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Permissible exposures without data

GTA Workshop 2018

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Threshold of Toxicological Concern (TTC)
Conservative approach

Default value for control of mutagenic impurities

Assumes carcinogenicity potency would be linear; generated from most potent carcinogens from lifetime dosing studies

Control levels may be difficult to achieve in drug substance (DS) or drug product (DP)

Use less than lifetime limitation for shorter duration exposures

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

ICH Q3A limits

Default limits in lieu of toxicology data for organic, non-mutagenic impurities

- Q3A for drug substance impurities
- Q3B for drug product impurities
- Q3C for residual solvents

Data support a default dose of 1 mg/day **for a lifetime** as not concerning for patient safety. Could consider higher levels for short duration trials (Harvey, et al.).

Classification systems

Cramer decision tree: decision scheme to categorize compounds into

- Class 1: low order of oral toxicity
- Class 2: intermediate toxicity
- Class 3: Significant toxicity potential

Munro: used Cramer classifications to further refine human exposure thresholds

- Class 1: 1.8 mg/day
- Class 2: 0.54 mg/day
- Class 3: 0.09 mg/day

Dolan: potency based classifications (1 µg to 100 µg) often used in occupational toxicology

Read-Across to set compound or class-limits

Use structurally analogous compounds with robust data to help set PDE

Careful consideration for the data set to be used

- How many compounds can contribute and defining similarity
- Quality of the data

Examples:

- Monofunctional chlorines and bromines
  - Data set of carcinogenic compounds reviewed for potency
  - Additional TD50s calculated where needed
  - Conclusion: 10-fold higher limit than default TTC
  - Outcome: can use this higher limit for monofunctional chloro- or bromo-impurities with unknown toxicities

Published limits

Could be from agencies without specific consideration for pharmaceutical impurities

- WHO, US-EPA, EFSA
- Risk level may be 10-fold more conservative than pharmaceuticals

Published values derived from estimated expected toxicity may be more conservative

Formaldehyde (Bercu, et al.)

- Different PDE for different routes (carcinogenic via inhalation route)
- Published limits 10 mg/day oral route within range of daily endogenous exposure

Endogenous/Daily exposure

Use language from guidelines for exposure > from food (ICH M7)

Published values may point to higher levels than TTC or ICHQ3x

Vinyl acetate (Bercu, et al.)

- Toxicity attributed to acetaldehyde; rapidly metabolized to naturally occurring acetaldehyde
- Ames negative; site of contact tumors
- Assigned PDE based on PDE of acetaldehyde

Arginine

- Structurally alerting and Ames positive
- Acceptable as a food additive (FDA), estimated whole body production/consumption up to 25 g/day
- Controlled as an ordinary impurity

Examples where no defined limit set: No data

Hoat and HATU

- Ames negative
- No carcinogenicity data
- No general toxicity data
  - LD50 data in RTECS
- Could not set a defined lifetime PDE
- Recommended following ICHQ3A qualification thresholds (Bercu, et al)

Example where no defined limit set: inadequate data

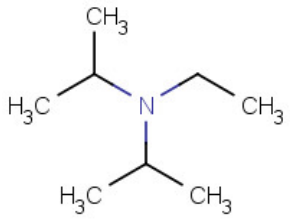
Tert-butyl chloride

- Ames negative
- LD50 data available; no repeat-dose toxicity data
- Carcinogenicity data is inadequate for evaluation
  - Strain sensitive to lung tumors not appropriate for human cancer risk assessment
  - Low survival
  - US-EPA considered study inadequate
  - Only repeat-dose study found
- Recommend following ICHQ3A qualification thresholds (Bercu, et al)

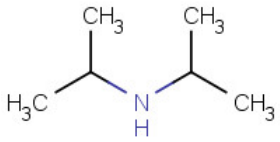
Discussion examples:
DIPEA

DIPEA (diisopropylethylamine)

- Ames negative
- No repeat dose toxicity studies nor carcinogenicity studies
- Munro, et al: cite a 0.56 µg/kg/day RfD based on read across from diisopropylamine (DIPA)



DIPEA



DIPA

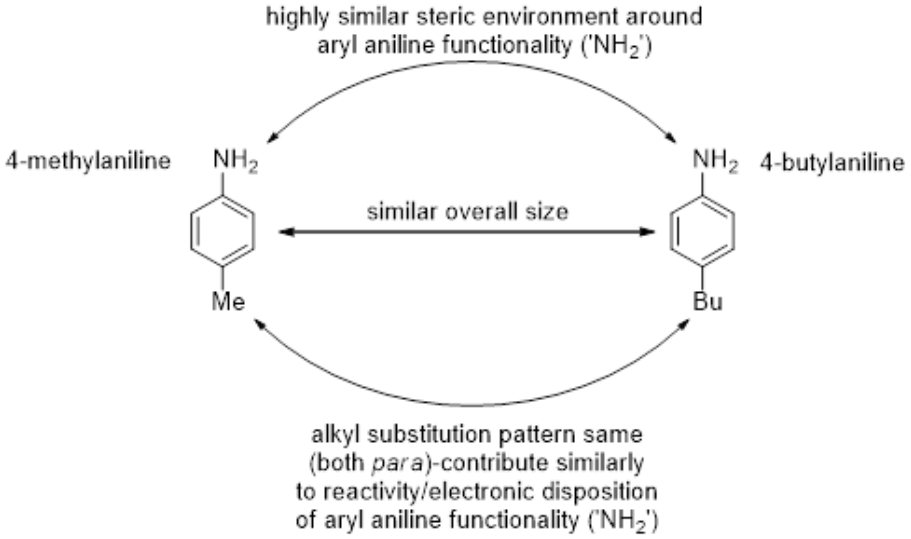
Discussion Examples:
4-butyl aniline

No alerts for mutagenicity; No Ames data

No repeat dose-toxicity or carcinogenicity data found

Highly similar to 4-methylaniline

- Ames Neg; 4-methylaniline
  - HCl positive with hamster S9
- - Liver carcinogen in mouse feed studies



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Disclosures

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