Toxicological Safety Evaluations of Extractables & Leachables
Trainer

Kevin Breesch, MSc
Manager Toxicology
Nelsonlabs Europe

- Master in Biochemistry
- Preclinical Toxicology - program Manager (2010-2017)
- Manager Toxicological safety assessments (2017-current)
• 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?
Training Course Outline

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

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

Concept of NOAEL

No Observed Adverse Effect Level

“The Dose Makes the Poison”

Paracelsus, Swiss MD (1492-1541)
Connecting People, Science and Regulation®
THE DOSE-RESPONSE RELATIONSHIP

RESPONSE

Toxic Impurity

Typical “Dose – Response” Curve

LOG (DOSE)
THE DOSE-RESPONSE RELATIONSHIP

- Typical “Dose – Response” Curve
- Uncertainty Assessment
- Acceptable Risk / Exposure

LOG (DOSE)

RESPONSE
EXAMPLE: ACUTE SYSTEMIC TOXICITY

RESPOSE = Acute Systemic Toxicity

50% Response

e.g. 5% response 0% response

Typical “Dose – Response” Curve

• 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
Training Course Outline

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

Toxicological endpoints to be considered (non-limitative):

- Acute and sub-chronic Systemic Toxicity
- Genotoxicity
- Irritation
- Sensitization
- Reproduction Toxicity
- Carcinogenicity

Often most readily available information (e.g., LD50, NOAEL, LOAEL, ...)

The “BIG FIVE”
**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
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)
Interaction with DNA → covalent binding / strand brakes → DNA damage → Repair or non-repair:

Examples:
(a) Substitute 1 base pair
(b) Delete 1 base pair
(c) Insert 1 base pair

Based pair substitutions
Frameshift mutations
“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**

  0.05 to 0.1 ml
  histidine-dependent *Salmonella* bacteria
  (≤10^9 bacteria)

  0.05 ml
  test compound or solvent alone

  0.5 ml
  *in vitro*
  liver homogenate with NADPH
  regenerating system or buffer

  2 ml molten top agar
  with biotin and trace of histidine

  glucose minimal agar

  37°C for 48 hr

  count number of revertant
  histidine-independent colonies

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.
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
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 \( \geq 3 = \text{positive} \)  
**EC3 value** = % at which SI = 3
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
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 TOXICOLOGICAL DATA

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
Training Course Outline

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

- **Before** drug products 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 through **Decision tree**
  - Defines the requirements 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
ICH DECISION TREE FOR QUALIFICATION STUDIES

- **Reduce to ≤ identification threshold?**
  - **NO** → **No further action**
  - **YES** → **Structure identified?**
    - **NO** → **Greater than id threshold?**
      - **NO** → **No further action**
      - **YES** → **Any known human relevant risks?**
        - **YES** → **Reduce to safe level**
        - **NO** → **Greater than qualification threshold?**
          - **NO** → **No action**
          - **YES** → **Reduce to ≤ qualification threshold?**
            - **YES** → Consider need for:
              1. Genotox studies (point mutations, chromosomal aberrations)
              2. General tox studies (1 species, min 14 days, max 90 days)
              3. Other specific tox endpoints, as appropriate
            - **NO** → **Any clinically relevant adverse effects?**
              - **YES** → **Reduce to safe level**
              - **NO** → **Qualified**
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
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”

PQRI for PODP

<table>
<thead>
<tr>
<th>Tox Endpoint</th>
<th>Others</th>
<th>Sensitizer &amp; Irritant</th>
<th>Carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Class I</td>
<td>Class II</td>
<td>Class III</td>
</tr>
<tr>
<td>Threshold Level (μg/day)</td>
<td>50</td>
<td>5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>≤1 month</th>
<th>&gt;1-12 months</th>
<th>&gt;1-10 years</th>
<th>&gt;10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake (μg/day)</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

FDA Qualification Threshold even for acute administration
Haber’s Rule

\[ C \times t = k \]

With

- \( C = \text{Concentration} \)
- \( t = \text{time} \)
- \( k = \text{constant} \)

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

<table>
<thead>
<tr>
<th>Duration of treatment</th>
<th>≤ 1 month</th>
<th>&gt;1 - 12 months</th>
<th>&gt;1 - 10 years</th>
<th>&gt;10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

HABER’s RULE:

\[ C_1 t_1 = C_2 t_2 \]

Acceptable cumulative daily dose:

\[ 1.5 \mu g/day \times 25,550 \text{ days} = 38.3 \text{ mg} \times 1 \text{ day} \]
**THRESHOLD RECOMMENDATIONS**

### Acceptable Daily Intake, µg/day

<table>
<thead>
<tr>
<th>Toxicological Endpoint</th>
<th>Duration of Therapy</th>
<th>≤ 1 month</th>
<th>1 – 12 months</th>
<th>1 – 10 years</th>
<th>&gt; 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutagenicity, TTC (SCT)</td>
<td></td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>Sensitization – irritation(^1)</td>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>General(^1), QT</td>
<td></td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

**Conclusion:**
- The **need to have the correct chemical structure & Identity** above the Q.T.
  - For **Chronic Treatments**: Q.T. = 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.

Staged Approach as described in ICH M7

Will be changed in final PQRI PDP document to 5 µg/day
The threshold approach – AET

**ANALYTICAL EVALUATION THRESHOLD (AET)**

➤ Translating the SCT into Analytical Thresholds for Extractables studies

\[
\text{AET (µg}_{\text{test item}} = \frac{\text{SCT (µg)}}{\text{number of doses/day}} \times \frac{\text{number of doses}}{\text{test item}}
\]

➤ Screening methods are semi-quantitative: correction factor of 50%

\[
\text{Final AET = } \frac{\text{AET}}{2}
\]

**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.
The threshold approach – AET

**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?

\[
\text{AET} = \frac{\text{threshold \ dose/day}}{\text{dose/day}} \times \frac{\text{total \ # \ doses}}{\text{test item}} \\
= \frac{1.5 \, \mu g/day}{1 \, \text{dose/day}} \times \frac{1 \, \text{dose}}{\text{test item}} \\
= 1.5 \, \mu g/\text{test item}
\]

**Final AET**

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

50% uncertainty for screening methods
Training Course Outline

- Basic Toxicological Principles
- Key Toxicological Endpoints
- Applicable Safety Limits and Thresholds
- General Impurity Qualification
- Best Practice Conclusions
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-than-lifetime, staged TTC
  • Route of Exposure

• Hazard assessment
  • Literature search
    ▪ Classifications
    ▪ Experimental Data
  • Prediction methods
    ▪ DEREK
    ▪ CASE Ultra

• Risk assessment
  • 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

Mostly no or limited data available
Exclude mutagenicity & sensitisation potential

In parallel or Stepwise
General Impurity Qualification

Prediction methods

- **(Q)SAR systems:**
  - DEREK = Deductive Estimation of Risk from Existing Knowledge
    - **Endpoints 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”
    - **Endpoint 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, ...
General Impurity Qualification

<table>
<thead>
<tr>
<th>Chemical name; synonyms</th>
<th>formula</th>
<th>mol. wt.</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(1-Bromomethyl)hexyl-2,2,4,4-tetramethyl-cyclohexane; C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;Br Rubber Oligomer</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;Br</td>
<td>259.23</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation:**

**Derek predictions (summary and alerts found):**
- Carcinogenicity in human is PLAUSSIBLE; Alkylating agent
- Carcinogenicity in mammal is PLAUSSIBLE; Alkylating agent
- Chromosome damage in vitro in human is PLAUSSIBLE; Alkylating agent
- Chromosome damage in vitro in mammal is PLAUSSIBLE; Alkylating agent
- Irritation (of the eye) in human is PLAUSSIBLE; Alkyl halide
- Irritation (of the eye) in mammal is PLAUSSIBLE; Alkyl halide
- Irritation (of the respiratory tract) in human is PLAUSSIBLE; Alkyl halide
- Irritation (of the respiratory tract) in mammal is PLAUSIBLE; Alkyl halide
- Irritation (of the skin) in human is PLAUSIBLE; Alkyl halide
- Irritation (of the skin) in mammal is PLAUSIBLE; Alkyl halide
- Mutagenicity in vitro in bacteria is PLAUSIBLE; Alkyl 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

<table>
<thead>
<tr>
<th>ICH M7 Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Known mutagenic carcinogen</td>
</tr>
<tr>
<td>Class 2</td>
<td>Known mutagen</td>
</tr>
<tr>
<td>Class 3</td>
<td>Structural alert No Ames test data</td>
</tr>
<tr>
<td>Class 4</td>
<td>Alerting structure; similarity to Ames negative compound</td>
</tr>
<tr>
<td>Class 5</td>
<td>No structural alert or alerting structure with negative Ames test</td>
</tr>
</tbody>
</table>

**Experimental data** = (Q)SAR

**In silico assessment**
### General Impurity Qualification

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed action for control (details in Section 7 and 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Known mutagenic carcinogens</td>
<td>Control at or below compound-specific acceptable limit</td>
</tr>
<tr>
<td>2</td>
<td>Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)</td>
<td>Control at or below acceptable limits (appropriate TTC)</td>
</tr>
<tr>
<td>3</td>
<td>Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data</td>
<td>Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2</td>
</tr>
<tr>
<td>4</td>
<td>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</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
<tr>
<td>5</td>
<td>No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
</tbody>
</table>

- **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
So, we have a positive prediction we cannot invalidate? What Do We Do?
## General Impurity Qualification

<table>
<thead>
<tr>
<th>ICH M7 Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Known mutagenic carcinogen</td>
</tr>
<tr>
<td>Class 2</td>
<td>Known mutagen</td>
</tr>
<tr>
<td>Class 3</td>
<td>Structural alert; similarity to Ames negative compound</td>
</tr>
<tr>
<td>Class 4</td>
<td>Alerting structure; similarity to Ames negative compound</td>
</tr>
<tr>
<td>Class 5</td>
<td>No structural alert or alerting structure with negative Ames test</td>
</tr>
</tbody>
</table>

- Control at or below TTC (e.g. 1.5 µg/day)
- Experimental data
- Perform AMES
- In silico assessment
- PDE calculation
Deriving Permissible Daily Exposure (PDEs) for Impurities

\[ PDE = \frac{\text{NO(A)EL} \times \text{Weight Adjustment}}{F1 \times F2 \times F3 \times F4 \times F5} \]

- 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

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

**REMARK: NEVER USE LD50 TO CALCULATE A PDE!**

IF LD50 IS THE ONLY TOX INFORMATION, ADD LARGE ADDITIONAL SAFETY MARGINS!

*Literature mentions Safety factors for LD50 as high as 2000 to obtain a NOAEL*
DERIVING PDE’S FROM TOXICOLOGICAL DATA

EXAMPLE: SYSTEMIC TOXICITY

RESPONSE = Systemic Toxicity

PDE Calculations Translates data to applicable safety levels

Typical “Dose – Response” Curve

PDE / ADI

LOG (DOSE)

LOAEL

NOAEL

PDE Calculations Translates data to applicable safety levels
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.
  - 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)
• 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 must be verified by a certified Toxicologist.