Toxicological Safety Evaluations of Extractables & Leachables

Trainer

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- Preclinical Toxicology - program Manager (2010-2017)
- Manager Toxicological safety assessments (2017-current)

Training Course Outline

- Basic Toxicological Principles
- Key Toxicological Endpoints
- Applicable Safety Limits and Thresholds
- General Impurity Qualification
- Best Practice Conclusions

Learning Objectives

- Understanding the basic concepts in Toxicology
  - Important toxicological endpoints
  - Relevant toxicological studies and data to look for
- Application of relevant safety thresholds
  - TTC, SCT, AET, PDE,…
- Safety evaluation strategies for Extractables and Leachables
  - Literature search
  - QSAR models – predictive toxicology
  - Generic threshold or can we derive a PDE?

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THE DOSE-RESPONSE

"The Dose Makes the Poison"

Paracelsus, Swiss MD (1492-1541)

Hypothesis:

"All compounds are toxic, but below a certain dose – they are NOT"

➔ Concept of **NOAEL**

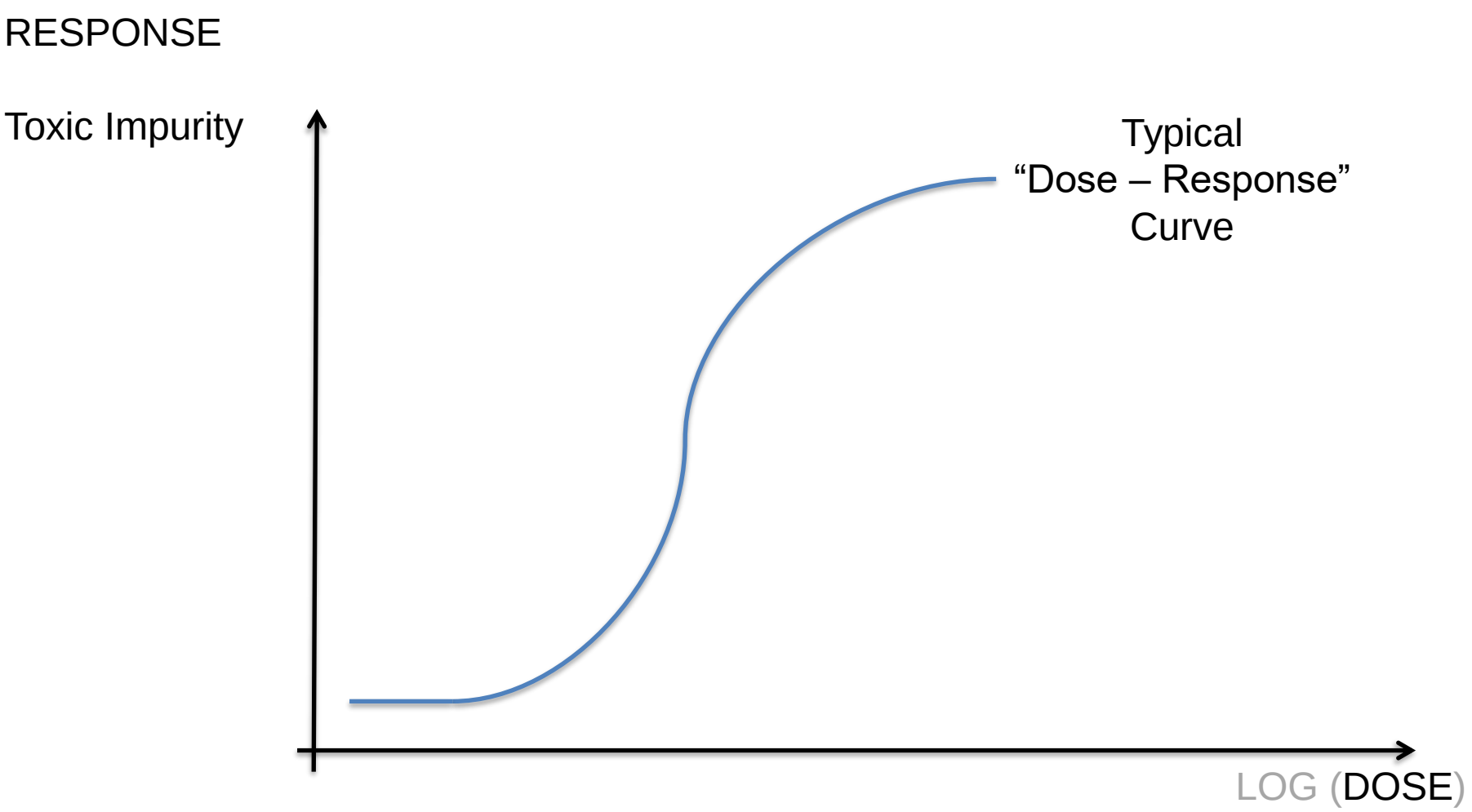
No **O**bserved **A**dverse **E**ffect **L**evel

THE DOSE-RESPONSE RELATIONSHIP

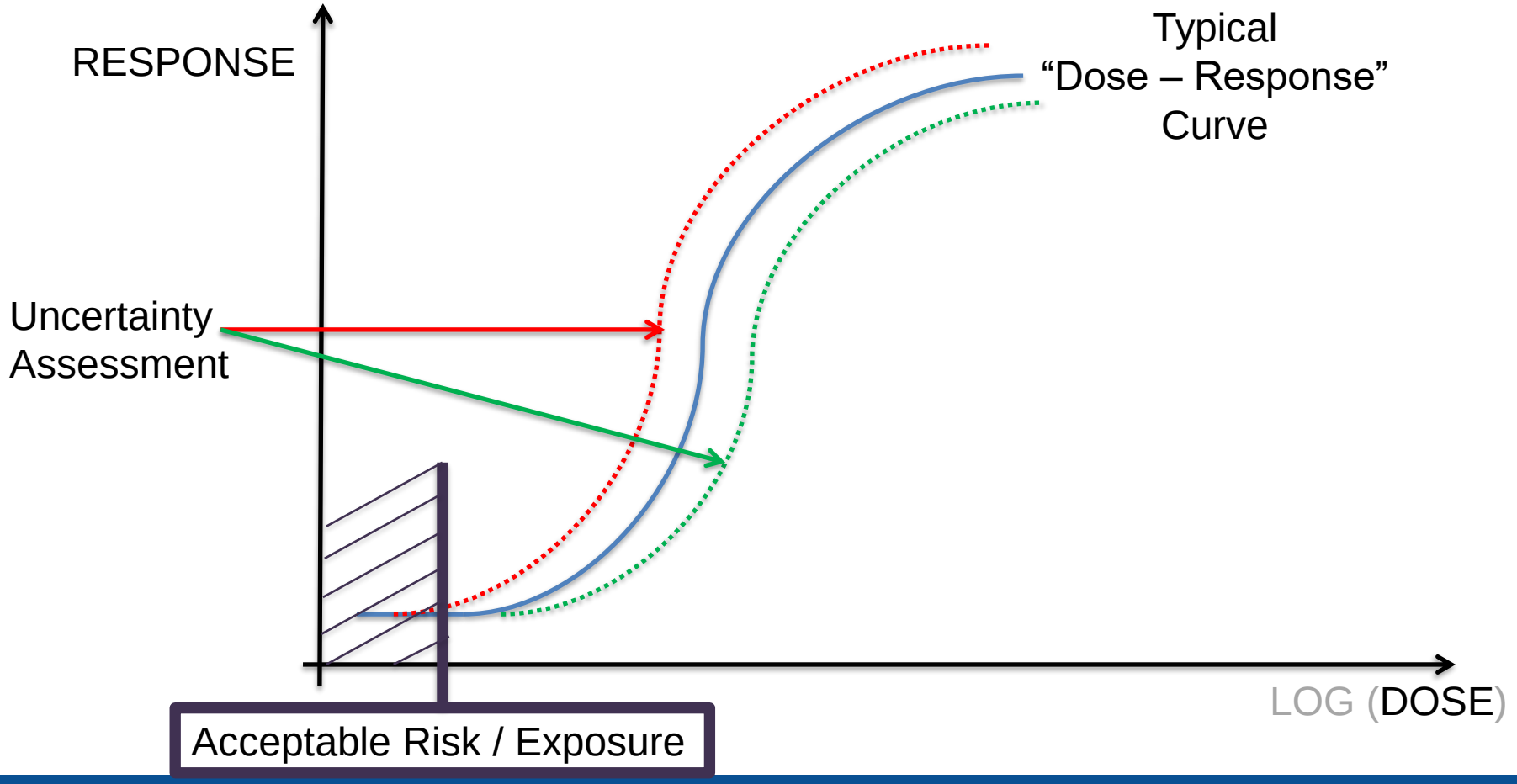
RESPONSE:

- Efficacy API
- Toxicity Impurity

THE DOSE-RESPONSE RELATIONSHIP

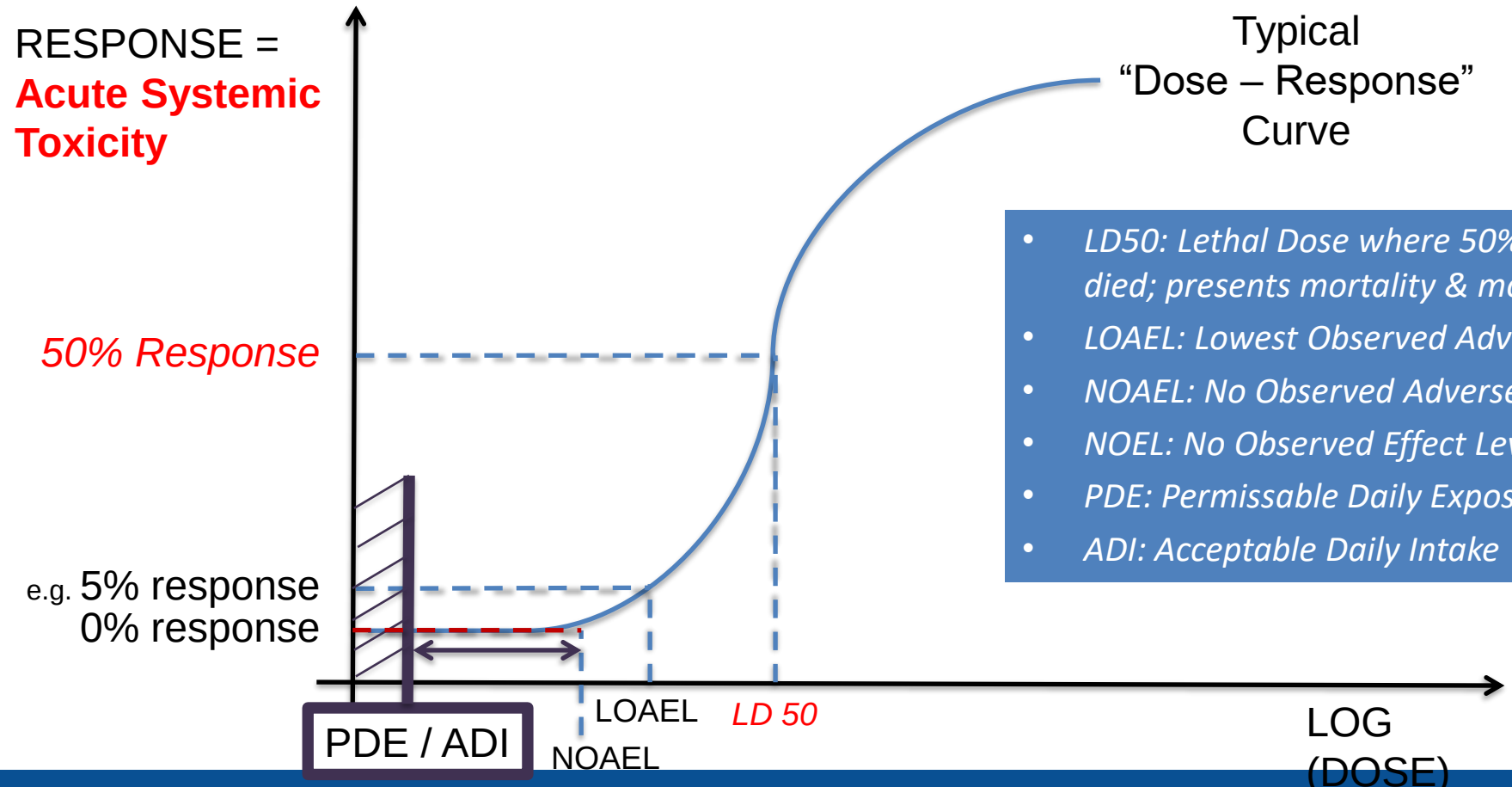


THE DOSE-RESPONSE RELATIONSHIP



THE DOSE-RESPONSE RELATIONSHIP

EXAMPLE: ACCUTE SYSTEMIC TOXICITY



- *LD50: Lethal Dose where 50% of the population has died; presents mortality & morbundity*
- *LOAEL: Lowest Observed Adverse Effect Level*
- *NOAEL: No Observed Adverse Effect Level*
- *NOEL: No Observed Effect Level*
- *PDE: Permissable Daily Exposure*
- *ADI: Acceptable Daily Intake*

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KEY ENDPOINTS

Toxicological endpoints to be considered (non – limitative):

Acute and sub-chronic Systemic Toxicity → Often most readily available information (eg LD50, NOAEL, LOAEL,...)

- Genotoxicity
- Irritation
- Sensitization
- Reproduction Toxicity
- Carcinogenicity

The "BIG FIVE"

KEY ENDPOINTS: SYSTEMIC TOXICITYITY

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**.

- Single dose exposure (<24 hrs)
- Major toxicity 1 or 2 organs
- LD50 value

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 **repeat exposure**.

- Daily exposure (negative control; LOW-; MID- and HIGH- dose group)
- Low dose ~ NOEL or NOAEL or LOAEL

OECD Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents

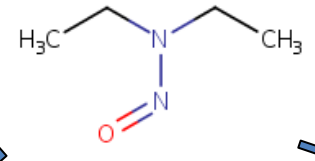
Source: alttox.org

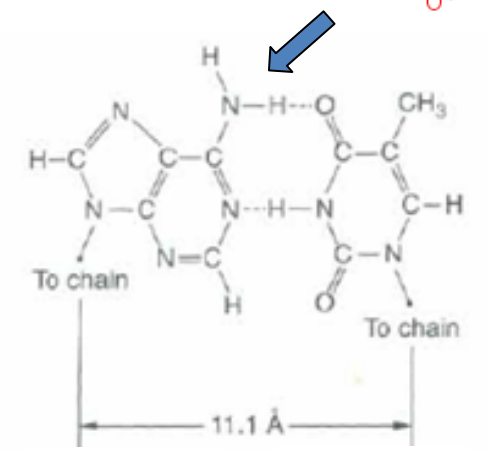
KEY ENDPOINTS: GENOTOXICITY

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.

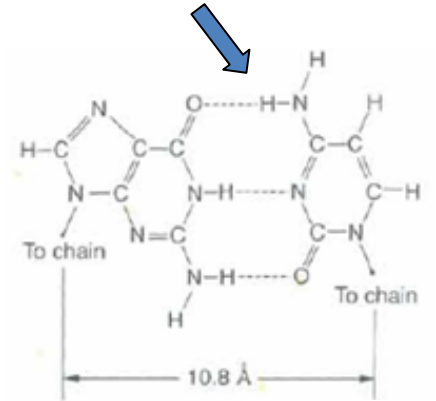
This term has been **replaced,** in the context of **ICH M7,** by the more specific term **mutagenicity** that relates specifically to **DNA mutation**.

OECD 471: Bacterial Reverse Mutation Test (AMES)



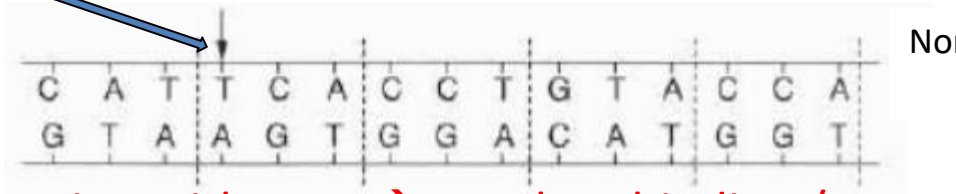


Adenine Thymine



Guanine Cytosine

DNA

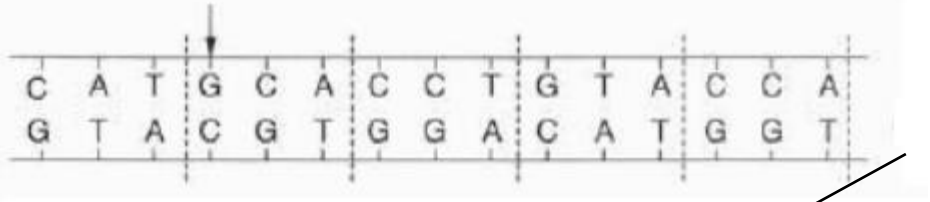


Normal

Interaction with DNA → covalent binding / strand brakes
→ DNA damage → Repair or non-repair:

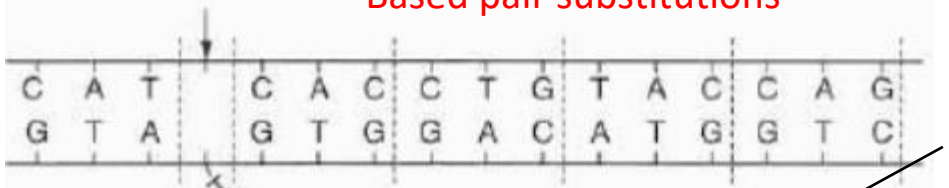
Examples:

(a) Substitute
1 base pair



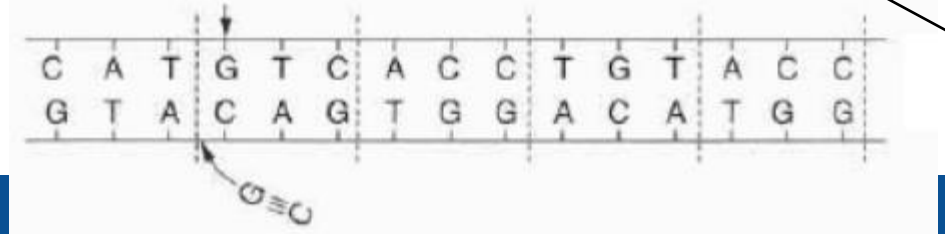
Based pair substitutions

(b) Delete
1 base pair



Frameshift mutations

(c) Insert
1 base pair



KEY ENDPOINTS: GENOTOXICITY

"Gold Standard" for evaluating gene mutations: AMES assay

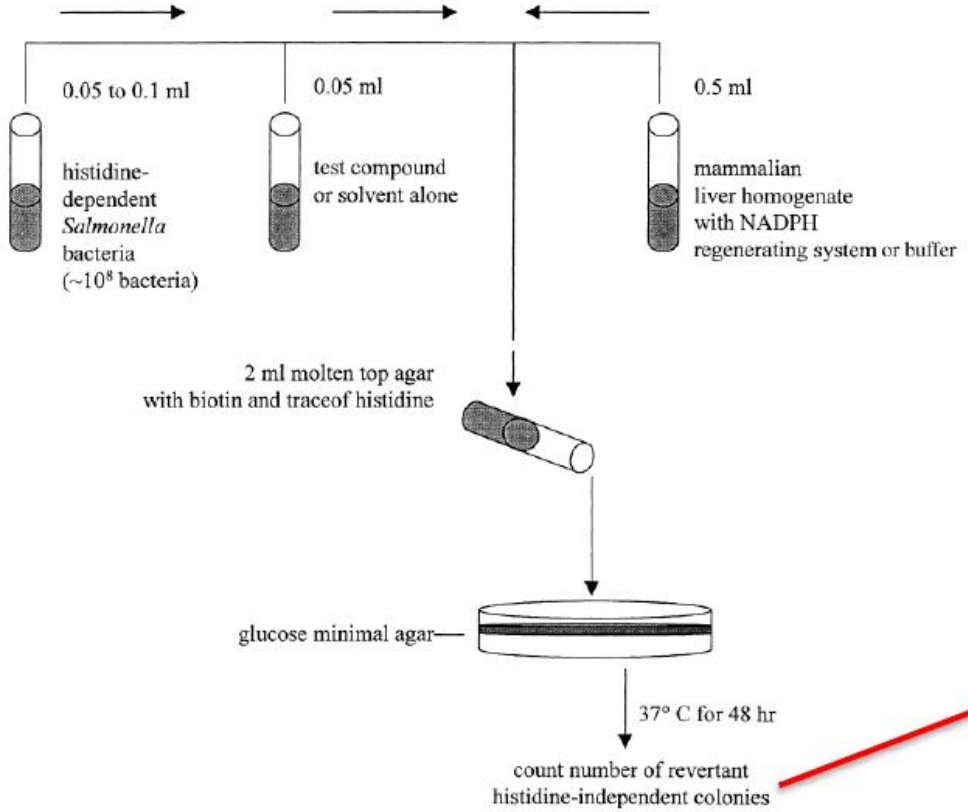
- protocol using 5 bacterial strains used (*Salmonella*)
- detect a variety of mutation events
- each strain contains a different combination of genetic modifications (histidine dependent – repair mechanism knocked out)

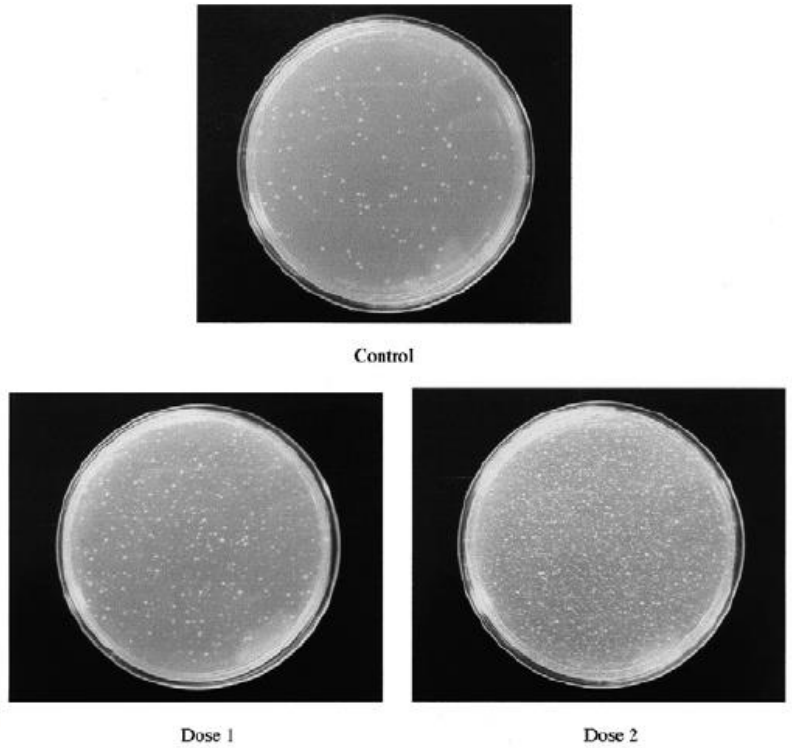
→ maximize the likelihood that test article induced genetic damage will be expressed as a mutation

- top dose = 5000 µg/plate for soluble, non-toxic test articles
- Impurities: 250 µg/plate (85% of mutagens are detected)
- incubations carried out with and without exogenous source of metabolic activation

KEY ENDPOINTS: GENOTOXICITY

- **Ames Assay**





Mortelmans K., Zeiger E. (2000) *Mut. Res.* 455:29-60 13

KEY ENDPOINTS; IRRITATION & CORROSION (e.g. Skin, mucosa)

Skin irritation and **skin corrosion** refer to **localized toxic effects** resulting from a **topical exposure of the skin to a substance.**

Skin irritation is “the production of **reversible damage** to the skin following the application of a test substance for up to 4 hours (i.e. rash development).

Skin corrosion is “the production of **irreversible damage** to the skin; namely, visible **necrosis** through the epidermis and into the dermis, following the application of a test substance for up to 4 hours.

OECD 404 Skin Irritation Test:

0,5g or 0,5 mL of pure substance is applied to the shaved skin of a rabbit, site of application is scored after 14 days of observation.

KEY ENDPOINTS; SENSITIZATION (e.g., Skin)

A ***skin sensitizer*** is "a substance that will induce an **allergic response following (repeat) skin contact**".

A substance is classified as a **skin sensitizer** when human data show it can **induce a sensitization response** following skin contact *"in a substantial number of persons"* or when *"there are positive results from an appropriate animal test".*

- **Allergic Responses: Often Dose Independent!!**

OECD 429 Local Lymphnode Assay (LLNA)

Source: alttox.org

KEY ENDPOINTS; SENSITIZATION (e.g., Skin)

Sensitization testing

OECD No. 429/442A or B: Local lymph node test (LLNA) - *in vivo*

General test principle:

Min. 4 female mice/group

Repeated exposure on the ears (day 1, 2, 3)

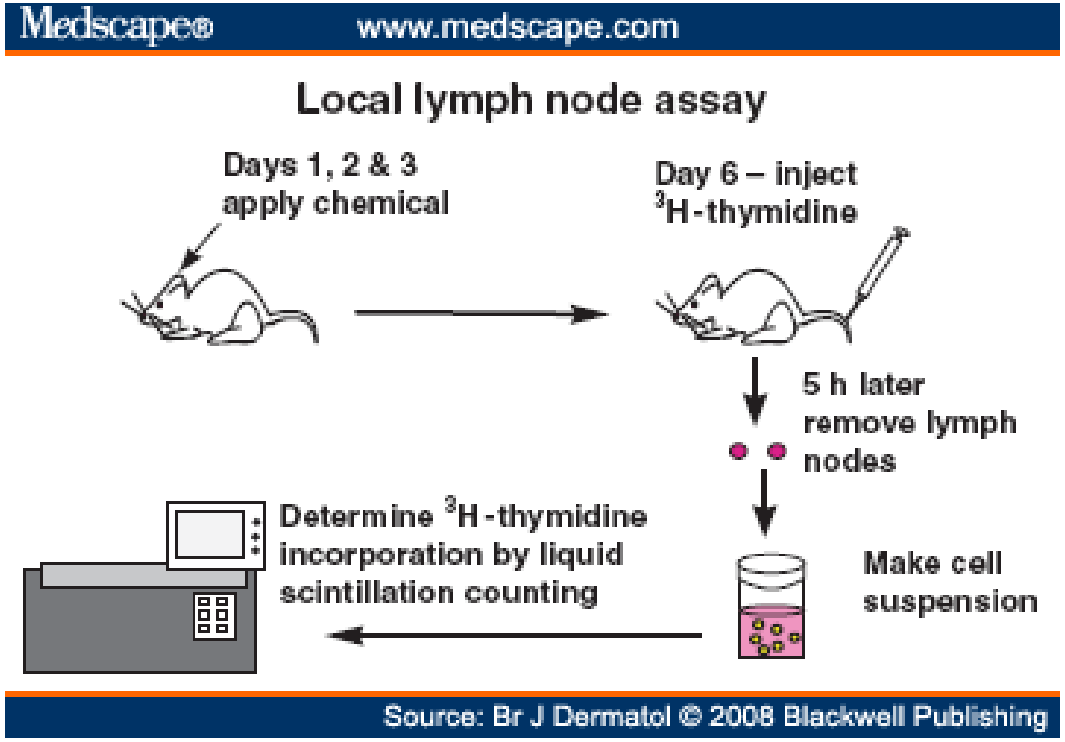
IV dosing of a radio-active (or other) label (day 6)

Observations

Collection of the auricular lymph nodes (5h later)

Stimulation Index (SI) versus control (≥3 = positive)

EC3 value = % at which SI = 3



KEY ENDPOINTS REPRODUCTIVE/DEVELOPMENTAL TOX

Reproductive toxicity includes the toxic effects of a substance on the reproductive ability of an organism and the development of its offspring (teratogenicity).

Reproductive toxicity is defined as "**adverse effects** [of chemicals] on **sexual function** and **fertility** in adult males and females, as well as **developmental** toxicity to the **offspring during pregnancy**".

Developmental toxicity considers "**adverse effects** induced during **pregnancy**, or as a result of **parental exposure** (i.e. via breast feeding)…manifested at any point in the life span of the organism".

Source: alttox.org

KEY ENDPOINTS CARCINOGENICITY

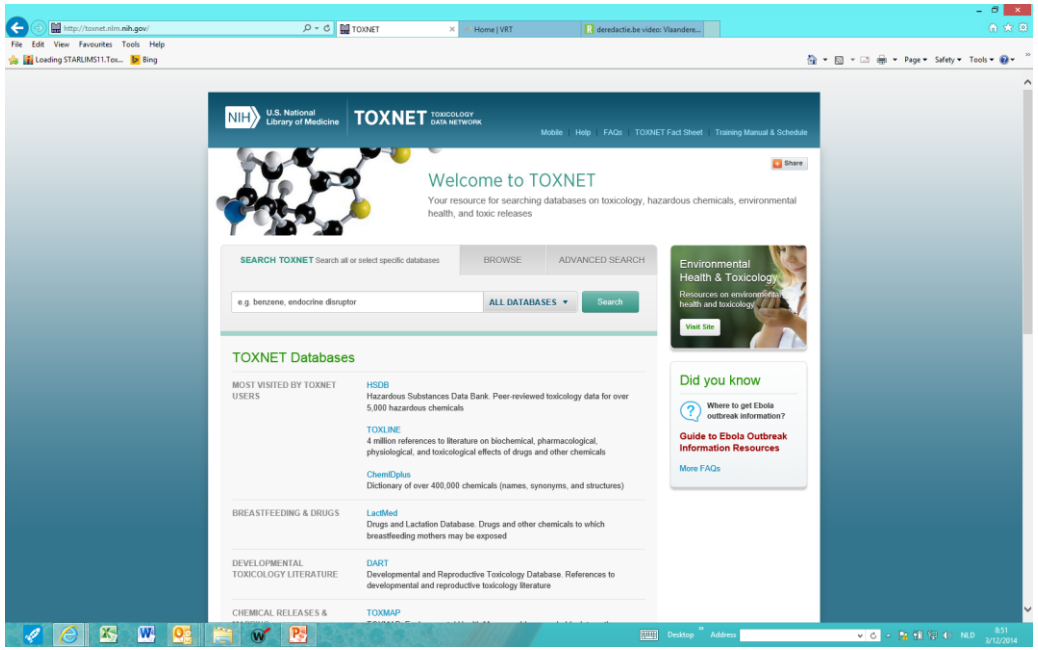
The term ***carcinogen*** denotes a chemical substance or a mixture of chemical substances which **induce cancer** or **increase its incidence**".

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* (directly altering the genetic material) or *non-genotoxic (secondary mechanism not related to direct gene damage)*.

1-2Y Carcinogenicity study: determine Toxic Dose 50% or TD50 at which exposure 50% of the test animals develop tumors.

SOURCES OF TOXICOGICAL DATA



http://toxnet.nlm.nih.gov ➔ https://pubchem.ncbi.nlm.nih.gov
http://echa.europa.eu/
http://www.epa.gov/hpvis/
http://webnet.oecd.org/hpv/
http://www.inchem.org/
http://ntpapps.niehs.nih.gov/ntp_tox/index.cfm

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- Basic Toxicological Principles
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- **Applicable Safety Limits and Thresholds**
- General Impurity Qualification
- Best Practice Conclusions

GENERAL IMPURITY QUALIFICATION; ICH Q3A / Q3B

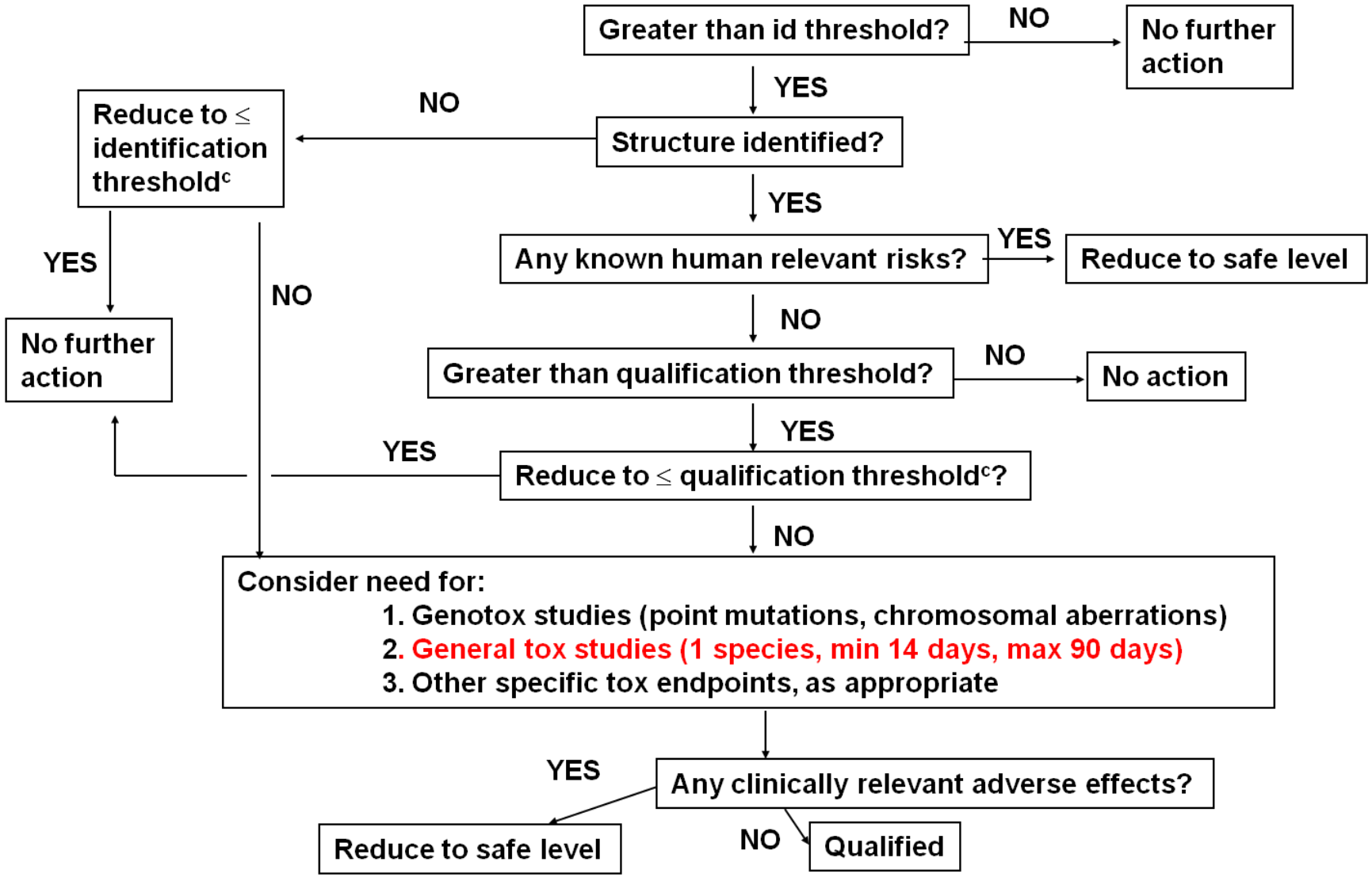
Impurity Qualification: The process of **acquiring** & **evaluating** data that establishes the **biological safety** of an **individual impurity** or **given impurity profile** at the level(s) specified.

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

- Qualification of Impurities is described in ICH Q3A (API) & ICH Q3B (drug product)
  - **Process** described through **Decision tree**
  - Defines the 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*

ICH Q3A AND Q3B: NOT FOR LEACHABLES!

ICH DECISION TREE FOR QUALIFICATION STUDIES



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

- **Mutagenicity** – Production of transmissible genetic alterations from cell to cell or generation to generation
- The concern is that mutagens can lead to cancer.

PURPOSE:

Provide a framework for

- Identification
- Categorization
- Quantification
- Control

... of mutagenic impurities to limit potential carcinogenic risk

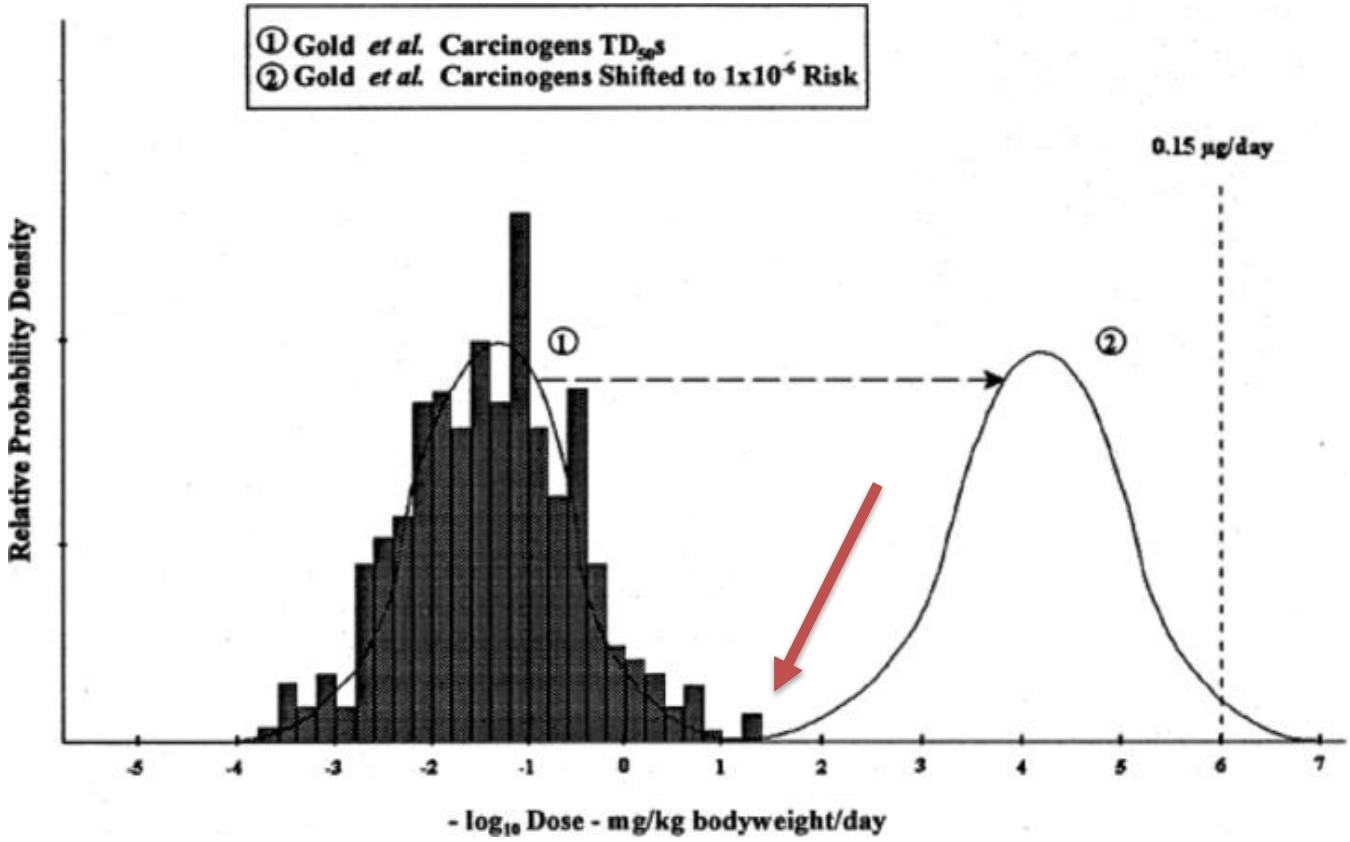
Establish levels of Mutagenic Impurities that are expected to pose negligible Carcinogenic Risk.

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 **1.5 µg/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.



1,5 mg/kg/day (safe dose for all carc.) x 50 kg BW
= 75 mg/day (TD50 value) ½ chance ➔ 1 in 100,000
= 75 mg/day / 50,000 ➔ 1,5 µg/day

PQRI / ICH M7 THRESHOLD APPROACH

SAFETY CONCERN THRESHOLD (SCT)

"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

FDA Qualification Threshold even for acute administration

PQRI for OINDP

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

"Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects"

ICH M7 guideline

Duration of treatment	≤1 month	>1 -12 months	>1 -10 years	>10 years
Daily intake (µg/day)	120	20	10	1.5

Haber's Rule

$$C \times t = k$$

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

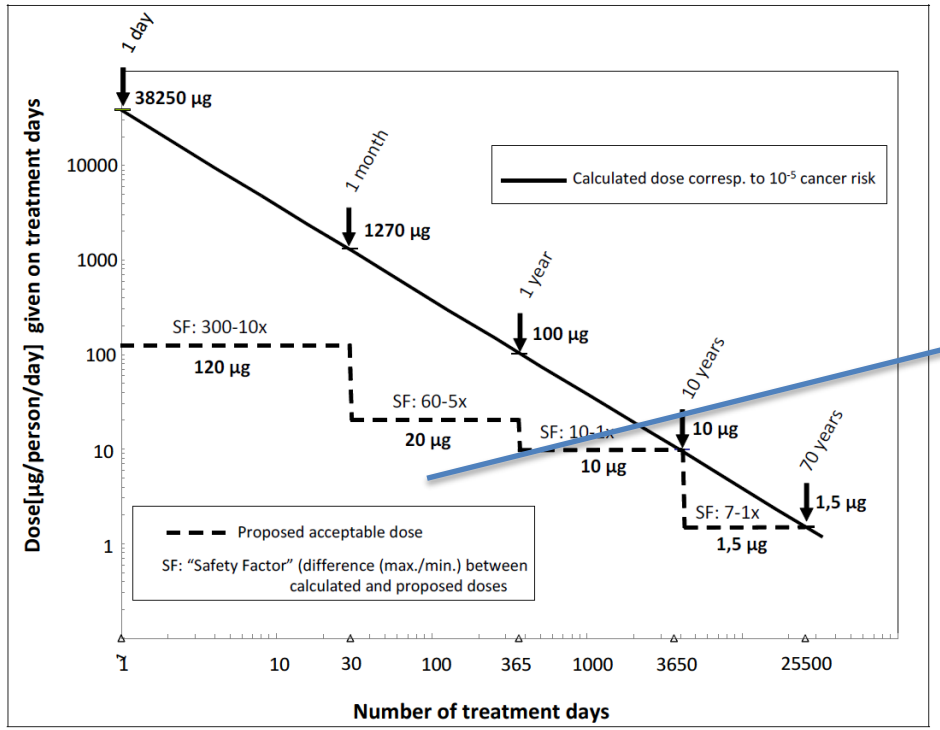
This means that the toxic effect e.g. stays the same when concentration is doubled in half of the time of exposure

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

ICH M7 AND THE STAGED TTC

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5



Uniformly distributed over total Number of exposure days

HABER's RULE:

$$C_1t_1=C_2t_2$$

Acceptable cumulative daily dose:

1,5µg/day x 25.550 days = 38,3 mg x 1 day

THRESHOLD RECOMMENDATIONS

Acceptable Daily Intake, µg/day				
Toxicological Endpoint	Duration of Therapy			
	≤ 1 month	1 – 12 months	1 – 10 years	> 10 years
Mutagenicity, TTC (SCT)	120	20	10	1.5
Sensitization – irritation[1]	5	5	5	5
General[1], QT	~~50~~	~~50~~	~~50~~	~~50~~

Staged Approach as described in ICH M7

changed in final PQRI PDP document to 5 µg/day

Conclusion:

- The **need to have the correct chemical structure** & **Identity** above the Q.T.
  - *For **Chronic** Treatments: SCT. = **1,5** µg/day*
  - *For **All other** treatments: Q.T. = **5** µg/day*
- **Compound Identity** can make the **link to** the **toxicology** (mutagenic carcinogen or sensitizer?)
- As such, the **Qualification Threshold** (QT) **becomes** an **Identification Threshold**!
- As it is applicable to **Leachables**, a **screening step at the SCT** should be built into the Leachables Study Design.

PQRI / ICH M7 THRESHOLD APPROACH

SAFETY CONCERN THRESHOLD (SCT) - PARENTERAL DRUG PRODUCTS

"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

Draft PQRI for PODP

FDA Qualification Threshold even for acute administration

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5

PQRI PDP 2022

Compound specific PDE

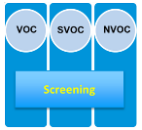
Qualification Threshold

SCT

Use the SCT of 1,5 µg/day to derive your Analytical Evaluation Threshold (AET) in x µg/mL

ANALYTICAL EVALUATION THRESHOLD (AET)

➔ **Translating the SCT into Analytical Thresholds for Extractables studies**



$$\text{AET}\left(\frac{\mu g}{test\ item}\right) = \frac{\text{SCT}\left(\frac{\mu g}{\text{day}}\right)}{\text{number of doses/day}} \text{ x } \frac{\text{number of doses}}{\text{test item}}$$

➔ **Screening methods are semi-quantitative: Uncertainty Factor of 50% or**

➔ **Response Factor database**

$$\text{Final AET} = \frac{\text{AET}}{2}$$

Cornerstone of all E&L testing:

Compounds detected below the (Final) AET are considered to be toxicologically safe and should not be considered for toxicological assessment

Calculation AET – example 1 (small volume parenteral)

- Vial with rubber stopper
- Filling volume : 1 mL
- Maximum daily intake: 1 vial/day or 1 mL/day
- Final AET based on SCT for PDPs?

$$\text{AET} = \frac{\text{threshold}}{dose/day} \text{ x } \frac{total\ \#\ doses}{test\ item}$$

$$= \frac{1.5\ \mu g/day}{1\ dose/day} \text{ x } \frac{1\ dose}{test\ item}$$

$$= 1.5\ \mu\text{g/test item}$$

$$\text{Final AET} = \frac{1.5\ \frac{\mu g}{test\ item}}{2} = 0.75\ \mu\text{g/test item}$$

50% uncertainty for screening methods

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GENERAL FRAMEWORK

- **Exposure assessment**
  - Concentration of stopper in solvents / drug product
  - Dosing volume: 500 mL/d (10 bottles of 50 mL → 10 stoppers)
  - Frequency of Dosing: Less-then-lifetime, staged TTC
  - Route of Exposure
- **Hazard assessement**
  - **Literature search**
    - Classifications
    - Experimental Data
  - **Prediction methods**
    - DEREK
    - CASE Ultra

  → Mostly no or limited data available

  → Exclude mutagenicity & sensitisation potential

  In parallel or Stepwise
- **Risk assessement**
  - **Thresholds**
    - TTC (lifetime, staged, less-than-lifetime) or TD50 → 1:100,000 risk
    - PQRI limits (have overruled Cramer limits)
    - PDE calculation (or ADI/RfD…)
  - **Safety margin**
    - Calculation
    - Conclusion

Toxicological Assessment at the Leachables Level

- Worst Case Scenario assumption: Maximum Daily Dose and length of therapy
  - Highest levels across shelve life – highest daily exposure to the patient
  - Assess compounds > SCT /QT (µg/day) or > AET (µg/mL)
  - Start the toxicological safety assessment only at end of Shelve life?

- There are three hurdles to take to qualify a Leachable:
  1. Mutagenicity @ 1,5 µg/day (or staged TTC)
  2. Sensitization and irritation @ 5µg/day
  3. When non-mutagenic, sensitizing or irritating ➔ derive the PDE

Hurdle 1: Mutagenicity @ 1,5 µg/day (or staged TTC)

- Litterature review for mutagenicity information
  - ➔ AMES assay: OECD 471 Bacterial Reverse Mutation Test
- When positive – check for carcinogenicity data (TD50 extrapolation)
- When negative – proceed to hurdle 2
- When no data is available – Proceed to (Q)SAR prediction model

Prediction methods

- **(Q)SAR systems:**
  - **DEREK = Deductive Estimation of Risk from Existing Knowlegde**
    - **Enpoints selected:** bacterial mutagenicity (5 strains)
    - **Reporting:**
      - **Alerts found:** e.g. : 352 Aromatic amine or amide
      - **Reasoning:** e.g. Mutagenicity is PLAUSIBLE / PROBABLE …
  - **Multicase (CASE Ultra) → *"toxicophores"***
    - **Enpoint selected:** mutagenicity (5 strains)
    - **Reporting:**
      - **Alerts found:** NEGATIVE or POSITIVE / DEACTIVATING
        e.g.: Alert ID 49: cH:c (-C3H2):c
      - **Probability :** < 40 (negative); 40-60 (inconclusive); >60 (positive)
  - **Leadscope, Sarah, ToxTree, OECD Toolbox, …**

Rule-based

Statistically -based

General Impurity Qualification

Chemical name; synonyms [CAS No.] formula mol. wt.	Structure
1-(1-Bromomethylethenyl)-2,2,4,4-tetramethyl-cyclohexane; $C_{13}H_{23}Br$ Rubber Oligomer [n.n.] $C_{13}H_{23}Br$ 259.23	

Evaluation:

Derek predictions (Reasoning summary and alerts found):

- Carcinogenicity in human is PLAUSIBLE; Alkylating agent
- Carcinogenicity in mammal is PLAUSIBLE; Alkylating agent
- Chromosome damage in vitro in human is PLAUSIBLE; Alkylating agent
- Chromosome damage in vitro in mammal is PLAUSIBLE; Alkylating agent
- Irritation (of the eye) in human is PLAUSIBLE; Allyl halide
- Irritation (of the eye) in mammal is PLAUSIBLE; Allyl halide
- Irritation (of the respiratory tract) in human is PLAUSIBLE; Allyl halide
- Irritation (of the respiratory tract) in mammal is PLAUSIBLE; Allyl halide
- Irritation (of the skin) in human is PLAUSIBLE; Allyl halide
- Irritation (of the skin) in mammal is PLAUSIBLE; Allyl halide
- Mutagenicity in vitro in bacterium is PLAUSIBLE; Allyl halide; Alkylating agent
- Rapid prototypes: nephrotoxicity in human is EQUIVOCAL; 1,1-Dimethylcyclohexane
- Rapid prototypes: nephrotoxicity in mammal is EQUIVOCAL; 1,1-Dimethylcyclohexane
- Skin sensitisation in human is PLAUSIBLE; Haloalkane
- Skin sensitisation in mammal is PLAUSIBLE; Haloalkane

Classification: Class III

Suggested TTC: 1.5 µg/day

- Impurity Harard Categorization

ICH M7 Class	Description	
Class 1	Known mutagenic carcinogen	Experimental data
Class 2	Known mutagen	
Class 3	Structural alert No Ames test data	In silico assessment
Class 4	Alerting structure; similarity to Ames negative compound	
Class 5	No structural alert or alerting structure with negative Ames test	

= (Q)SAR

General Impurity Qualification

Class	Definition	Proposed action for control (details in Section 7 and 8)
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 (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

based on TD_{50}

based on TTC:
lifetime / staged
- less-than-lifetime

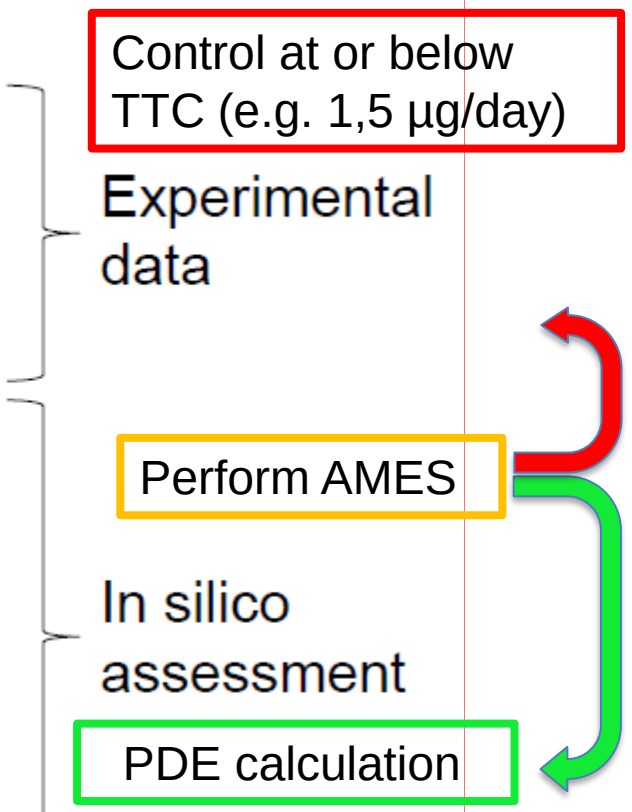
Higher threshold:
predefined limits
based on NOAEL
or QT (no data)
or Read-Across

General Impurity Qualification

So, we have a positive prediction we cannot invalidate ?
What Do We Do?

General Impurity Qualification

ICH M7 Class	Description
Class 1	Known mutagenic carcinogen
Class 2	Known mutagen
Class 3	Structural alert No Ames test data
Class 4	Alerting structure; similarity to Ames negative compound
Class 5	No structural alert or alerting structure with negative Ames test



Hurdle 2: Sensitization and irritation @ 5µg/day

- OECD 429 Local Lymphnode Assay (LLNA) or OECD 406 GMT (MD)
  - concentration series such as 100%, 50%, 25%, 10%, 5%, 2.5%, 1%, 0.5%, etc.
- OECD 404 Skin Irritation Test
  - 0,5g or 0,5 mL of pure substance is applied to the shaved skin of a rabbit, site of application is scored after 14 days of observation.
  - Concentration based ➔ might be derisked at LEA levels

- No data available ➔ revert to (Q)SAR systems?
  - Additional weight of evidence – No guarantee for regulatory acceptance
  - *Currently (1992!), quantitative structure-activity relationships are not yet sufficiently developed to play a significant role in the assessment of the skin-sensitisation potential*
  - Conduct the test on the pure substance or alternatively on an extract of the material
  - ISO/DTS 21726:2018(E) : TTC for medical devices is clear: Not Applicable for IRR & SENS

Hurdle 3: General Toxicity – Below the PDE?

Based on **repeated dose toxicity studies**, compound-specific limits or '**PDE values**' can be established based on NO(A)EL values, which are health-based exposure limits that are unlikely to cause adverse effects in humans. Safety factors (F1-5) should be applied:

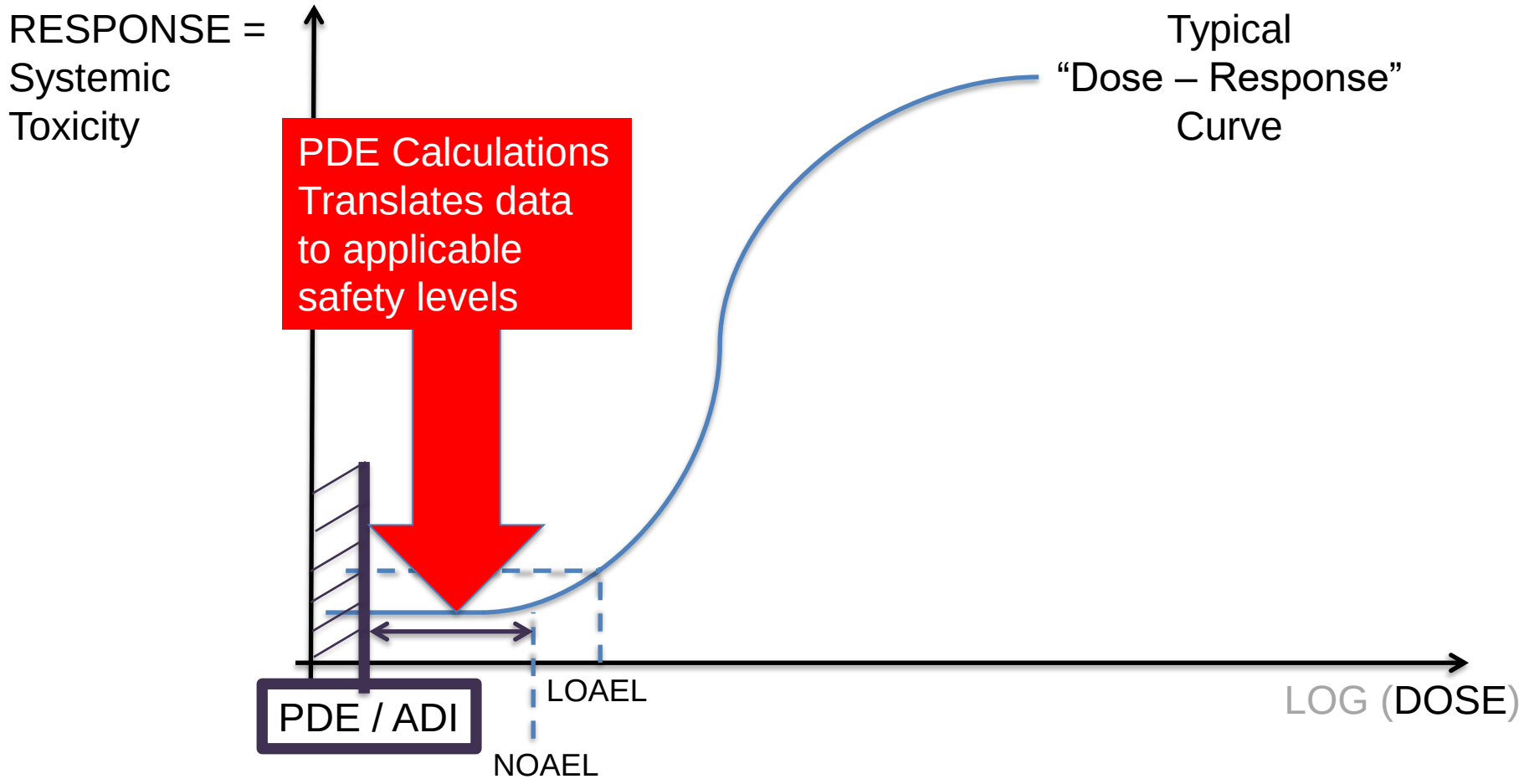
$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

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 LOAEL

Further correction may be applied for the **rate of absorption** (apply F6 factor).

DERIVING PDE'S FROM TOXICOLOGICAL DATA

EXAMPLE: SYSTEMIC TOXICITY



Training Course Outline

- Basic Toxicological Principles
- Key Toxicological Endpoints
- Applicable Safety Limits and Thresholds
- General Impurity Qualification
- **Best Practice Conclusions**

BEST PRACTICE CONCLUSIONS

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

- NOAEL/NOEL Levels in Systemic Toxicity testing allow to calculate PDE levels when not:
  - Mutagenic – carcinogenic
  - Sensitizing or irritating

- 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 µg/day, when TD_{50} are available or by read across

  - Staged TTC Approach (based upon Haber's Rule) can be used where the identified compound is identified to be a potential carcinogen, mutagen or genotoxic compound *(and compound is not sensitizer/irritant)*

  - This concept CANNOT be used as an IDENTIFICATION THRESHOLD in Extractables & Leachables (concern for sensitizers)

BEST PRACTICE CONCLUSIONS

- Conservative approach taken for Mutagenic Impurities
  - If a compound has Actual Toxicity Data on Carcinogenicity/Mutagenicity, USE AVAILABLE DATA, instead of generic approach
    - Often, this will allow you to increase the level of concern for the compound.

- Final Toxicological Assessment needs to be done on the "quantitative" Leachable results

- Leave toxicology to toxicologists; all assessments should be verified by a certified Toxicologist.