



# **Best Practices for OINDP Pharmaceutical Development Programs Leachables and Extractables**

## **III. Safety Evaluation of Extractables and Leachables**

*PQRI Leachables & Extractables Working Group*

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# L&E Hypothesis

- ▶ Scientifically justifiable thresholds can be developed for the reporting and safety qualification of leachables in OINDP and the reporting of extractables from critical components used in corresponding container/closure systems.
- ▶ Safety qualification of extractables would be scientifically justified on a case-by- case basis

# Definitions – Safety Concern & Qualification Thresholds

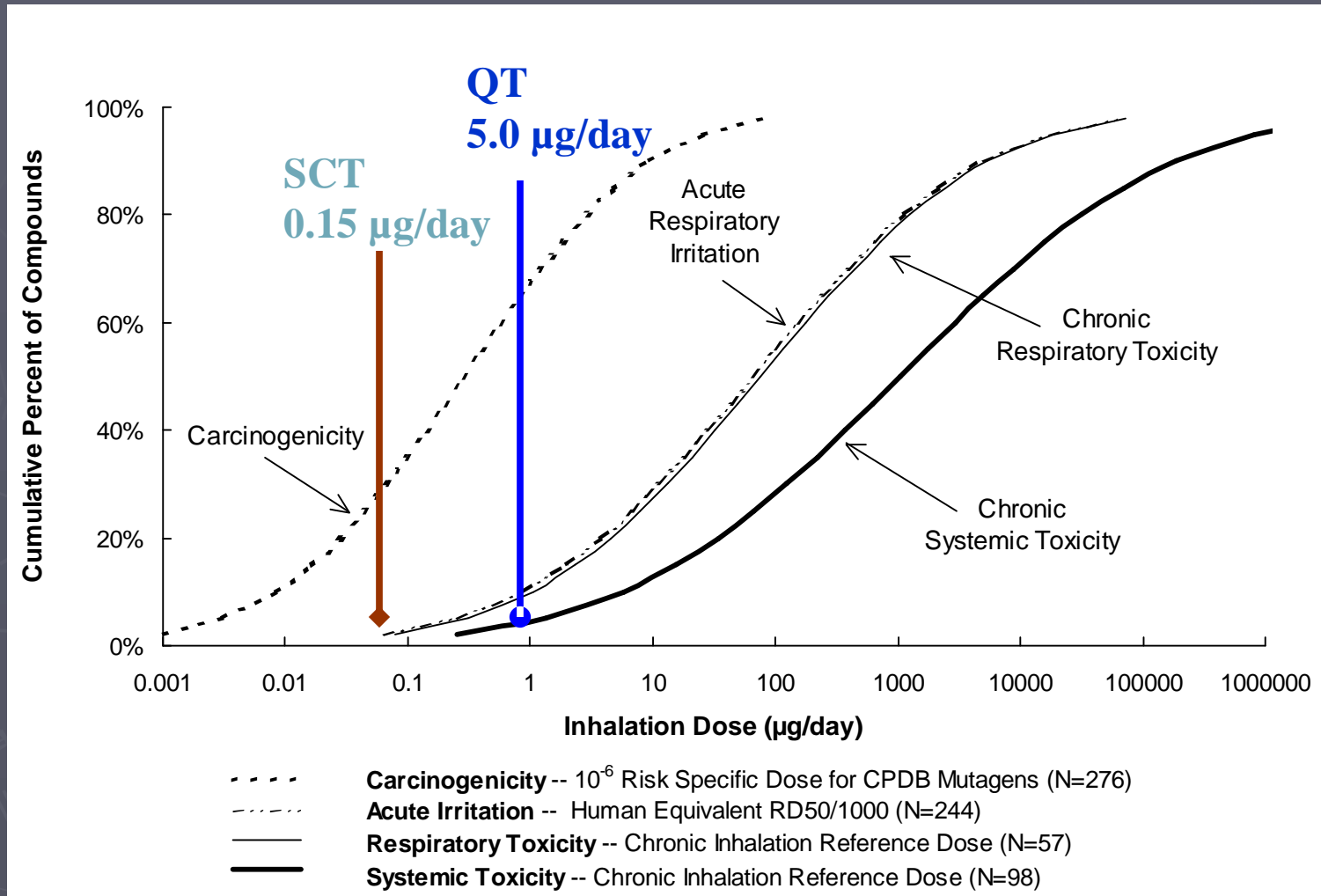
## ► Safety Concern Threshold:

- § Dose below which concern for carcinogenicity and noncarcinogenic toxicity is negligible
- § Identification of leachables below this threshold generally would not be necessary

## ► Qualification Threshold

- § Dose below which concern for noncarcinogenic toxicity is negligible
- § Leachables below this threshold without structural alerts for carcinogenicity or irritation would not require compound-specific risk assessment

# Safe Human Inhalation Exposures for Different Toxicity Endpoints



# Safety Concern Threshold (SCT) is Based on Carcinogenicity Risk

- ▶ Carcinogenicity typically occurs at lower intakes than noncarcinogenic toxicity
- ▶ Thus, intakes with acceptable cancer-risk entail negligible concern for noncarcinogenic toxicity
- ▶ Based on quantitative risk estimates, the SCT limits carcinogenicity risk of unidentified leachables to an acceptable level ( $10^{-6}$ )
- ▶ Similar to approach for FDA Threshold of Regulation for indirect food additives, but with some methodological differences

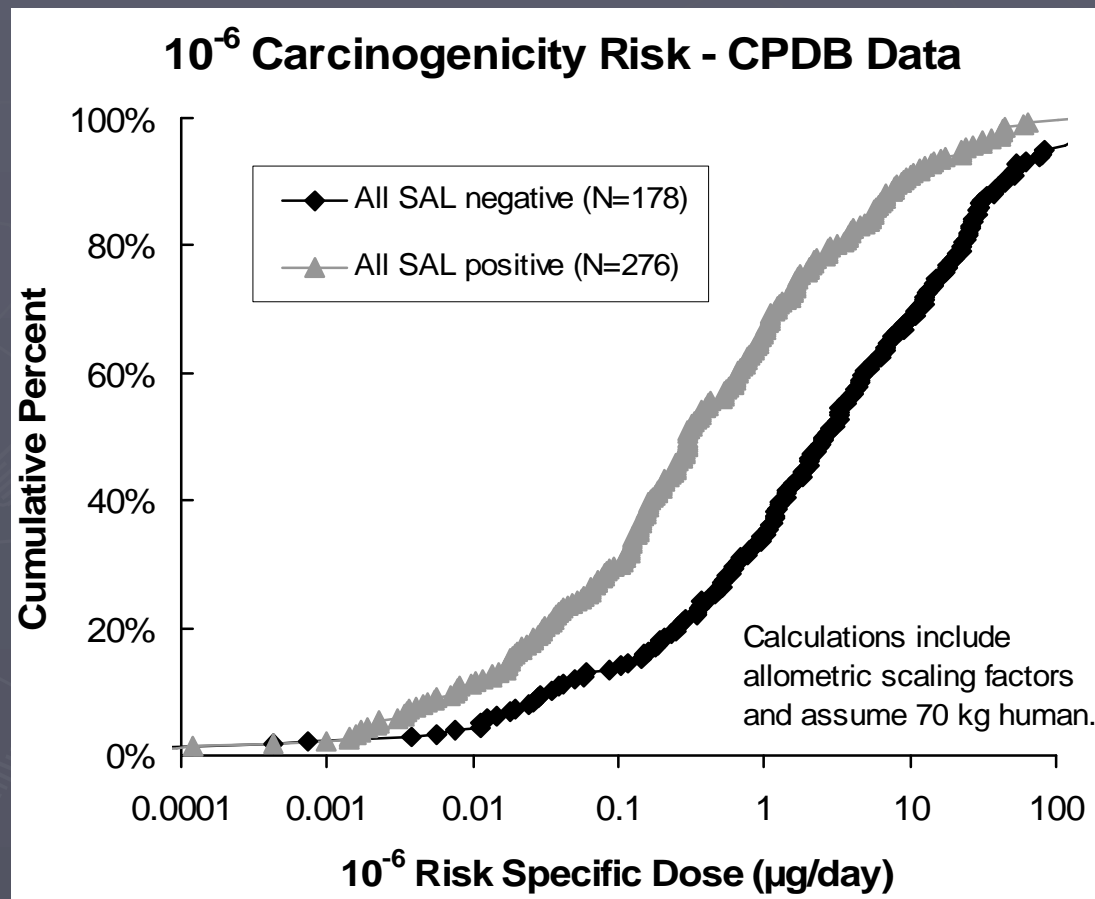
# Carcinogenicity Risk Approaches and Assumptions to Derive Threshold

- ▶ Based on distribution of  $10^{-6}$  risk-specific doses
- ▶ Extrapolated from  $TD_{50}$  values in Carcinogen Potency Database (CPDB)
- ▶ For genotoxic (SAL-positive) carcinogens
- ▶ Assumes potency via inhalation comparable to other routes (principally oral)
- ▶ Extrapolation used:
  - § Allometric dose-scaling
  - § Central risk estimates rather than upper bound
  - § Geometric mean rather than most sensitive species

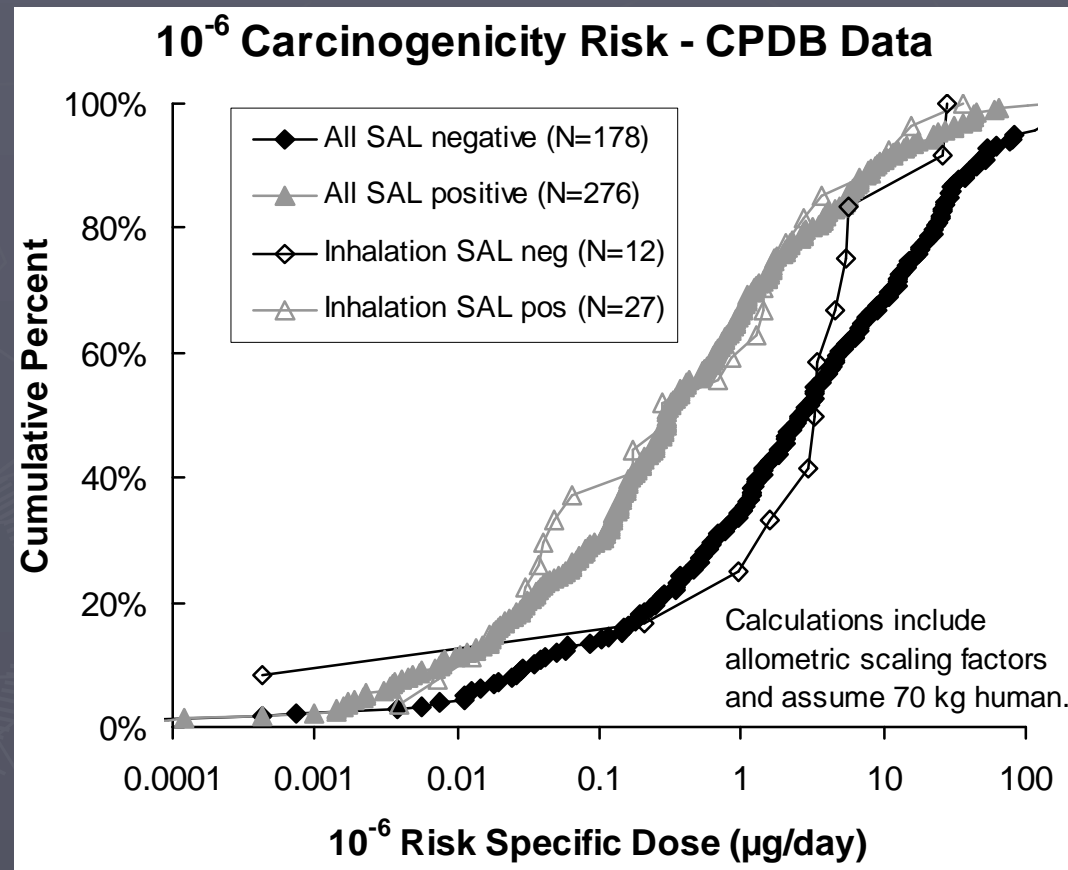
# Based on Genotoxic Carcinogens

- ▶ 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 genotoxins

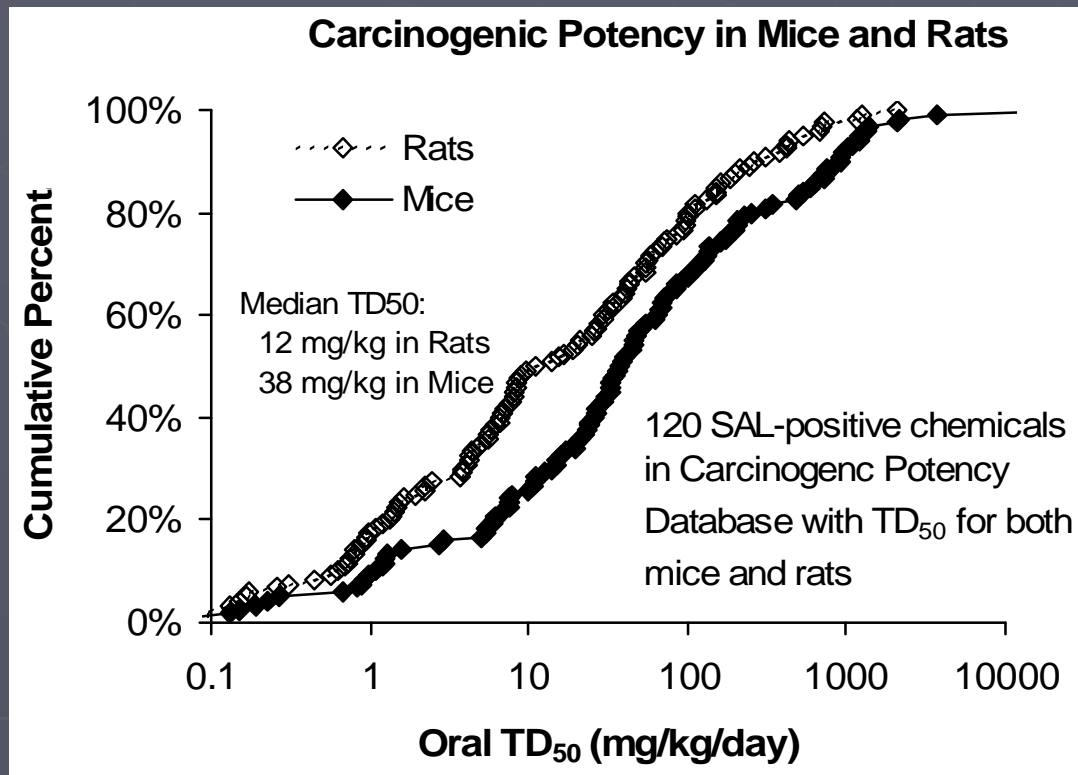
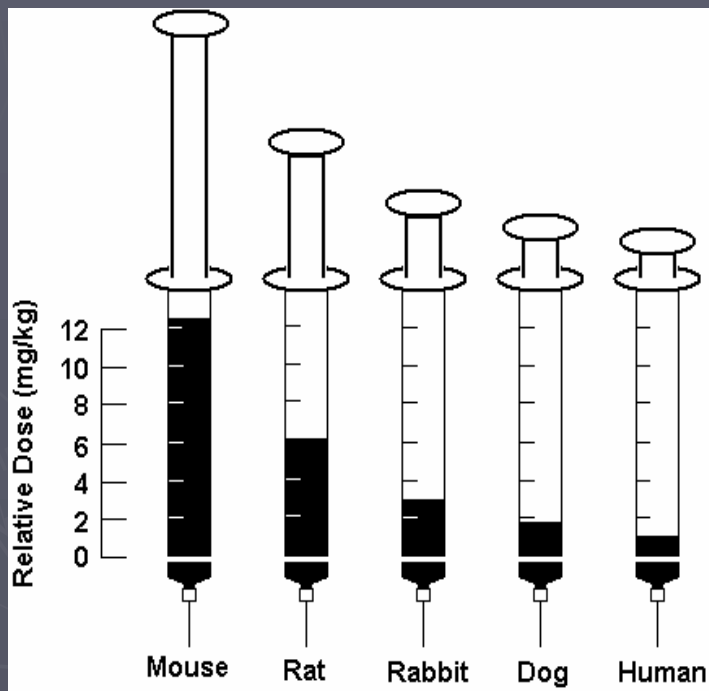
# Genotoxic Carcinogens More Potent Than Non-genotoxic Carcinogens



# Potency of Inhaled Carcinogens is Similar to Other Routes



# Why Allometric Dose-Scaling?



~ 3-4x greater sensitivity of rats vs mice to CPDB carcinogens supports dose-scaling

# Safety Concern Threshold

- ▶ Corresponds to the 37<sup>th</sup> 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  $0.41 \times 10^{-6}$
- ▶ If <20% of random chemicals are genotoxic carcinogens, <7% of all compounds would exceed  $10^{-6}$  increased cancer risk at intakes <0.15  $\mu\text{g}/\text{day}$  lifetime exposure

# Safety Concern Threshold

- ▶ 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
  - § Exception: some specific, highly potent leachables (eg, nitrosamines, PAHs) may need identification at lower levels

# Qualification Threshold is Based on Non-Carcinogenic Toxicity Endpoints

## ▶ Chronic Respiratory & Systemic Toxicity

### § Distribution of chronic "Reference Exposures"

- ▶ US EPA – Inhalation Reference Dose (RfD)
- ▶ CAL EPA – Reference Exposure Level (REL)
- ▶ ATSDR – Minimal Risk Level (MRL)

### § Exposures presenting negligible human risk for non-carcinogenic toxicity; typically based on animal NOAEL and safety factor (~100x)

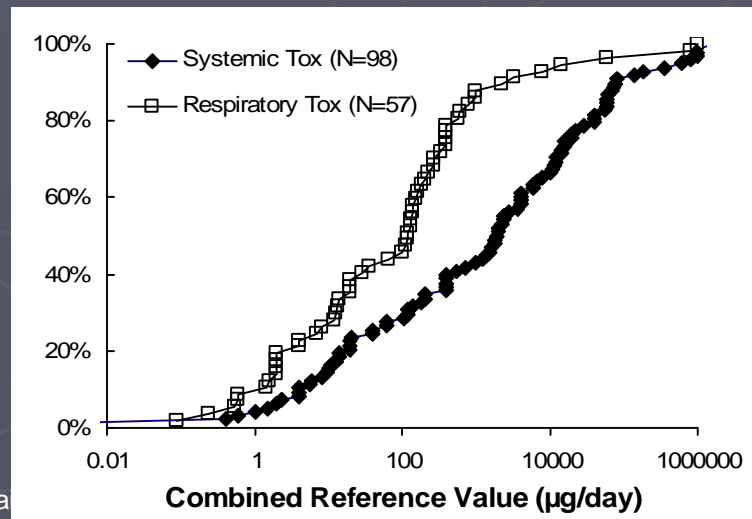
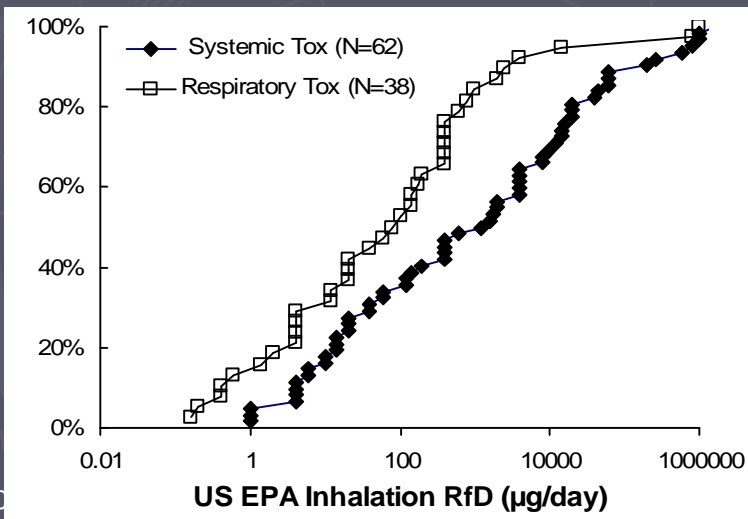
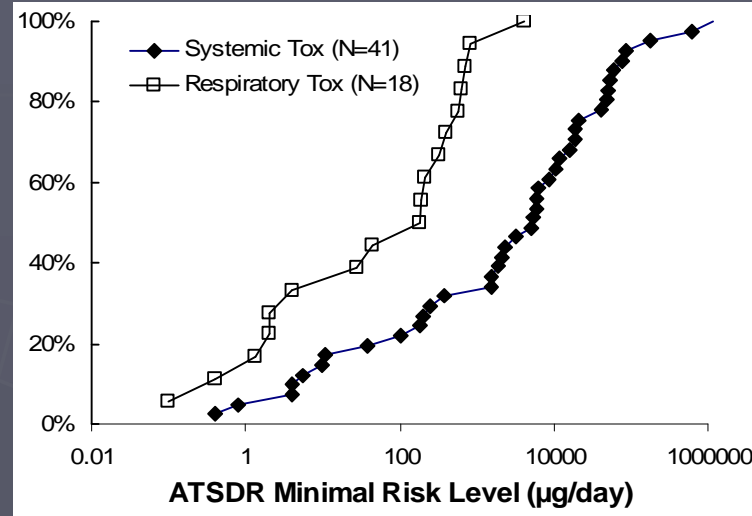
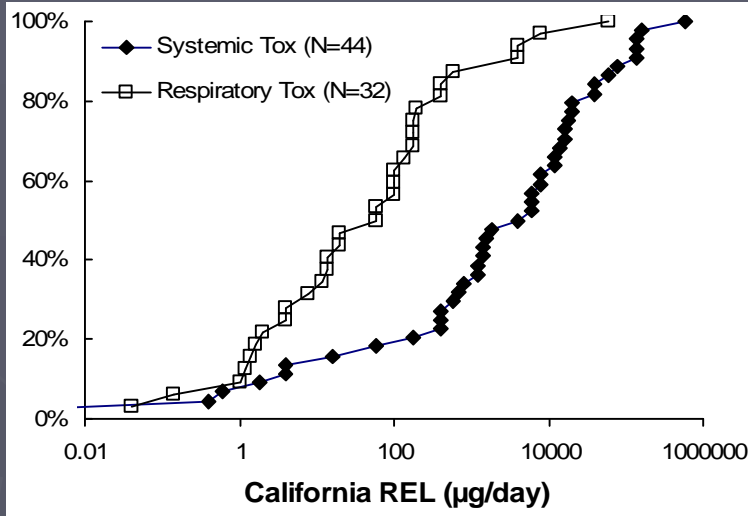
## ▶ Acute Irritation Potential

### § Distribution of acute exposure limits

- ▶ NIOSH – Short Term Exposure Limit (STEL)
- ▶ CAL Acute REL

### § RD<sub>50</sub>/1000 (added safety factor for asthmatics)

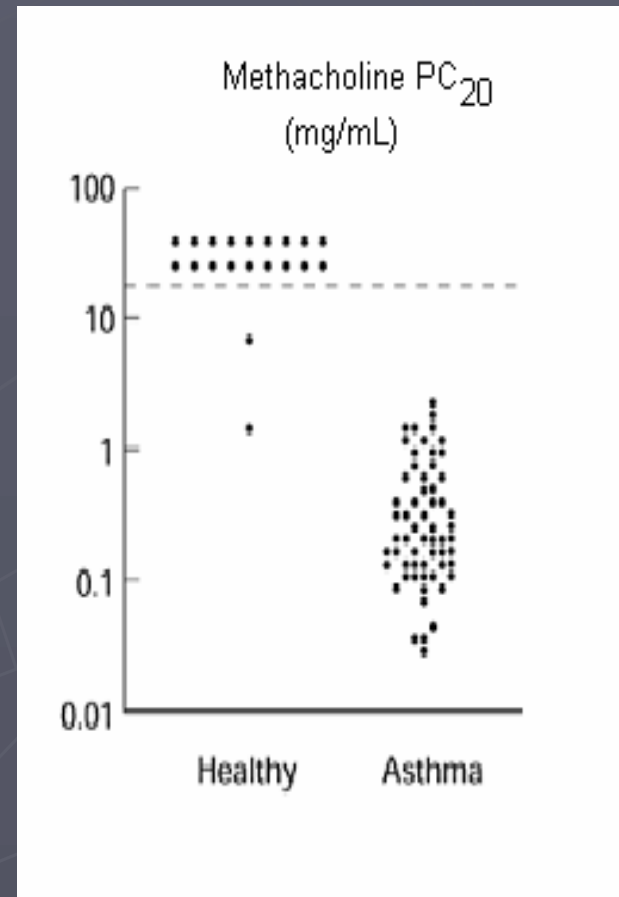
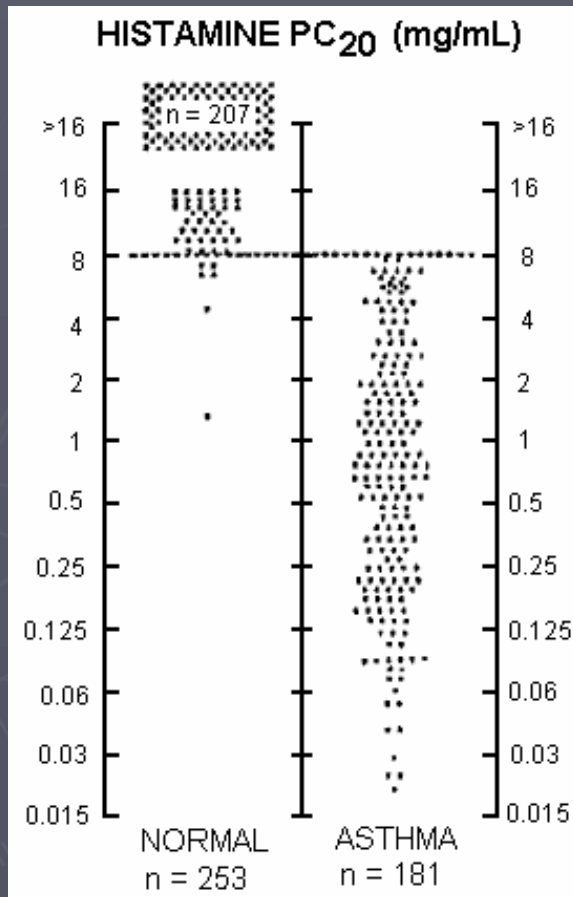
# Chronic Reference Exposures



# Acute Respiratory Irritation

- ▶ Evaluated from point of view that asthmatics are the most sensitive population
- ▶ Used mouse RD<sub>50</sub> database as starting point
  - § Validated, well-accepted, extensive database of commodity chemicals
  - § RD<sub>50</sub> is the inhaled concentration that reduces respiratory frequency by 50%
- ▶ Correlation of RD<sub>50</sub> to human exposure
  - §  $RD_{50} \times 0.1 \approx$  tolerable acute human exposure
  - §  $RD_{50} \times 0.03 \approx$  daily exposure limit (TLV-TWA)
  - §  $RD_{50} \times 0.001 \times 10$  minutes should be safe for most asthmatics

# Hyperresponsiveness in Asthmatics



# Hyperresponsiveness (continued)

Compound	STEL	Bronchoconstriction in Asthmatics
Formaldehyde <sup>1</sup>	2 ppm	None at 3 ppm for 3 hr
Sulfuric Acid <sup>2</sup>	3 mg/m <sup>3</sup>	None at 46 µg/m <sup>3</sup> (65-fold below STEL) Some at 130 µg/m <sup>3</sup> (23-fold below STEL)
Sulfur Dioxide <sup>3</sup>	5 ppm	Range = 0.25 to 4 ppm (20- to 1.2-fold below STEL)
Toluene Diisocyanate <sup>4</sup>	0.02 ppm	Most at >0.002 ppm (10-fold below STEL) A few at ≤0.001 ppm (≤20-fold below STEL)

1. Sauder et al. Toxicol Ind Health 1987;3(4):569-78.
2. Avol et al. Am Rev Respir Dis 1990;142(2):343-8.
3. Rubinstein et al. Am Rev Respir Dis 1990;141(2):381-5.
4. O'Brien et al. Clin Allergy 1979;9(1):7-15.

# Bad Actors at <math><5 \mu\text{g}/\text{Day}</math>


## Chemicals with Inhalation Reference Exposures Below 5 $\mu\text{g}/\text{day}$

Respiratory Toxicity: Compound	Reference Exposure ( $\mu\text{g}/\text{day}$ )	Systemic Toxicity: Compound	Reference Exposure ( $\mu\text{g}/\text{day}$ )
chromic acid mists	0.09	chlorinated dioxins	0.0008
beryllium and compounds	0.24	cadmium	0.4
hexamethylene diisocyanate	0.52	arsenic	0.6
acrolein	0.58	arsine	1.0
2-chloroacetophenone	0.60	manganese	1.5
toluene diisocyanate mixture	1.4	mercury	1.9
glutaraldehyde	1.6	chlordane	2.4
nickel and compounds	2.0	dicyclopentadiene	4.0
cobalt	2.0	2-nitroaniline	4.0
titanium tetrachloride	2.0	disulfoton	4.0
nickel oxide	2.0	1,2-dibromoethane	4.0
antimony trioxide	4.0	1,2-dibromo-3-chloropropane	4.0
chlorine	4.0	hydrazine	4.0
chlorine dioxide	4.0		
hexachlorocyclopentadiene	4.0		

# Qualification Threshold

- ▶ Corresponds to:
  - § 9<sup>th</sup> percentile of Reference Exposures for systemic toxicity
  - § 21<sup>st</sup> percentile of Reference Exposures for respiratory toxicity
  - § 22<sup>nd</sup> percentile of RD50/1000
- ▶ Incorporates large safety margins for chronic toxicity
- ▶ Most chemicals of concern below 5 µg/day have obvious structural alerts for irritation or toxicity (eg, heavy metals, aldehydes, isocyanates, organic phosphates)
- ▶ Leachables below this threshold without structural alerts for carcinogenicity or irritation should not require compound-specific risk assessment

# Integrated Approach to Developing a Container Closure System

The background of the slide is a dark blue-grey color with a subtle, light-colored pattern of irregular, interconnected lines. In the lower-left corner, there is a faint, stylized graphic of a compass rose with a gear-like element, suggesting a technical or engineering theme.

# Integrated Approach (1)

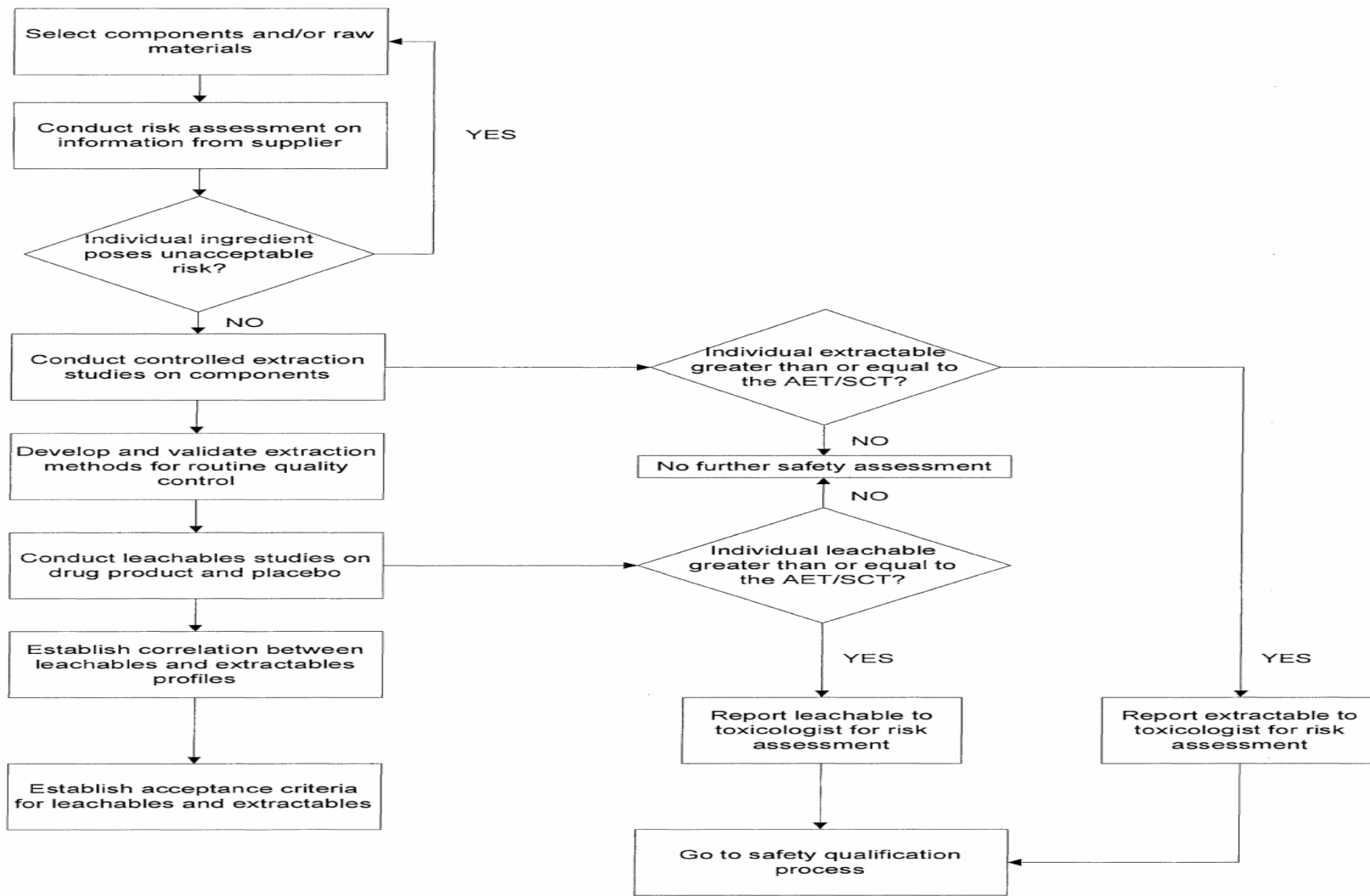
- ▶ Materials purchased from supplier
  - § Container Closure Team (CCT) formed
    - ▶ Comprised of chemists, toxicologists, packaging, procurement
  - § Quality materials chosen by the CCT
    - ▶ Suppliers provide formulation and general extract information
    - ▶ Cost a secondary factor
  
- ▶ Toxicologist evaluates material extract profile
  - § Initial evaluation made early in the container closure development process
    - ▶ Safety information from the supplier (e.g., USP results)
    - ▶ In silico evaluation
  - § Preliminary qualification of each material based on accepted safety thresholds and anticipated TDI

# Integrated Approach (2)

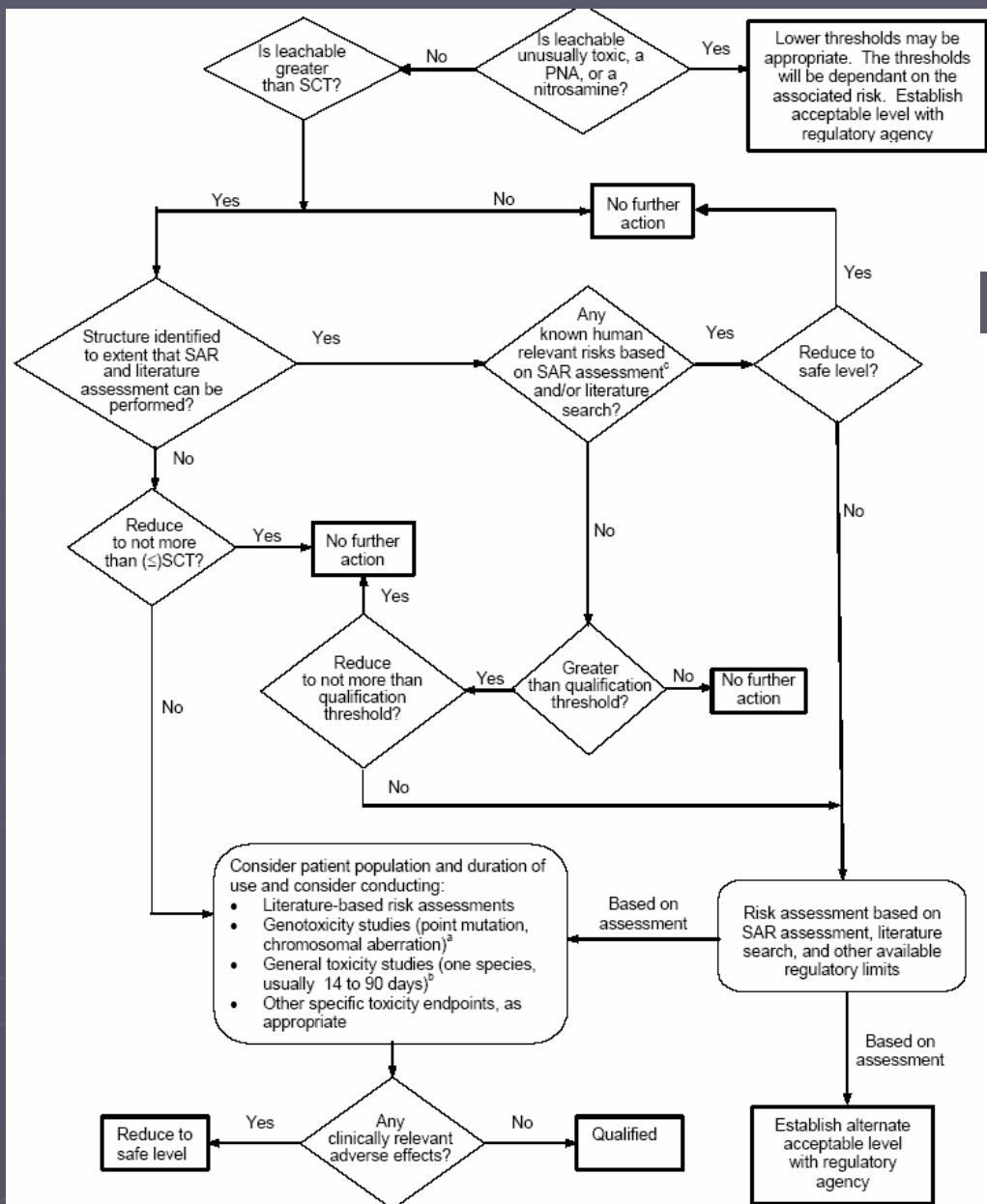
- ▶ Container Closure developed for DP
  - § Total extract profiling conducted by chemists
    - ▶ Analytical methods based on material formulation and general extract profile obtained from supplier
    - ▶ Analytical LOD based on qualification thresholds
  
- ▶ Toxicological Qualification of CCS
  - ▶ Based on leachable profile of DP
  - ▶ Leachables below SCT considered qualified
  - ▶ Leachables greater than the SCT and less than the QT
    - § Qualify with in silico data and published data
    - § Additional in vitro, in vivo testing on a case-by-case basis
  - ▶ Leachables above the QT can be qualified on a case-by-case basis
    - § Develop qualification strategy and work with regulators to establish qualification of leachables above the QT

# Integrated Approach Flow Chart

**Figure 1. Typical Pharmaceutical Development Process for L&E in OINDP**



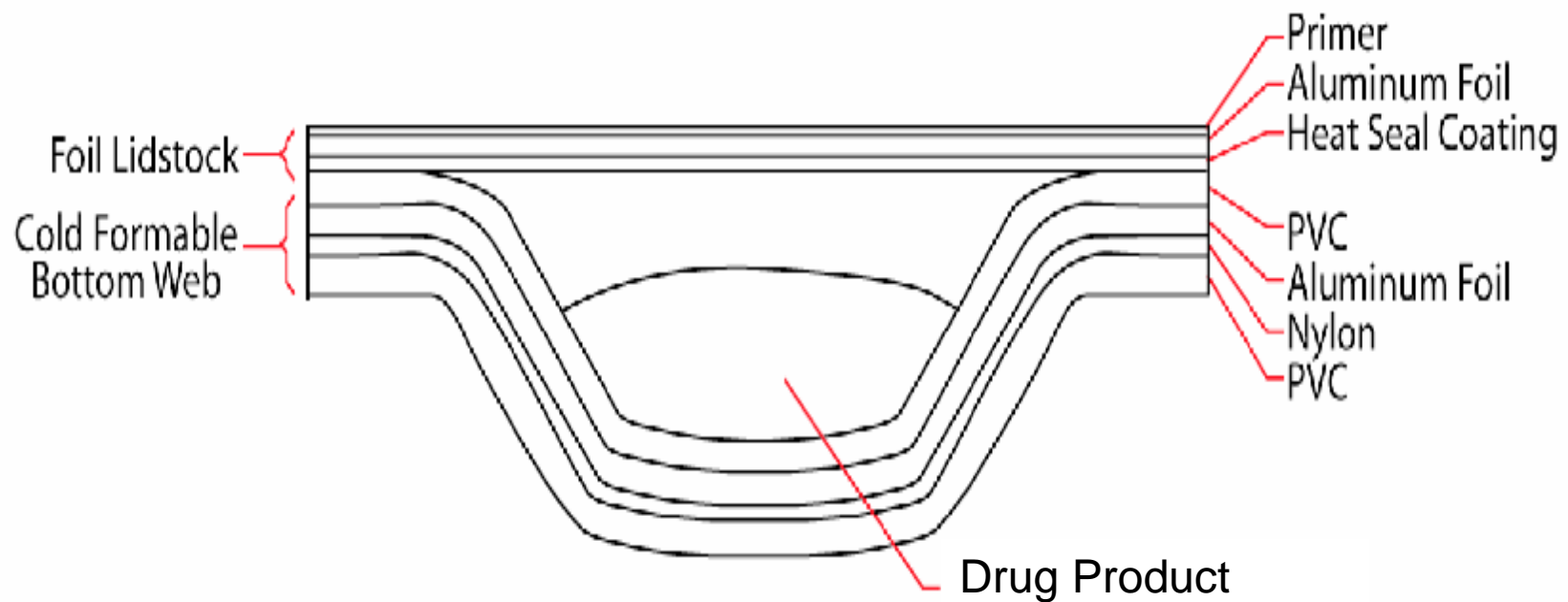
# Safety Qualification Decision Tree



# Case Example

## Oral DP in Blister Package

- ▶ Blister composition is foil/multilaminate



# Blister Leachable Profile

Ethanol (2.3 µg)	4,6-Dimethyl-2-heptanone (0.3 µg)	Undecyl dodecanoate (0.2 µg)
Acetone (<0.2 µg)	Diisobutyl ketone (0.5 µg)	Diethylhexyl phthalate (< 0.3 µg)*
Isopropanol (1.7 µg)	1-Undecene (0.4 µg)	Squalene (0.7 µg)
Butanal (0.3 µg)	Undecane (0.4 µg)	Bis (ethylhexyl) sebacate (1.5 µg)*
1-Butanol (6.5 µg)	2,2,4,6,6-Pentamethylheptane (0.3 µg)	2-Methyl-1-propanol (0.2 µg)
Ethyl acetate (< 0.2 µg)	2-Ethyl-1-hexyl acetate (0.4 µg)	Methanol (0.6 µg)
Cyclohexanone (0.8 µg)*	Di-butyl phthalate (0.5 µg)*	Camphene (0.2 µg)
Methyl methacrylate (0.2 µg)	(Z)-9-Octadecenoic acid (0.2µg)	1-Undecanol (0.3 µg)
Caprolactam (< 0.6 µg)	(E)-9-Octadecenoic acid (0.2µg)	Tetratriacontatetraenoate, methyl ester (0.5 µg)
2-Ethyl-1-hexanol (7.0 µg)	Propanoic acid, 2-methyl-, 1-(1,1-dimethylethyl)-2-methyl-1,3-propanediyl ester (0.4 µg)*	2-Ethylhexyl mercaptoacetate (0.2 µg)
1-Methoxy-2-propyl acetate (0.3 µg)	Docosane (0.6 µg)	2-Butanone (< 0.2 µg)
Butyl methacrylate (0.3µg)	Erucamide (< 0.6 µg)	----

\* These chemicals are reported as process impurities and not blister leachables since they are found in the API following spray drying. However, a risk assessment of these chemicals is reported in this document.

# 1-Butanol: Data

- ▶ TDI is 6.5 µg, or 0.09 µg/kg for a 70 kg person.
- ▶ Negative in the Ames and sister-chromatid exchange assays.
- ▶ Acute oral LD50 values in rats and mice are 790 mg/kg and 2,680 mg/kg, respectively, which classifies it as "moderately toxic."
- ▶ Acute inhalation (4 hour) LC50 in rats is 8,000 ppm (24.24 mg/L), resulting in a pulmonary dose of 3,989 mg/kg.
- ▶  $(24.24 \text{ mg/L} \times 240 \text{ min} \times 0.24 \text{ L/min} \div 0.35 \text{ kg} = 3,989 \text{ mg/kg})$
- ▶ In various oral and inhalation reproductive toxicology studies in rats, several effects have been reported, but the doses that produce them were in the g/kg range.
- ▶ Is permitted as a direct food additive in the United States (21CFR 172.515).
- ▶ In the United States, a reference dose for chronic oral exposure (RfD) for humans of 100 µg/kg/day has been established by the Environmental Protection Agency. Thus, this estimates the daily oral intake of 1-butanol that is likely to be without appreciable risk of deleterious effects during a lifetime.
- ▶ In the United States, OSHA has established an 8-hour TWA of 100 ppm (0.303 mg/L) for 1-butanol. Thus, the total acceptable daily pulmonary dose for a 70 kg person is 18,699 µg/kg. Regulatory authorities in several European countries have established the same or a similar TWA.
- ▶  $(0.303 \text{ mg/L} \times 480 \text{ min} \times 9 \text{ L/min} \div 70 \text{ kg} = 18.699 \text{ mg/kg or } 18,699 \text{ µg /kg})$
- ▶ It is a Class 3 solvent (ICH Q3C Guideline for Residual Solvents), and therefore it is considered that amounts of 50 mg/day (or 714 µg/kg/day for a 70 kg person) would be acceptable without justification.

# 1-Butanol: Assessment

- ▶ The anticipated TDI of 1-butanol ( $0.09 \mu\text{g}/\text{kg}$ )
  - §  $> 1000$ -fold lower than the RfD
  - §  $\sim 8,000$ -fold lower than the permissible daily exposure limit outlined in the Q3C solvent guidelines
  - § TDI of 1-butanol is more than  $200,000$ -fold lower than its acceptable daily pulmonary exposure limit set by OSHA
- ▶ These profound safety margins indicate that that the amount of 1-butanol in this formulation poses **negligible risk to humans**

# 1-Butanol: Reference List

- ▶ Center for Drug Evaluation and Research. Guidance for Industry. Q3C Impurities: Residual Solvents (website).
- ▶ Connelly J, Hasegawa R, McArdle J, et al. Residual solvents. *Pharmeuropa* 1997;9:S54.
- ▶ National Institute of Occupational Safety and Health (website).
- ▶ Ollroge I. Threshold values and recommendations. In: Marquardt H, Schäfer S, McClellan R, et al, editors. *Toxicology*. New York: Academic Press; 1999: p. 1201-29.
- ▶ Registry of Toxic Effects of Chemical Substances (website).
- ▶ Toxnet (website).
- ▶ Zbinden G. Acute toxicity. In: Zbinden G, editor. *Progress in toxicology*. New York: Springer-Verlag; 1973: p. 24.

## 2-Ethyl-1-Hexanol: Data

- ▶ TDI is 7.0 µg, or 0.1 µg/kg for a 70 kg person.
- ▶ Negative in several genotoxicity assays including the Ames, mammalian cell gene mutation, in vitro cytogenetics, in vivo cytogenetics, UDS (rat hepatocytes), in vitro cell transformation and dominate lethal assay in mice. A weak mutagenic response was reported in the 8-azaguanine-resistance assay in Salmonella.
- ▶ Characterized as a weak peroxisome proliferator in rats.
- ▶ Acute oral LD50 values in rats and mice are 3,730 mg/kg and 2,500 mg/kg, respectively, which classifies it as "moderately toxic."
- ▶ Acute inhalation (6 hour) LC50 in rats is >2,000 ppm (>10.64 mg/L), resulting in a pulmonary dose of >2,627 mg/kg.
- ▶ ( $>10.64 \text{ mg/L} \times 360 \text{ min} \times 0.24 \text{ L/min} \div 0.35 \text{ kg} = >2,627 \text{ mg/kg}$ )
- ▶ In a 3-month inhalation toxicology study in rats, the highest vapor concentration of 120 ppm (0.638 mg/L) administered 6 hours/day was the NOAEL, which resulted in a pulmonary dose of 157 mg/kg/day.
- ▶ ( $0.638 \text{ mg/L} \times 360 \text{ min} \times 0.24 \text{ L/min} \div 0.35 \text{ kg} = 157 \text{ mg/kg/day}$ )
- ▶ In a 13-week oral toxicology study in rats and mice, the NOAEL in both species was 125 mg/kg/day.
- ▶ An inhalation teratology study in rats with exposure to a vapor concentration of 0.850 mg/L (7 hours/day) caused no teratogenic effects, which resulted in a pulmonary dose of 245 mg/kg.
- ▶ ( $0.850 \text{ mg/L} \times 420 \text{ min} \times 0.24 \text{ L/min} \div 0.35 \text{ kg} = 245 \text{ mg/kg}$ )
- ▶ In an oral reproductive toxicology study in mice, a dose of 191 mg/kg/day caused no developmental findings.
- ▶ In an oral reproductive toxicology study in rats, oral doses ranging from 800-1600 mg/kg/day caused malformations including hydronephrosis, heart malformations, and tail and limb defects.
- ▶ Was not carcinogenic in a rat oral oncogenicity study up to the highest dose of 500 mg/kg/day. The NOAEL for systemic toxicity in this study was 50 mg/kg/day.
- ▶ Was not carcinogenic in a mouse oral oncogenicity study in males up to a highest dose of 750 mg/kg/day, and in females up to 200 mg/kg/day. A weak or equivocal trend in increased incidence of liver tumors occurred in female mice given the highest dose of 750 mg/kg/day. The NOAEL for systemic toxicity in this study was 200 mg/kg/day.
- ▶ No apparent injury has been reported in humans from its use in industry. The probable oral lethal dose in humans is estimated to be from 500 mg/kg - 5,000 mg/kg.

# 2-Ethyl-1-Hexanol: Assessment

- ▶ TDI of 2-ethyl-1-hexanol ( $0.1 \mu\text{g}/\text{kg}$ ) in humans
  - § is more than one million-fold lower than doses in animals that failed to produce systemic toxicity
    - ▶ (via the pulmonary and oral route) or,
    - ▶ carcinogenicity (via the oral route)
  - § TDI of 2-ethyl-1-hexanol is at least five million-fold lower than the estimated oral lethal dose in humans
- ▶ Profound safety margin indicates that that the amount of 2-ethyl-1-hexanol in this formulation poses negligible risk to humans

# Erucamide: Data

- ▶ TDI is  $<0.6 \mu\text{g}$ , or  $<0.009 \mu\text{g}/\text{kg}$  for a 70 kg person
- ▶ SAR was negative for genotoxicity and/or carcinogenicity alert (DEREK)
- ▶ The stearyl derivative of erucamide was negative in the Ames test
- ▶ Is permitted as an indirect food additive in the United States (CFR 175.105)

# Erucamide: Assessment

- ▶ small dose (i.e., 0.6  $\mu\text{g}$  TDI or  $<0.009$   $\mu\text{g}/\text{kg}$  for a 70 kg adult)
- ▶ Listed as an indirect food additive
- ▶ No structural alerts for genotoxicity or carcinogenicity
- ▶ Erucamide poses negligible risk to humans