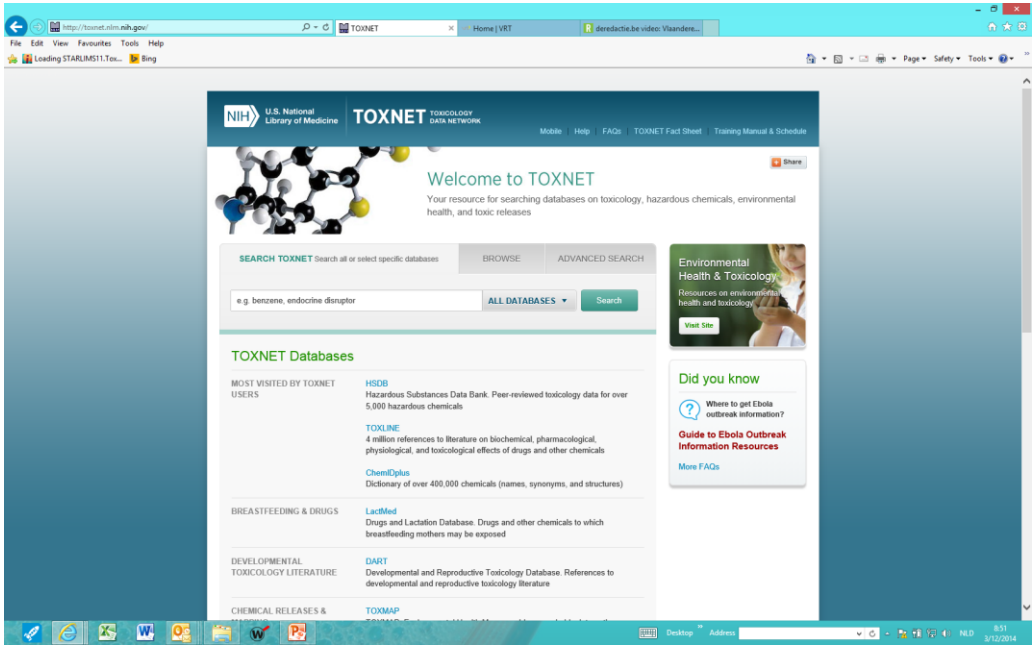


Basic qualification assessment



DERIVING LIMITS FROM TOX DATA MOVE!

Where can we find the Toxicological Data to be used in the assessment?



http://toxnet.nlm.nih.gov
http://echa.europa.eu/
http://www.epa.gov/hpvis/
http://webnet.oecd.org/hpv/
http://www.inchem.org/
http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm

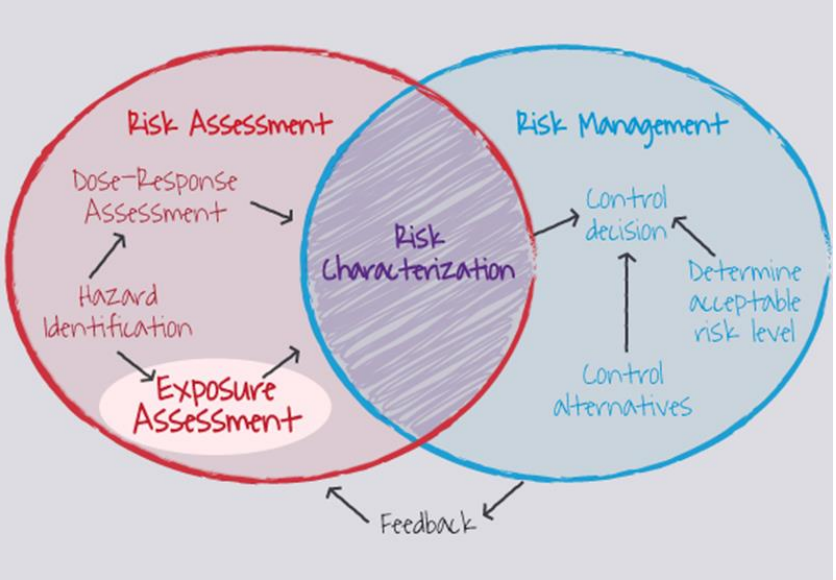
Role of Toxicologist:

- Find as much information as possible
- On all possible Toxicological End-Points
- Evaluate the weight of Evidence
- Judge the Quality of Data!!

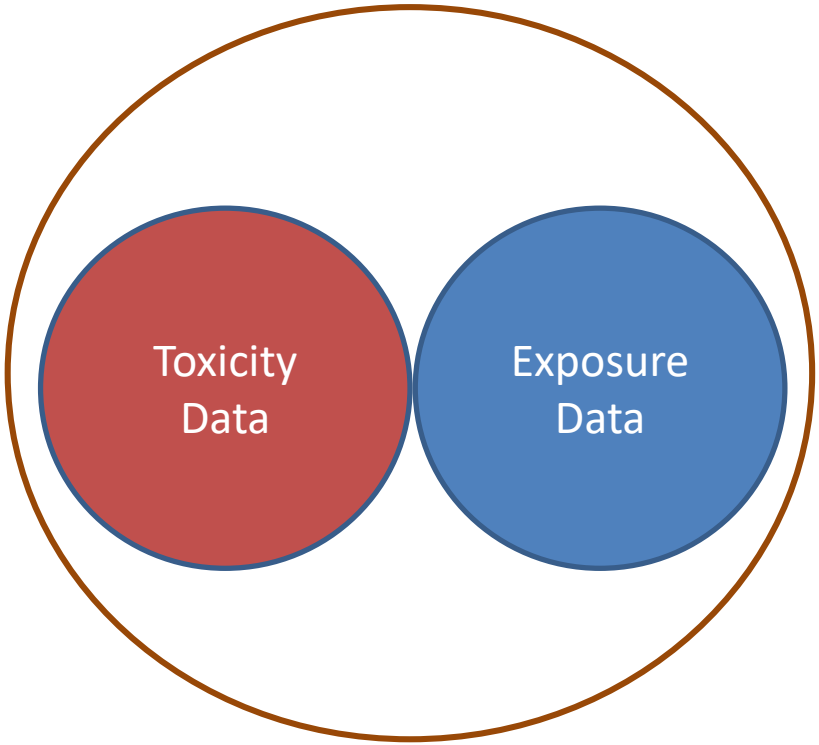
DERIVING PDE'S FROM TOX DATA

How to evaluate the Quality and Relevancy of Tox Data?

- Duration of Studies
- Nature of Studies
- Quality of the dose-response established
- Route of Administration
- Mechanisms
- Relevance to Humans

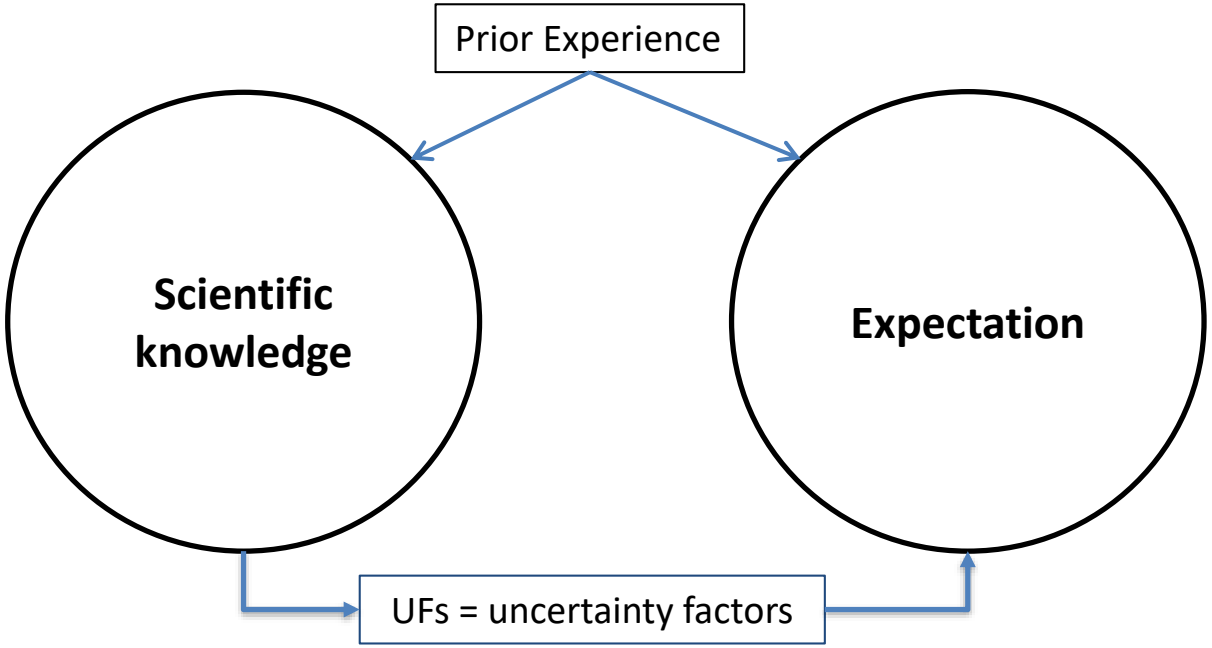


Toxicological Risk Assessment

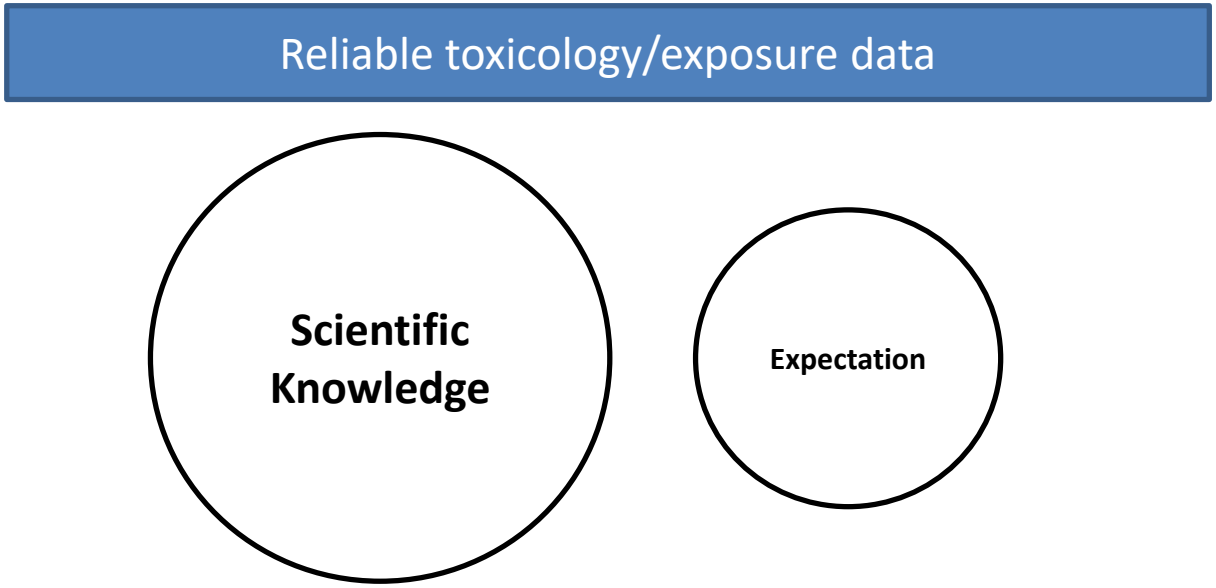


How significant is expert judgement (e.g., UFs)?

What is Expert Judgement?



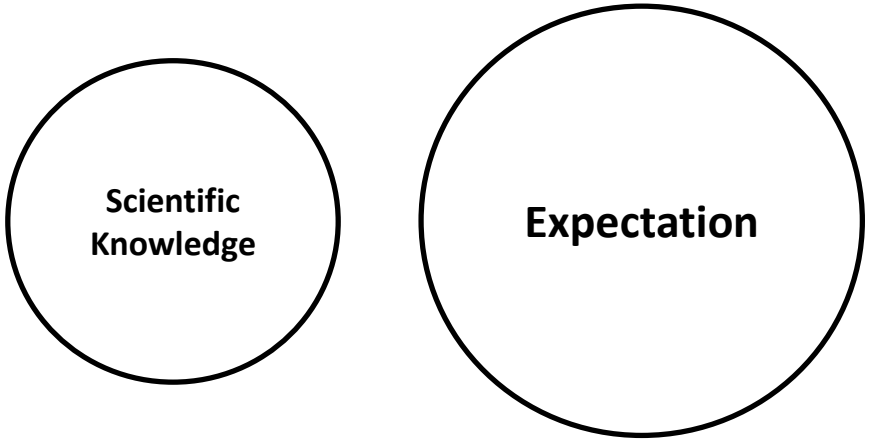
What is Expert Judgement?



Uncertainty is reduced as data reliability increases

What is Expert Judgement?

Unreliable toxicology/exposure data



Uncertainty increases as data reliability decreases

Permissible Daily Exposure (PDEs)

ICH Q3C(R4): Residual Solvents

DERIVING PDE'S FROM TOX DATA

ICH Q3C Appendix 3
WHO EHC 170

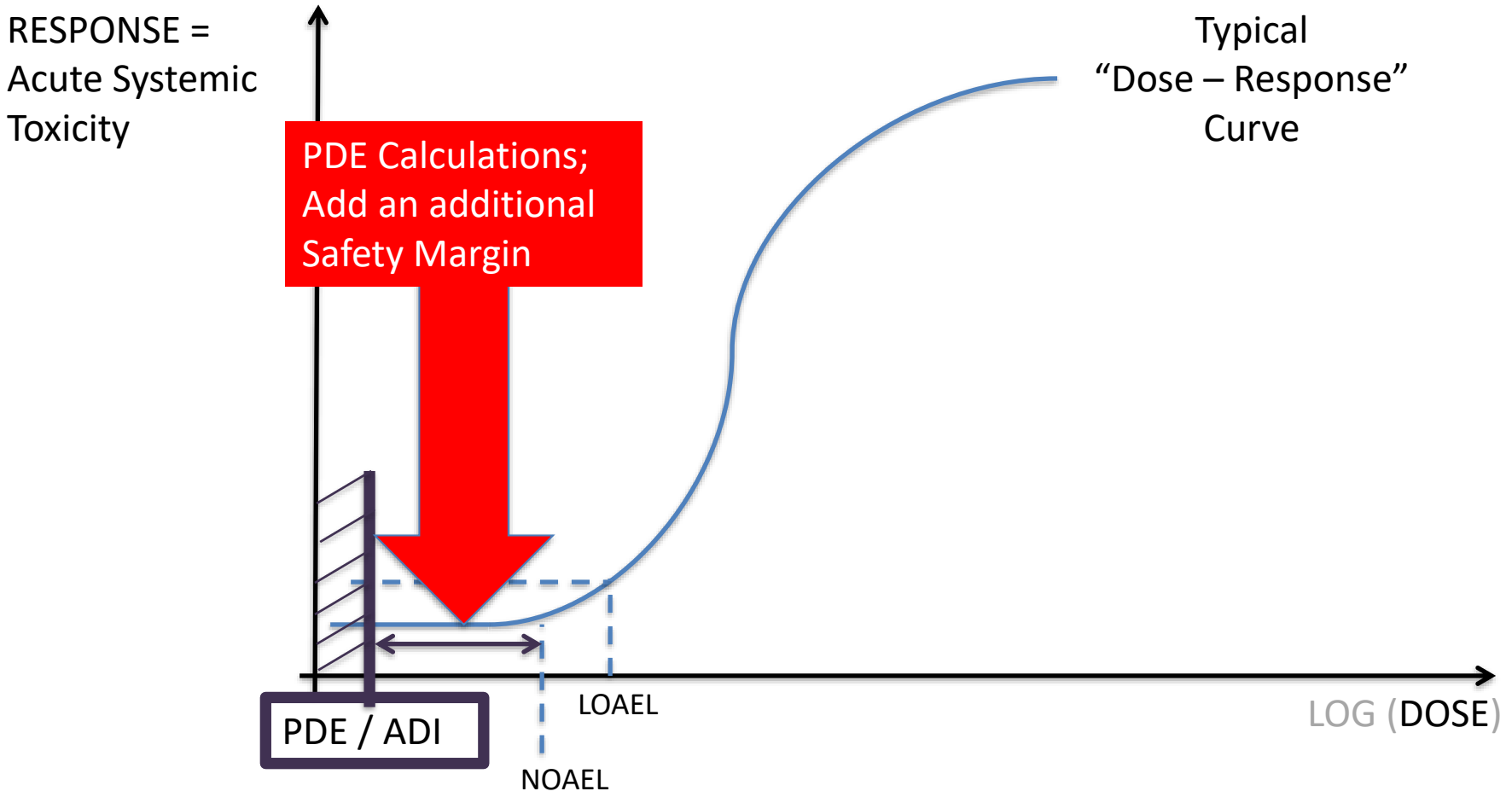
$$PDE = \frac{\text{NO(A)EL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

F1 = Variation between Species
F2 = for Variation between individual Humans
F3 = Short Duration in Animals to Chronical Human Exposure
F4 = Teratogenicity, Neurotoxicity and non-genotoxic carcinogens
F5 = 10 for using **L**OAEL

Sometimes **F6:** route of administration: factor 10 from oral to I.V.

DERIVING PDE'S FROM TOX DATA

EXAMPLE: **ACCUTE SYSTEMIC TOXICITY**



ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	Concentration limit (ppm)
Benzene	2
Carbon tetrachloride	4
1,2-Dichloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500

NB – Limits for Class 1 Solvents are expressed in terms of concentration limits

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	PDE (mg/day)
Acetonitrile	4.1
Chlorobenzene	3.6
Chloroform	0.6
Cyclohexane	38.8
1,2-Dichloroethene	18.7
Dichloromethane	6.0
1,2-Dimethoxyethane	1.0
N,N-Dimethylacetamide	10.9
N,N-Dimethylformamide	8.8
1,4-Dioxane	3.8
2-Ethoxyethanol	1.6
Ethyleneglycol	6.2
Formamide	2.2
Hexane	2.9
Methanol	30.0
2-Methoxyethanol	0.5
Methylbutyl ketone	0.5
Methylcyclohexane	11.8
N-Methylpyrrolidone[1]	5.3
Nitromethane	0.5
Pyridine	2.0
Sulfolane	1.6
Tetrahydrofuran[2]	7.2
Tetralin	1.0
Toluene	8.9
1,1,2-Trichloroethene	0.8
Xylene*	21.7

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

Table 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

PDE > 50 mg/day

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Mutagenic Impurities

ICH M7: Assessment & Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH M7: DNA REACTIVE IMPURITIES

PURPOSE:

Provide a framework for

- Identification
- Categorization
- Quantification
- Control

... of mutagenic impurities to limit potential carcinogenic risk

To establish levels of Mutagenic Impurities that are expected to pose negligible Carcinogenic Risk.

ICH Q3A&B: Provide Guidance for Qualification & Control of Majority of Compounds

Limited Guidance for Impurities that are DNA Reactive

ICH M7 Complements ICH Q3A, ICHQ3B and ICH M3(R2)

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

Provide Guidance for

- New Drug Substances
- New Drug Products

During Clinical Development & subsequent Marketing Applications.

Also Applies for **New Marketing Applications** & **Post Approval Submissions, for Changes in:**

- Drug Substance SYNTHESIS
- Formulation, Composition or Manufacturing Process
- Dosing Regimen

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

LEACHABLES

» Although not intended, the safety assessment principles, outlined in ICH M7, can be used for the assessment of Leachables

EXCIPIENTS

» If used for the first time in a DP and are chemically synthesized.

EXCLUDED from SCOPE:

» Excipients, used in Existing Marketed Products

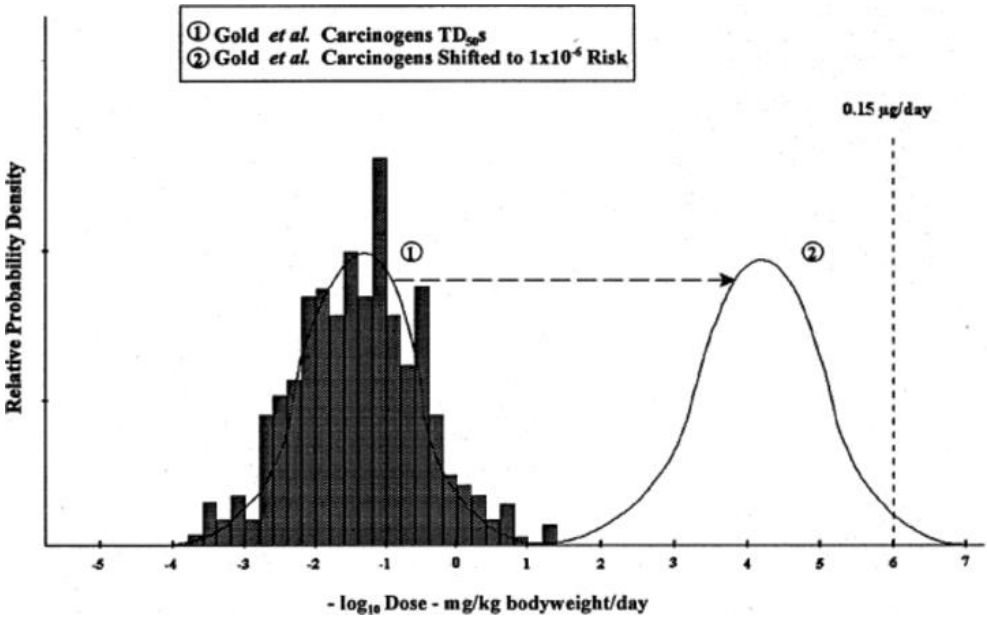
» Flavoring Agents

ICH M7: DNA REACTIVE IMPURITIES

KEY PRINCIPLES:

Limits are predicated on the basis of the **Threshold of Toxicological Concern (TTC)**

TTC based on analysis of **730 carcinogens** (genotoxic and non-genotoxic), using **linear extrapolation** from animal onco data; estimates daily exposure to 1.5µg/day for most (genotoxic) carcinogens **not likely to exceed lifetime cancer risk** of 1 in 10^5 – risk considered acceptable for pharmaceuticals as drugs have a benefit, not normally used for lifetime and precedent of benzene in Q3C.



Exceptions include aflatoxin-like, azoxy and N-nitroso compounds – need case-by-case assessment.

ICH M7: DNA REACTIVE IMPURITIES

HAZARD ASSESSMENT:

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control (details in Section 7)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data.	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	Treat as non-mutagenic impurity

THE DOSE-RESPONSE RELATIONSHIP –

Haber's Rule

$$C \times t = k$$

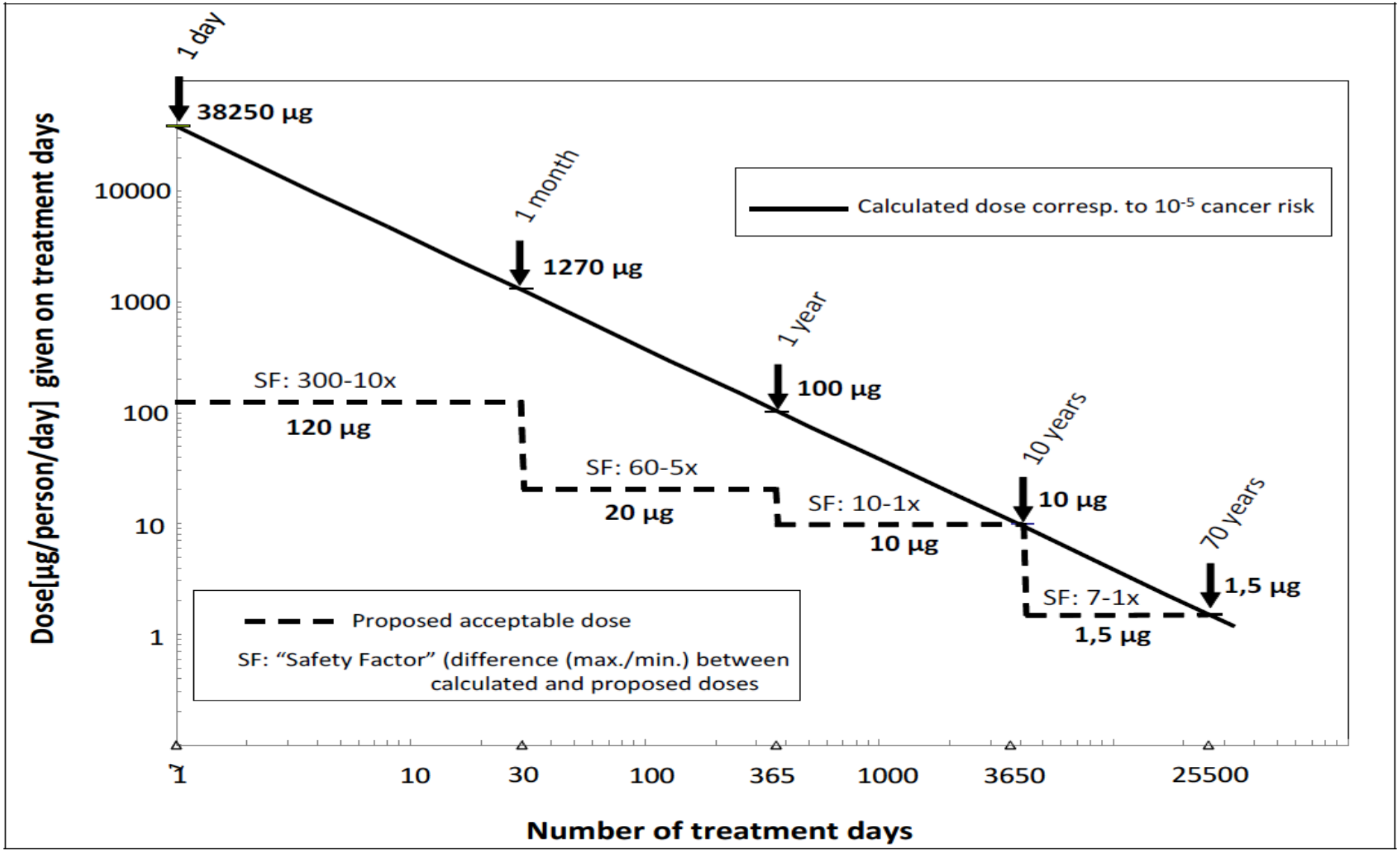
With *C = Concentration*
t = time
k = constant

This means that the toxic effect e.g. stays the same when concentration is doubled in half of the time of exposure

IMPORTANT, because this is the basis for the ***Staged Approach****, suggested in* ***ICH M7***

Remark: Not applicable to all toxicological end points – Can it be applied to general toxicity ?

ICH M7: DNA REACTIVE IMPURITIES

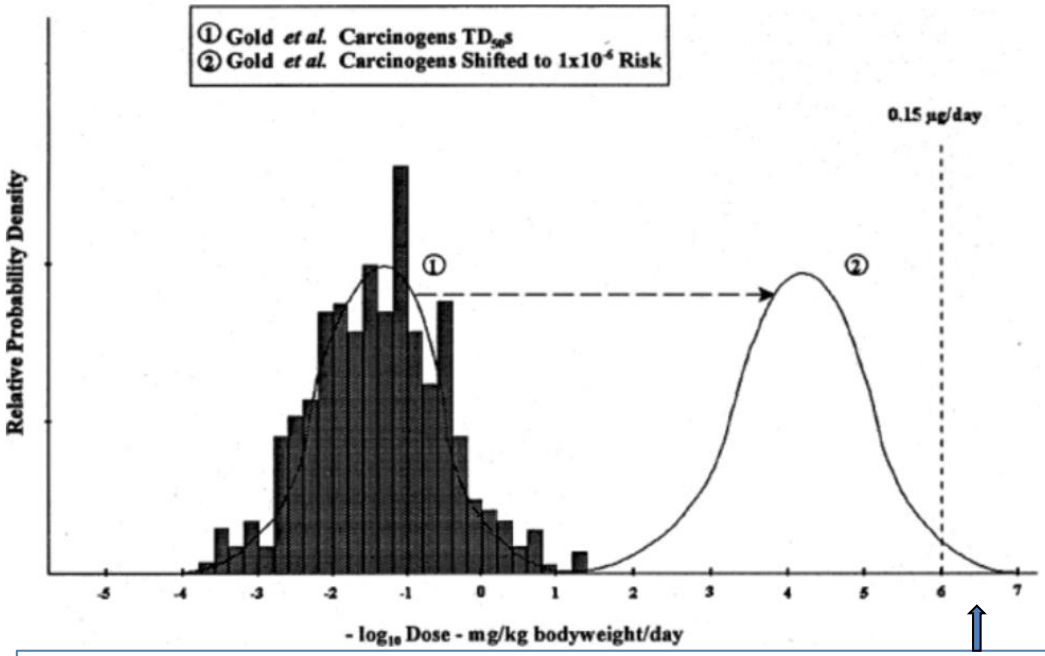


ICH M7 - Compound Specific Limits

Introduction

TTC based on data from **approximately 800 carcinogens**

Put another way we have carcinogenicity data on 800 compounds which can be used where relevant to calculate individual specific limits.



Note that the TTC was derived from the more potent carcinogens after exclusion of cohort of concern

- In reality only a proportion of these are relevant to the synthesis of APIs but considerable data exists in respect to a number of common reagents

Compound Specific Limits

Historical Perspective

The rationale for conducting a compound-specific assessment rather than relying on a generic application of the TTC is highlighted in the EMEA guideline on the Limits of Genotoxic Impurities (EMEA, 2006) :

> *'The TTC concept should not be applied to carcinogens where adequate toxicity data (long-term studies) are available and allow for a compound-specific risk assessment.'*

The FDA draft guideline (FDA, 2008) also indicates support for such an approach and indeed goes further by indicating that the use of risk assessments based on structural similarity to known carcinogens, may also be appropriate to establish appropriate limits:

> 'When a significant structural similarity to a known carcinogen is identified, the drug substance and drug product acceptance criteria can be set at a level that is commensurate with the risk assessment specific to that of the known compound.'

Compound Specific Limits

ICH M7

Compound-specific risk assessments to derive **acceptable intakes** should be applied instead of the **TTC-based acceptable intakes** where **sufficient carcinogenicity data** exist.

For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency & linear extrapolation as a default approach.

PQRI –PODP (previous development):
The Threshold Approach for PODP
*(**P**arenteral and **O**phthalmic **D**rug **P**roducts)*

THE PQRI-PODP THRESHOLD APPROACH

Table III
Proposed Safety Classification of Extractables/ Leachables

Statistical Evaluation of Class 1

Dose (µg/day)	Pass (%) (Dose Margin ≥1)	90 % Confidence Interval		95% Confidence Interval		99% Confidence Interval	
		Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
50	55/60 (91.7)	82.8	96.4	80.9	96.9	76.8	97.6
150	48/60 (80.0)	69.4	87.8	67.3	88.8	63.1	90.6

Paskiet D et al. PDA J Pharm Sci and Tech 2013;67:430-447

CONCLUSIONS

CONCLUSIONS

- Safety principles underpinned by Paracelsian principle – poison is in the dose.

- Such concepts partially recognised in approaches to general qualification / solvents
  - ICH Q3A – 1mg limit
  - PDE approach to solvents – use of NOEL

CONCLUSIONS

- Conservative approach taken for Mutagenic Impurities
  - Use of Linear extrapolation to 1 in 100,000 risk, used to establish TTC – lifetime limit of 1.5 ug/day.
  - Highly theoretical – Ignores protective mechanisms

CONCLUSIONS

- Approach for E&Ls even more conservative
  - Based on principle of SCT, 0.15 ug/day
    (this being based on same principle as TTC, except 1 in 1,000,000 risk)
  - Also fundamental differences in terms of approaches
  - SCT used to define an AET
    - Evaluate ALL components > AET
  - ICH M7 more of a risk based approach -considers duration of exposure

Vs.