BartCrofts Scientific Services Pty Ltd

RISK IDENTIFICATION FOR MANUFACTURE IN SHARED FACILITIES

# Basic Principles of Human Health Risk Assessment


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# Synopsis

- Compliance will require an expert review
  - The review is substantial and potentially involved
  - Required for each product
- For **innovator Companies** data requirements and assessment not onerous
- For **generic companies** there are some real challenges & substantial costs involved
- Dedicated facilities for high risk products unavoidable
  - Potent Allergens
  - Potent Genotoxic actives
- A number of aspects of the Draft Guidance are peculiar (or just wrong) and disproportionate to risk – eg;
  - derivation of PDE based on life time exposure
  - Incorrect description of NOEL determination

# Components of the Requirements

Regardless of the Regulatory Regime there are common components of different nature

- Science – substance specific, requires specific expertise and data
  - What are the potential adverse effects in humans
  - How much is safe
- Policy general and specific - dictated
  - Uncertainty Factors
  - Thresholds
  - Model exposure periods (acute, sub acute chronic)
  - Degree of Conservatism
- QC/QA/GMP – regulatory and company – dictated and product stewardship related
  - Cleaning procedures
  - Determination of residues
  - Pattern of release in subsequent batch
- Process- Regulatory - dictated
  - Documentation
- Procedure – management – business in the real world
  - Manufacturing sequence
  - Cost containment
  - Profitability

# The New Process

- "Evidence based"
- Replaces requirement for
  - max 10 ppm cross contamination or 1/1000$^{th}$ of clinical dose, or
  - dedicated facility
- Hazard Characterisation is based on donating product, you will need;
  - An HHRA for every active in every product you manufacture
    - The PDE is specific to the active not the product or process so once determined there will be no need to repeat
    - This aspect is likely to require an external expert for most generic producers
  - An assessment of the potential residual levels of active following clean-up of the equipment
    - Product and process specific
    - This aspect will be within the capabilities of the QC/QA staff within most facilities

      ***Requires Expert Certification***
    - **Following an expert review,** …. provide a **discussion with respect to the critical endpoints of concern** and ..**rationale for** the …..**dose** …**used** in the **derivation of the PDE**. The pivotal ….studies .. for the …PDE should be **sourced to the original reference** and **reviewed** regarding their quality (**study design, description of finding, accuracy of the report etc**.). ……..**provide a clear rationale regarding the adjustment factors that were applied** in deriving the PDE.
- Exposure Assessment based on receiving Product you will need to;
  - consider both the preceding product and the subsequent product
  - Determine quantity and distribution of likely carry over

# Fairly simple decision tree

1. Is the active highly allergenic or sensitising
   - Unless a threshold has been identified
   - Require a Dedicated manufacturing facility
2. Is the active Genotoxic
   - Yes Go to 3
   - No Go to 4
3. For genotoxic substances can a threshold be Identified
   1. Yes – calculate PDE
   2. No – Apply TTC of 0.15 µg per person per day
4. For non genotoxic actives calculate PDE (&/or consider TTC)

# Determination of the PDE

- PDE = Permitted Daily Exposure
  - Amount that can be consumed daily for a lifetime without appreciable risk
  - This is an irrational standard for batch to batch contamination but is the requirement nonetheless
- Perform a standard Human Health Risk Assessment

# HHRA – Step 1 Hazard Identification

- **Gather all data** potentially relevant to the toxicology assessment of the substance of interest.
  - Requires a formal literature search strategy if based on published sources.
- **Screen data** for quality and reliability.
  - **GLP** status of the test facility
  - **Test Guideline Compliance**
  - **Transparency**, quality and detail of data and method presentation
  - **Suitability of study design**
- **Identify potentially treatment related effects** in each study, considering
  - **Dose response** in terms of incidence and severity of each effect
    - **Dose Metrics** includes the amount of substance administered but also the frequency, route, duration and form of administration
    - **Response pattern** may vary between gavage versus dietary administration, 7 day a week versus 5 day per week administration
  - **Magnitude of the apparent effect** compared to background variation, using
    - **Concurrent control**(s) in the specific study
    - **Baseline values** for individual animals/subjects determined prior to commencement of dosing
    - **Historical controls** for the specific strain & source of test species
    - **Species variation data** more broadly – for rare endpoints
  - **Concordance** of the observation with correlating parameters
  - **Statistical significance**

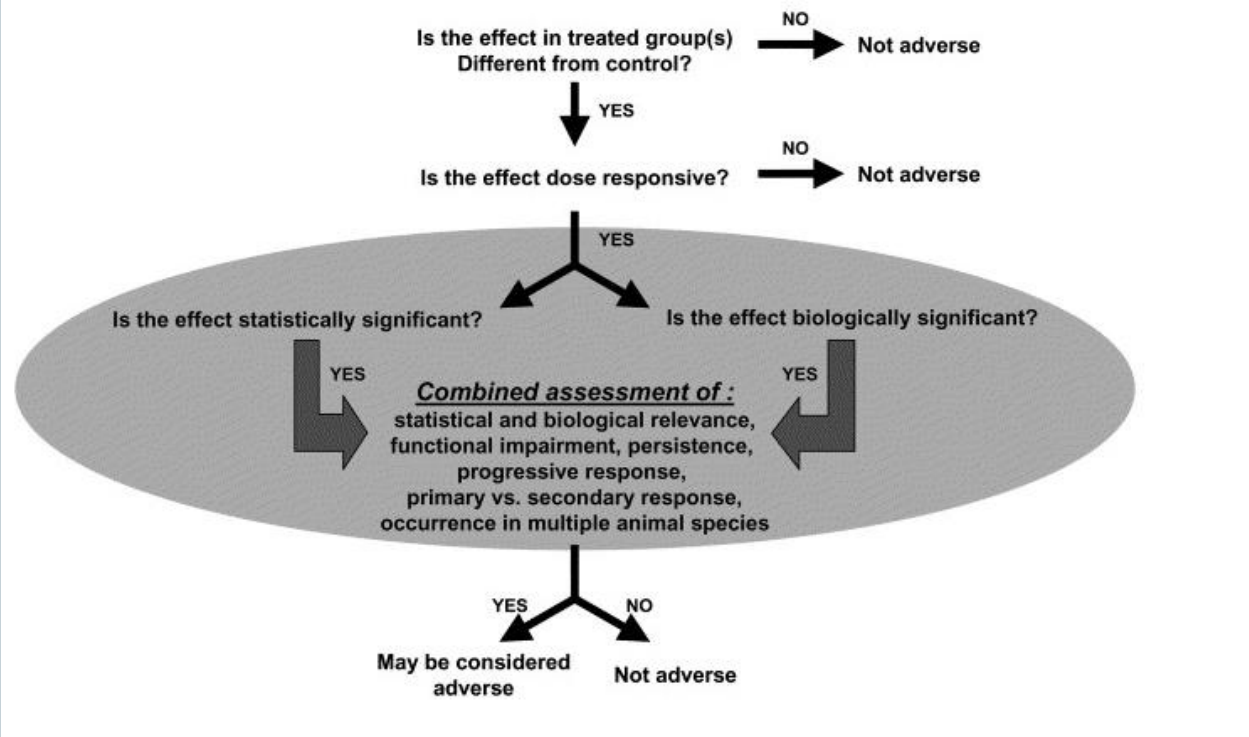
# Hazard Identification Cont

- **Assess the toxicological significance** of the observed effects ***to the model*** (or test population) in terms of
  - The **biology of the model**/test species/sub population considering
    - **Species specific ADME** of the compound (or any potential genetic PK differences in the test population)
    - **Presence or absence of specific targets** (organs/tissues/biochemical pathways)
  - **Toxicology**, differentiating between adaptive responses and adverse effects, considering
    - **reversibility** of the effect
    - **pathological significance** of the endpoint in terms of normal biological and physiological function, longevity of the test species
    - **Time of onset** in comparison to the life span of the test animal
    - **Progression** of the severity &/or incidence of the effect over time
    - **Species** specificity or cross species concordance of effect
    - **Primary or Secondary** nature of the effect
    - **Mode of Action** leading to the effect.
  - **Statistics**
    - **Differentiate** between random statistical significance due to multiple comparisons from true effects based on a consideration of;
      - **Concordance** with correlating parameters
      - **Consistency across studies** in the same model/species/test population
      - **Consistency across species**/models/test populations
      - **Nature of the dose response** in terms of incidence and severity
- Consider the **relevance of the test system**, study design, animal model or other data generation technique, to the population potentially at risk of exposure to the substance.
  - **Mode of action**
  - **Comparative biology, anatomy and behaviour** between test species and man
- **Identify the population potentially at risk** from those effects (gender, age group, life stages such as pregnancy, lactation).

# HHRA – Step 2 identify Critical effect

- **Identify Treatment related effects**
  - Differentiation of the normal random variation within a toxicology study from those effects that are genuinely treatment related
    - The presence and strength of any **dose relationship** in terms of both incidence and severity;
    - The presence of isolated animals in control or treatment groups that are driving the observed difference(s), known as **outliers**,
    - The use of a **measurement technique that has inherent limits of precision**,
    - The magnitude of the effect in relationship **to historical control values,**
    - The **biological plausibility** of the apparent effect in terms of;
      - consistency with known class effects of the test substance,
      - mode of toxicological action where that is known,
      - other knowledge of the nature and behaviour of the test substance,
    - Consistency and concordance of the observation with other biologically and mechanistically related parameters,
    - Consistency with findings in other studies of similar or longer duration in the same or other species
- **Distinguish between adaptive and adverse effects**

# HHRA Step 2 – Determine adversity




Approach to classifying toxicology study results as adverse or non-adverse (modified from Lewis et al., 2002 by Dorato and Englehardt 2005

# HHRA Step 3 identify the Point of Departure

- From the list of adverse effects across all studies
  - Identify the effect that occurs at the lowest dose in the most sensitive species – **that is relevant to humans**
  - Identify the highest dose at which the effect was not seen in that species
  - This is the overall NOAEL – (NOEL in EMA guidance) or Point of Departure (POD) and is the dose that will be used to calculate the PDE

# HHRA – Step 4 apply uncertainty factors

- Uncertainty factors are intended to compensate for the nature and potential magnitude of identified uncertainties
- The application of UFs is the largest single determinant of the PDE and can have a large impact on permitted production practices ($$$$$)
- Sounds scientific but in reality is arbitrary and primarily policy based.
- **EXPERT JUDGEMENT + SOLID DATA** can however moderate UFs downwards

# Calculate the PDE

- PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL) in the most relevant animal study as follows:
- $\text{PDE} = \frac{\text{NOEL x Weight Adjustment}}{(F1xF2xF3xF4xF5)}$

F1 = A factor to account for extrapolation between species

F1 = 5 for extrapolation from rats to humans

F1 = 12 for extrapolation from mice to humans

F1 = 2 for extrapolation from dogs to humans

F1 = 2.5 for extrapolation from rabbits to humans

F1 = 3 for extrapolation from monkeys to humans

F1 = 10 for extrapolation from other animals to humans

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure

F3 = 1 for studies > half a lifetime (1 yr rodents &rabbits;7 yrs cats, dogs & monkeys).

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents.

F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents.

F3 = 10 for studies of a shorter duration.

# Adjustment factors Continued

F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity

F4 = 5 for fetal toxicity without maternal toxicity

F4 = 5 for a teratogenic effect with maternal toxicity

F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established

**When only an LOEL is available**, a factor of up to 10 could be used depending on the severity of the toxicity.

**The weight adjustment** assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a

PDE.

If the formulation is for paediatric use, use adjustment for an appropriately lower body weight

# For potent pharmacological actives

- Check that the PDE is below the highest dose tested that is pharmacological inefficacious
- For toxicologically benign actives a pharmaco-dynamic NOEL based on ***Clinical*** studies can be used (eg macromolecules and peptides)
- **TOXICOLOGICALLY BENIGN =**
  - Not a Teratogen
  - Not a Reproductive toxin
  - Not a Genotoxin,
  - Not a Carcinogen, ***AND***
  - No target organ effects at doses below adverse pharmaco-dynamic effects (ie adverse effects due to excessive ***PRIMARY*** pharmacological effects)

# Threshold of Toxicological Concern (TTC)

- For genotoxins the TTC is generally 0.15 µg/person per day (some exceptions for potent genotoxins
- Not clear this approach is available for non genotoxins but worth including in any HHRA as a cross check and supporting consideration
- EC has generally accepted the principle across most other HHRA regulatory frameworks

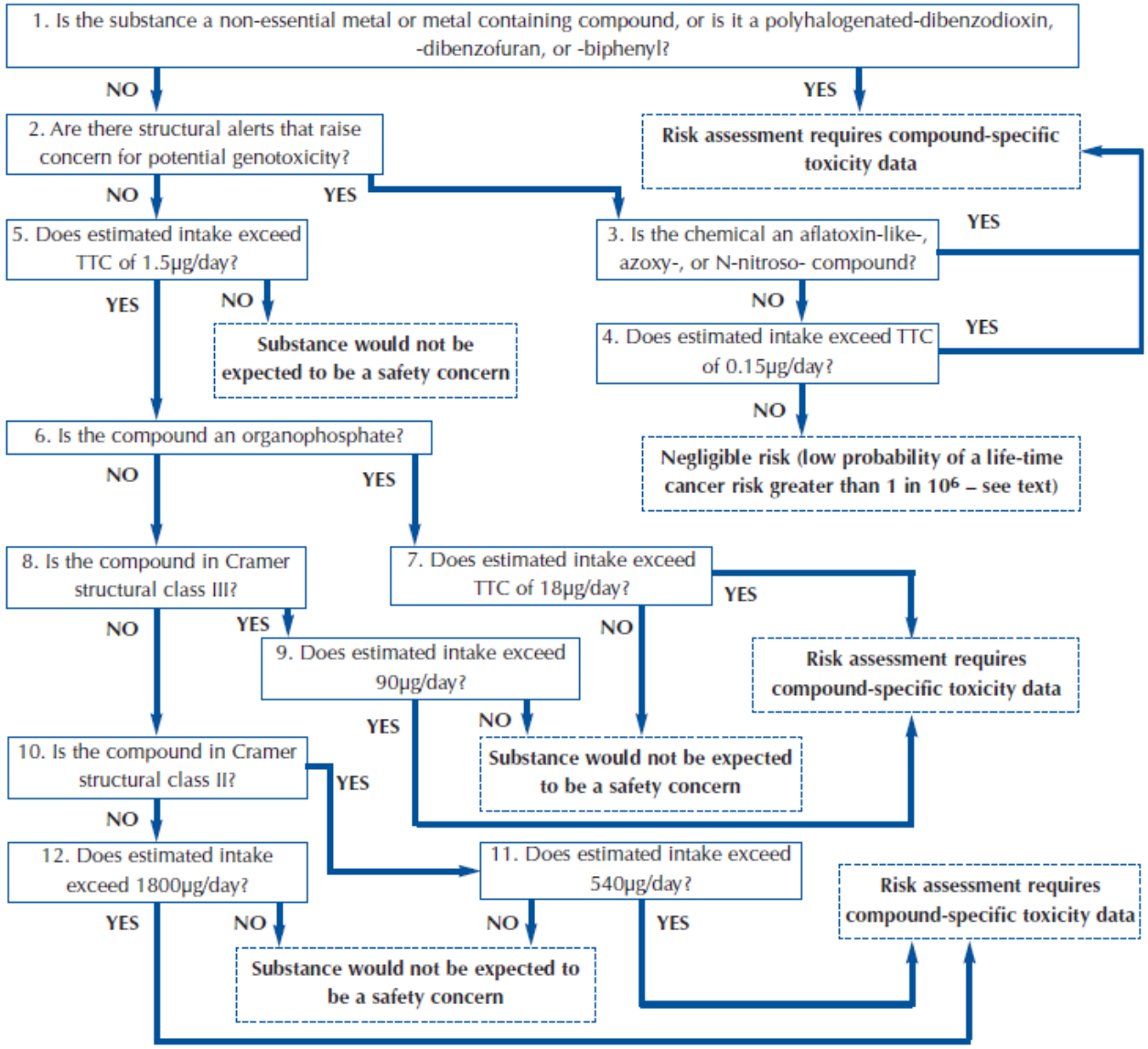
# EU/EC TTC Considerations

- "The SCs accept in principle the division (of chemicals) into Class I and Class III".
- For the lowest toxicity class
  - (Class I, 1800 µg/person/d corresponding to 30 µg/kg bw/d for substances without genotoxicity alerts), classification should be carefully considered and justified.
  - If classification in Class I cannot be justified the SCs recommend a general default value equivalent to Cramer Class III compounds (90 µg/person/d corresponding to 1.5 µg/kg bw/d **for substances without genotoxicity alerts**).

SCCS, SCHER, SCENIHR 2012 Opinion on **Use of the Threshold of Toxicological Concern (TTC) Approach for Human Safety Assessment of Chemical Substances with focus on Cosmetics and Consumer Products.** SCCP/1171/08

# BOX 6

**Decision tree proposed by ILSI Europe to decide whether substances can be assessed by the TTC approach (From Kroes *et al., Food and Chemical Toxicology* 42, p76, 2004)**



# TTC Approach – Cramer Classes

- The Cramer classification scheme divides chemicals into three classes according to their predicted toxicity as judged from structural alerts and metabolism:
  - *Class I:* substances of simple chemical structure with known metabolic pathways and innocuous end products that suggest a low order of toxicity
  - *Class II:* chemical structures that are intermediate they are chemicals that are less innocuous they may contain reactive functional groups but do not contain the structural features suggestive of toxicity
  - *Class III:* chemicals for which structural features or likely metabolic pathways permit no strong presumption of safety, or may even suggest significant toxicity.

# Conclusions

1. **A FORMAL, EXPERT, HHRA WILL BE REQUIRED FOR EVERY ACTIVE INGREDIENT** used within a facility UNLESS it is produced in a dedicated facility that produces no products containing other actives
2. For Generic manufacturers the data requirements and assessments will be extensive, costly and possibly challenging, particularly for older actives
3. Determination of PDEs is (mostly) a once off exercise for each active (with regular review to ensure new data has not emerged that would alter the PDE)
   - Weight factor is determined by receiving product however
4. Each new production sequence will require a Risk assessment based on the receiving product
   - Carry over per unit dose
   - Doses per day
   - Comparison of subsequent intake per day against PDE

**The literature search, data acquisition and HHRA may take considerable time**

- The time requirements should be included in business plans
- So don't leave it to the last minute