Safety Qualification Thresholds for Leachables in OINDP[1]

Douglas Ball; James Blanchard; Roger McClellan; Timothy McGovern; David Porter; Mark Vogel; Ronald Wolff

Thresholds

The PQRI Leachables and Extractables Working Group developed a ***Safety Concern Threshold (SCT)*** and a ***Qualification Threshold***.

The ***SCT*** is a threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects. The SCT would not be applied to certain classes of compounds with special safety concerns (e.g., nitrosamines, polynuclear aromatics, mercaptobenzothiazole, etc.). The SCT is ***0.15 µg/day***

The ***Qualification Threshold*** is a threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship concerns. ***The QT is 5 µg/day***.

These thresholds were developed using:

(i) information from well-established databases, guidelines[2], and the current literature and,

(ii) well-established risk assessment approaches.

Developing the SCT

To develop the ***SCT***, the Carcinogenic Potency Database (CPDB) was used along with risk assessment assumptions. The subset of all genotoxic (SAL-positive) compounds from the CPDB was chosen as the basis for estimating carcinogenicity risk to determine the SCT for OINDP. The following were also considered:

- CPDB is a large and robust database used for setting the threshold of regulation for indirect food additives.
- SAL-positive carcinogens are more potent than SAL-negative carcinogens
- Slope factor approach, assuming linear extrapolation to zero risk, is more applicable to genotoxic than non-genotoxic carcinogens.
- As a basis for the SCT, the genotoxic carcinogens are appropriate because it is the potentially mutagenic compounds for which chemical structural “alerts” are most likely predictive, and for which structural information for a leachable is particularly desirable
- Carcinogenic potency for the small set of carcinogens tested by the inhalation route mirrors that for the larger set of compounds tested by all routes
- The 10^{-6} level is an appropriately conservative level, and it has been used as an acceptable carcinogenicity risk by US regulatory agencies such as FDA and EPA.
- Dose scaling is appropriate for adjusting carcinogenic potency estimates in humans for the more rapid clearance of chemicals by rodents, but combining this approach with estimates based on the most sensitive species and upper confidence limits of carcinogenic slope will likely overestimate human risk
- 50 vs 70 kg for default human weight makes relatively little difference in risk estimate, but the more protective 50 kg value is consistent with the approach often used for US pharm aceutical labeling

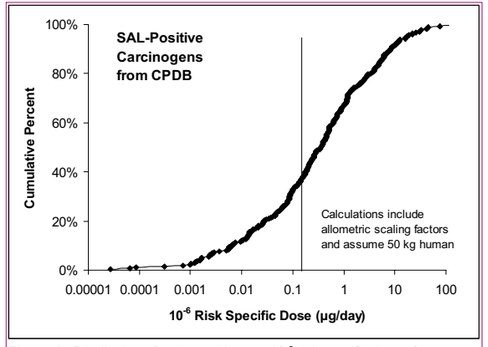


Figure 1. Distribution of estimated human 10^{-6} risk specific doses for 276 SAL-positive carcinogens from Carcinogen Potency Database (CPDB).

Based on this distribution of known genotoxic carcinogens, a level of 0.15 µg/day as the SCT was established. 0.15 µg/day corresponds to the 37th percentile of SAL-positive carcinogens in the CPDB. The median excess cancer risk for a SAL-positive carcinogen at 0.15 µg/day is 0. 41 x 10^{-6}.

In establishing the threshold of regulation for indirect food additives, FDA analysis assumed that 20% of all chemicals are likely to be human carcinogens. Coupling that with the 0.15 µg/day exposure level provides a level at which less than 10% of all compounds (20% x 37% = 7.4%) would present more than a 10^{-6} carcinogenicity risk.

Developing the QT

The ***QT*** was developed using safe exposure levels of airborne pollutants based on ***noncarcinogenic endpoints***.

The Group examined databases used by the US EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), and the California Environmental Protection Agency (CAL EPA).

A total of 150 inhalation reference values from these databases were combined for analysis in a single data set (**Figure 2**).

The toxic effect upon which the reference values were determined was a systemic toxicity endpoint for 93 chemicals (e.g., neuro-toxicity, hepatic toxicity, etc.) and a respiratory toxicity endpoint for 52 chemicals (e.g., nasal or tracheal toxicity); for 5 chemicals no organ toxicity was defined at the high-dose, but were included in the toxicity distributions for both systemic and respiratory exposure.

In cases where more than one reference value was available, a combined reference value was calculated as the geometric mean of the available reference values.

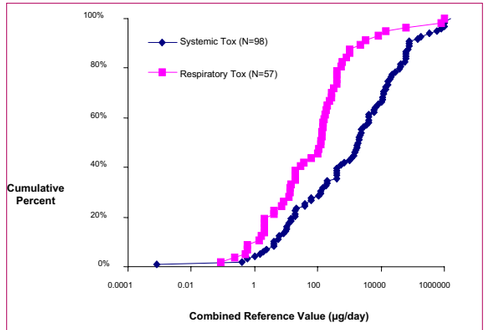


Figure 2. Distribution of reference values for the combined database

For the combined data set, the median reference value for chemicals with respiratory toxicity endpoints was ***120 µg/day***, and the median reference value for chemicals with systemic toxicity endpoints was ***1940 µg/day***.

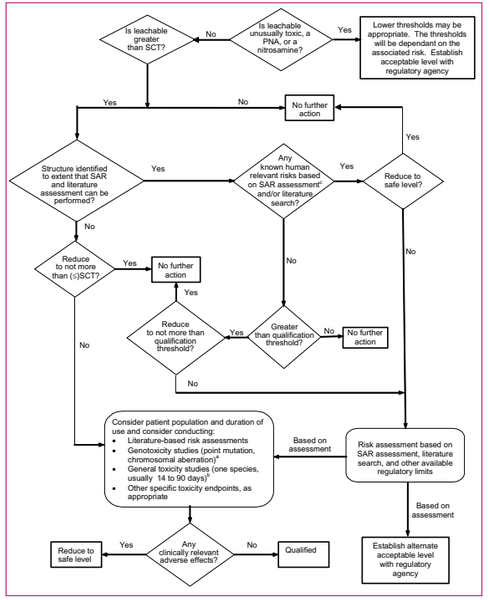
The cumulative percent on the vertical axis is the percentage of cases falling below a reference value specified within the distribution of reference values.

A ***QT*** of 5 µg/day was established. Data from inhalation reference values for environmental pollutants show that a qualification threshold for leachables of 5 µg TDI meets the criterion of a dose that is sufficiently low as to present negligible safety concerns for noncarcinogenic toxic effects.

The inhalation reference values for most of the chemicals in the data set are well above the 5 µg/day level. Chemicals with reference values less than 5 µg/day are primarily metals, irritants, and highly toxic substances unrepresentative of the types of organic chemicals that leach from components of OINDP. This threshold value is protective of over 80% of compounds in the combined database.

Application of Thresholds

The flowchart demonstrates how the SCT and the QT can be used in a safety qualification process for OINDP.



Footnotes for flowchart

(a) If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

(b) If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of a leachable. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

(c) For example, do known safety data for this leachable or its structural class preclude human exposure at the concentration present?

References

1. The views presented in this poster do not necessarily reflect those of the Food and Drug Administration
2. Guidelines and databases:
   - ICH Q3A, Impurities in New Drug Substances
   - ICH Q3B, Impurities in New Drug Substances
   - ICH Q3C, Impurities in New Drug Substances
   - Carcinogenic potency database (CPDB)
   - Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST)
   - California Environmental Protection Agency
   - World Health Organization (WHO) guidelines for drinking-water quality
   - Agency for Toxic Substances and Disease Registry (ATSDR)
   - Environmental Protection Agency, National Ambient Air Quality Standards for Particulate matter