


Development and Justification of a Safety Concern Threshold

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Identification of Leachables -- How Low Should You Go?

- There are levels of chemical exposure below which the risks to human health are negligible (*de minimis*).
- Leachables in OINDP below data-supported threshold levels are generally not of concern.
- The Safety Concern Threshold was developed as a starting point for development of an analytical threshold for leachables.

Definitions – Safety and Analytical Thresholds

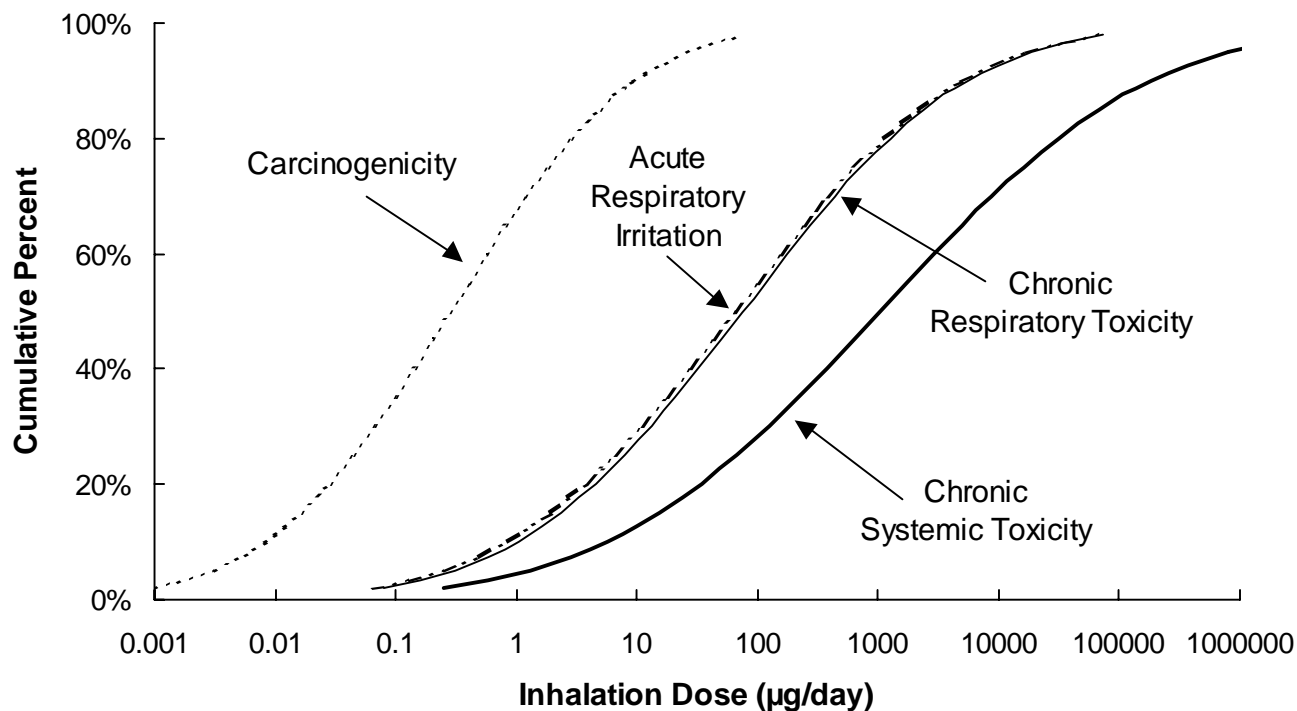
- **Safety Concern Threshold (SCT):**
Dose in $\mu\text{g}/\text{day}$ below which a leachable would present negligible concern for adverse carcinogenic and noncarcinogenic effects.
- **Analytical Evaluation Threshold (AET):**
Concentration (eg, $\mu\text{g}/\text{canister}$) in drug product, corresponding to the SCT, at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment.



Safety Concern Threshold is Based on Carcinogenicity Risk

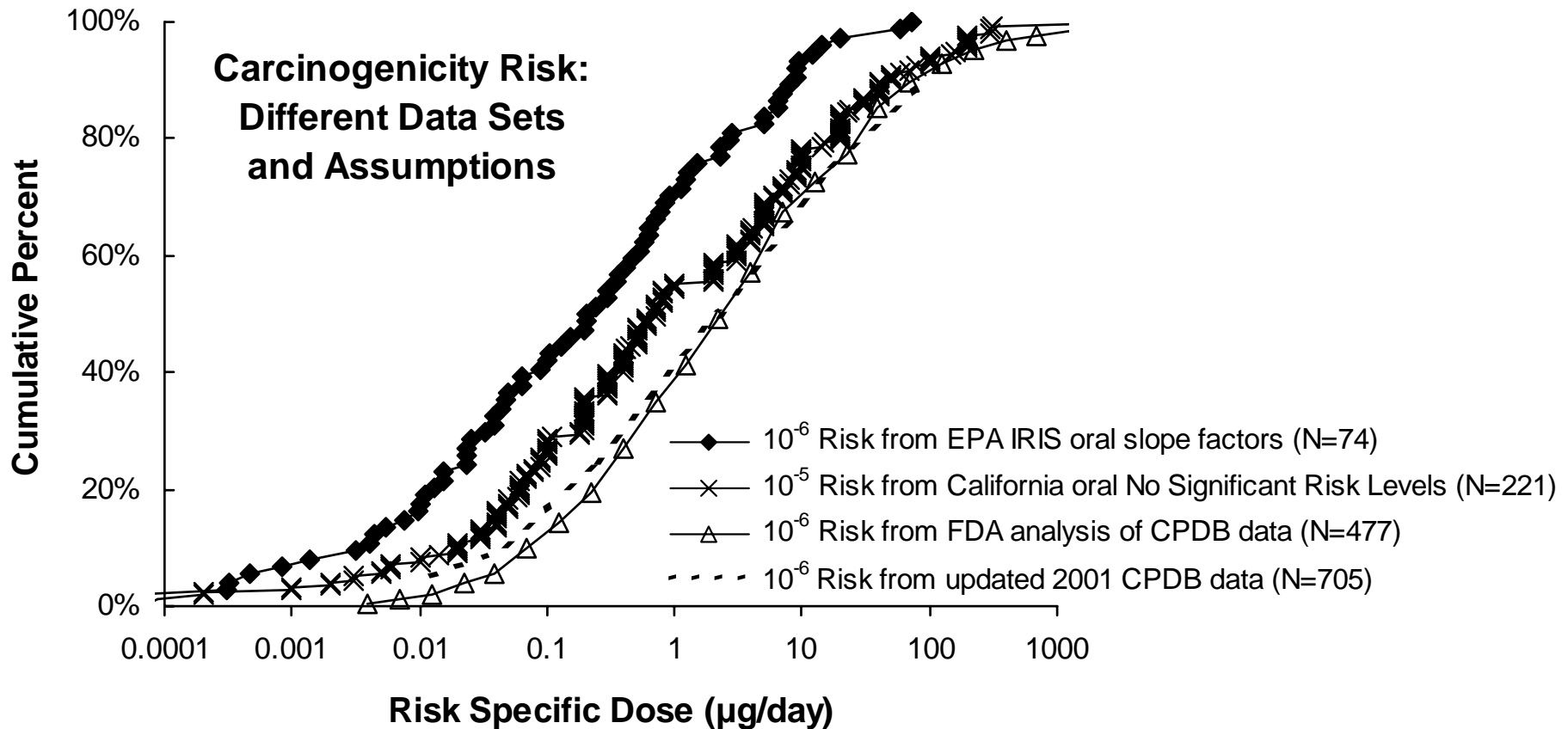
- Based on quantitative risk analysis, the SCT limits carcinogenicity risk of unidentified leachables to an acceptable level.
- Carcinogenic effects typically occur at intakes lower than those at which noncarcinogenic toxic effects occur.
- Thus, intakes with acceptable cancer-risk will also meet the criterion for negligible safety concerns from noncarcinogenic toxicity.

Safe Human Exposures for Different Toxicity Endpoints

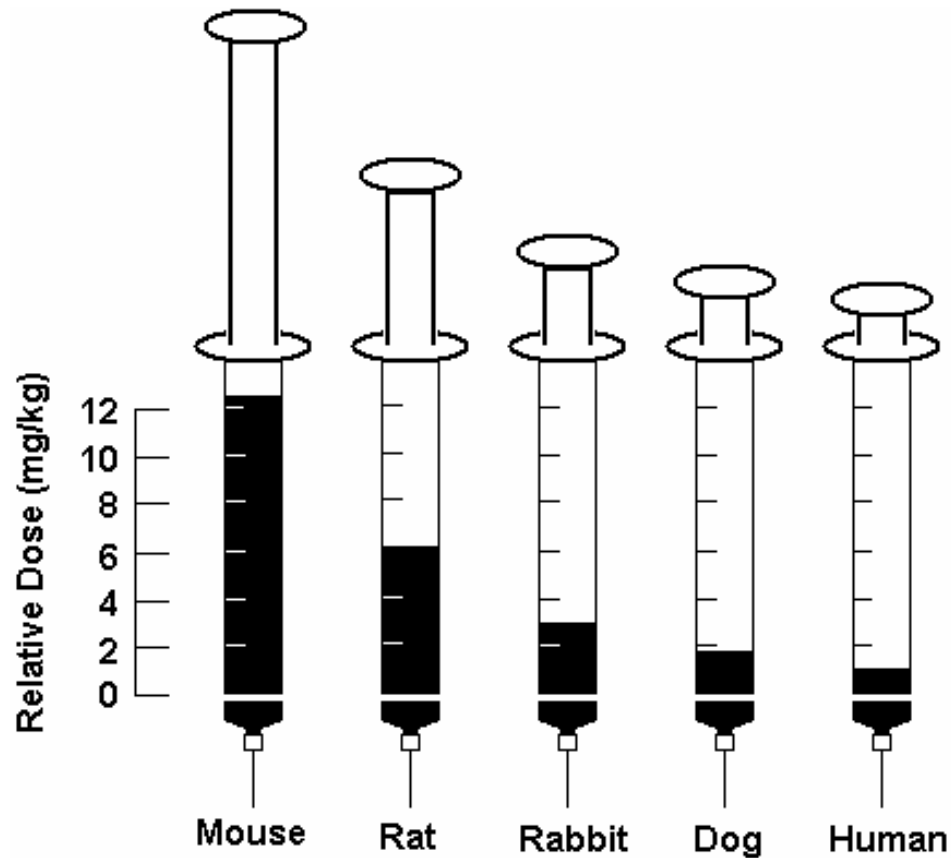


- Carcinogenicity, 10^{-6} Risk Specific Dose for CPDB Mutagens (N=276)
- .-.-.- Acute Irritation, Human Equivalent RD50/1000 (N=244)
- Respiratory Toxicity, Chronic Inhalation Reference Dose (N=57)
- Systemic Toxicity, Chronic Inhalation Reference Dose (N=98)

Different Carcinogenicity Risk Assumptions



What About Dose Scaling?



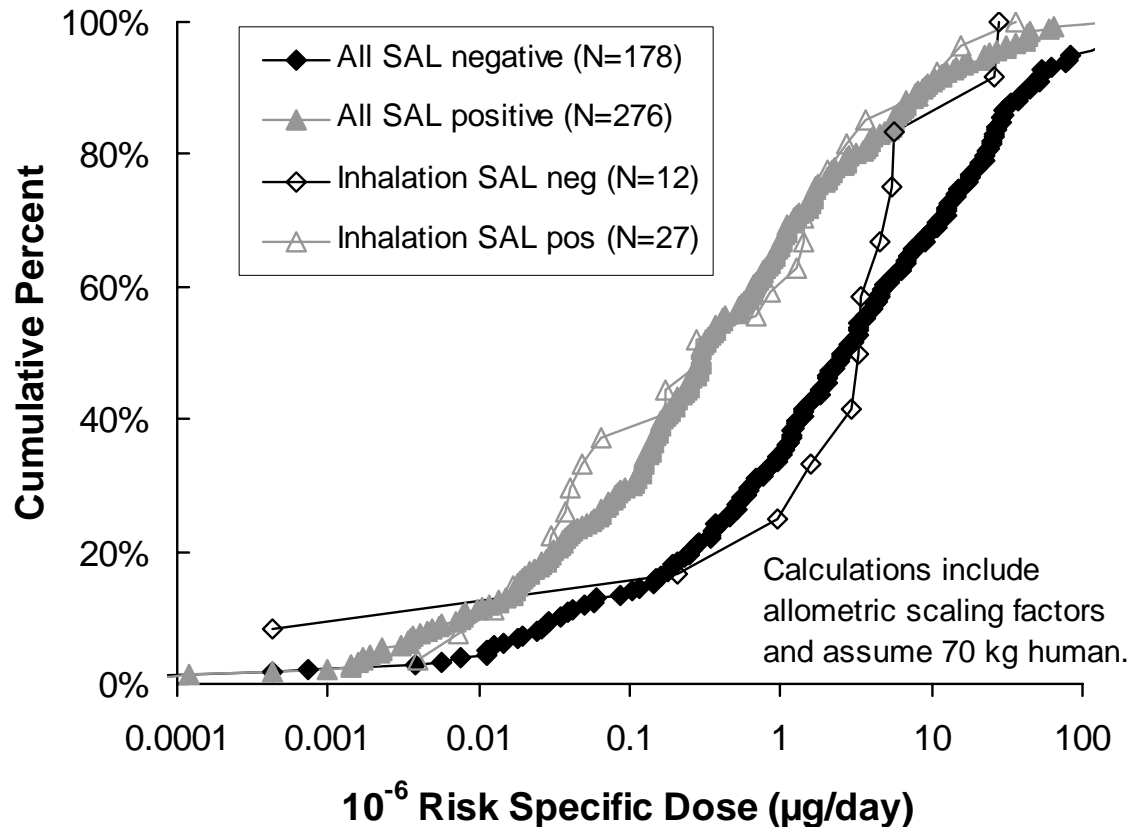


Dose Scaling (continued)

- US EPA uses dose scaling in quantitative carcinogenicity risk assessment.
- US prescription labeling uses dose scaling (mg/m² dose) in absence of systemic exposure.
- ICH uses dose scaling for residual solvent PDEs.
- CPDB data support dose scaling (~3x higher TD₅₀ in mice vs rats).
- Dose scaling can overestimate risk if combined with other conservative assumptions.

Genotoxic Carcinogens Are More Potent Than Are Non-Genotoxic

10^{-6} Carcinogenicity Risk - CPDB Data



What Carcinogenicity Risk Level is “Safe” ?

- FDA and EPA have used 10^{-6} risk
- CPMP proposes 10^{-5} for drug impurities
- California “Prop 65” uses 10^{-5} risk
- Occupational limits may use 10^{-4} risk
- 10^{-6} risk level is appropriate for leachables
 - Greater protection for multiple leachables
 - Leachables less “drug-like” than API-related
 - “Lifetime” exposure not uncommon (asthma)



Basis for the Safety Concern Threshold

- The CPDB is a large robust database used previously for setting the threshold of regulation for indirect food additives.
- Genotoxic (SAL-positive) carcinogens are particularly relevant for safety concern:
 - More potent than SAL-negative carcinogens
 - Linear extrapolation to zero risk (ie, no risk-free dose) more applicable to genotoxic carcinogens
 - Most known human carcinogens are genotoxic
 - Structural alerts are more predictive for genotoxics

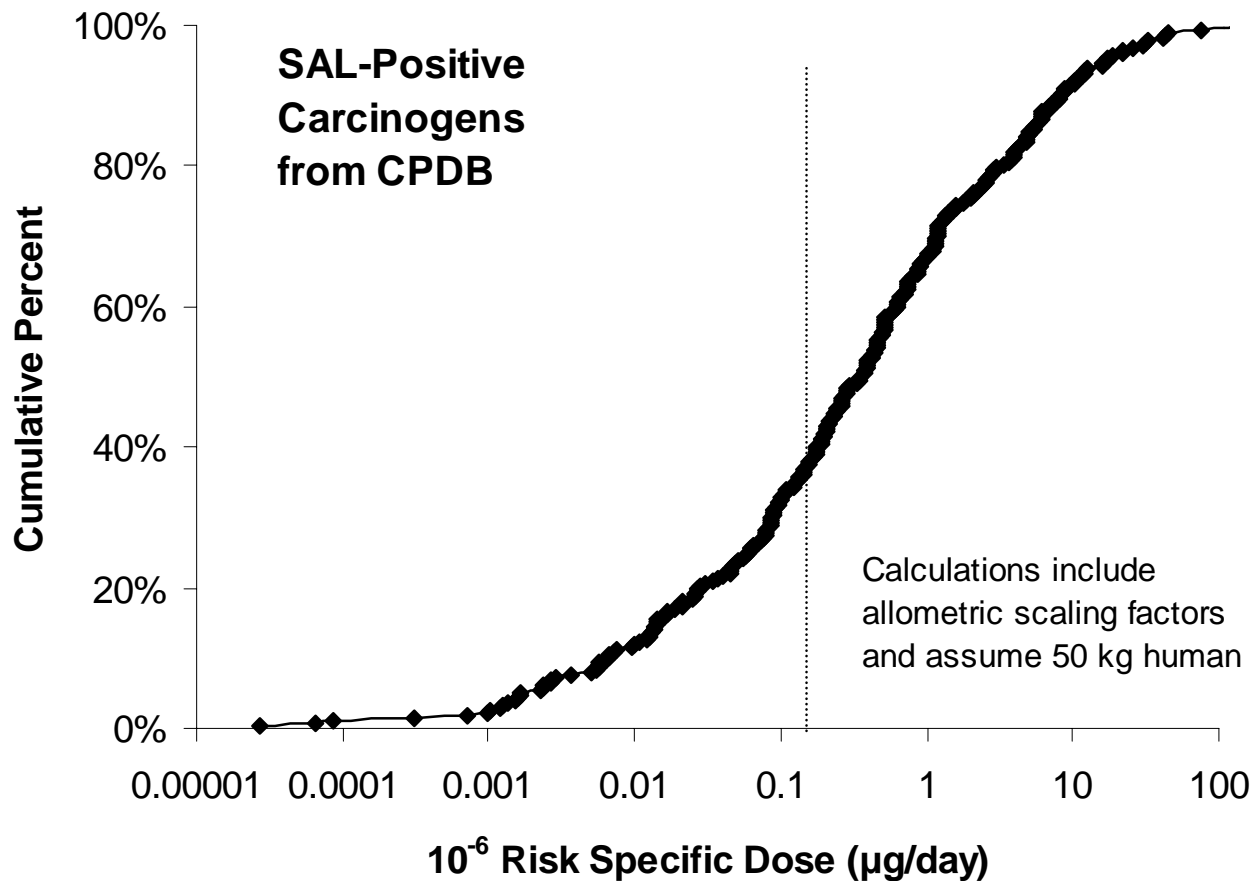
Basis for the Safety Concern Threshold (continued)

- Carcinogenic potency of carcinogens tested by inhalation is similar to that of the larger set of compounds tested by all routes.
- The 10^{-6} level has been used as an acceptable carcinogenicity risk by US regulatory agencies such as FDA and EPA.

Basis for the Safety Concern Threshold (continued)

- Dose-scaling appropriately adjusts carcinogenic potency for the more rapid clearance of chemicals by rodents, but using the most sensitive species and upper confidence limits of carcinogenic slope with dose-scaling overestimates human risk.
- Using 50 vs 70 kg for human weight makes relatively little difference in risk estimate; the 50 kg value is typically used for US pharmaceutical labeling.

Identifying the Safety Concern Threshold





SCT of 0.15 $\mu\text{g}/\text{day}$

- Corresponds to the 37th percentile of SAL-positive carcinogens in the CPDB.
- Median excess cancer risk for a SAL-positive carcinogen at 0.15 $\mu\text{g}/\text{day}$ is 0.41×10^{-6} .
- If 20% of random chemicals are genotoxic carcinogens, <10% of all compounds would present $>10^{-6}$ increased cancer risk at 0.15 $\mu\text{g}/\text{day}$.



Conclusion

- Unknown leachables in OINDP at intakes below a Safety Concern Threshold of 0.15 $\mu\text{g}/\text{day}$ present negligible concern for carcinogenic or non-carcinogenic health risks.
- Identification of leachables below this threshold is generally not necessary.
- But ... some specific, highly potent leachables (eg, nitrosamines, PAHs) may need identification at lower levels.



Acronyms

- CPDB – Carcinogen Potency Database
- CPMP – Committee for Proprietary Medicinal Products
- EPA – Environmental Protection Agency
- IRIS – EPA Integrated Risk Information System
- OINDP – orally inhaled and nasal drug products
- PAH – polynuclear aromatic hydrocarbons
- PDE – Permitted Daily Exposure
- SAL – Salmonella bacterial mutagenicity
- SCT – Safety Concern Threshold
- TD₅₀ – carcinogen dose that halves the lifetime probability of remaining tumor-free