

Pharmaceutical Applications of the TTC

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WORLDWIDE RESEARCH & DEVELOPMENT
Drug Safety R&D

Agenda

- Derivation of the TTC
 - Cramer Classification
- Application of the TTC
 - ICH M7
 - Leachable and Extractable (L&E) Qualification
- Case studies
 - Process-related mutagenic impurity
 - L&E qualification using a modified Cramer Classification strategy
- Conclusions

Threshold of Toxicological Concern – Brief History

- The TTC is a concept that a safe level of exposure can be identified for an individual chemical (Kroes, 2000)
- The TTC evolved from a review by Munro for the FDA Threshold of Regulation food contact chemicals (1990)
 - The TTC level then developed for Indirect Food Additives (Federal Register, 1993)
- Munro (1999) further refined based on extensive data used by Cramer to develop a 3 tier decision tree (Cramer, 1978)
- Cramer decision tree used by the European Food Safety Authority to evaluate flavoring agents (EFSA, 2004)
- Kroes extended the approach to cover chemicals with structural alerts for mutagenicity (Kroes, 2004)

TTC – Basic Principles

- The TTC provides a method to evaluate human risk based on:
 - Already available data (chemical structure, in vitro, in vivo, and in silico data)
 - Potential dose and route of intake
 - The predicted in vivo toxicity based on the known toxicity of chemicals with related structures

Cramer Decision Tree

- The Cramer classification scheme (tree) relies primarily on chemical structures and estimates of total human intake
- The procedure uses recognized pathways for metabolic deactivation and activation, toxicity data and the presence of a substance as a component of traditional foods or as an endogenous metabolite
- Substances are classified into three classes:

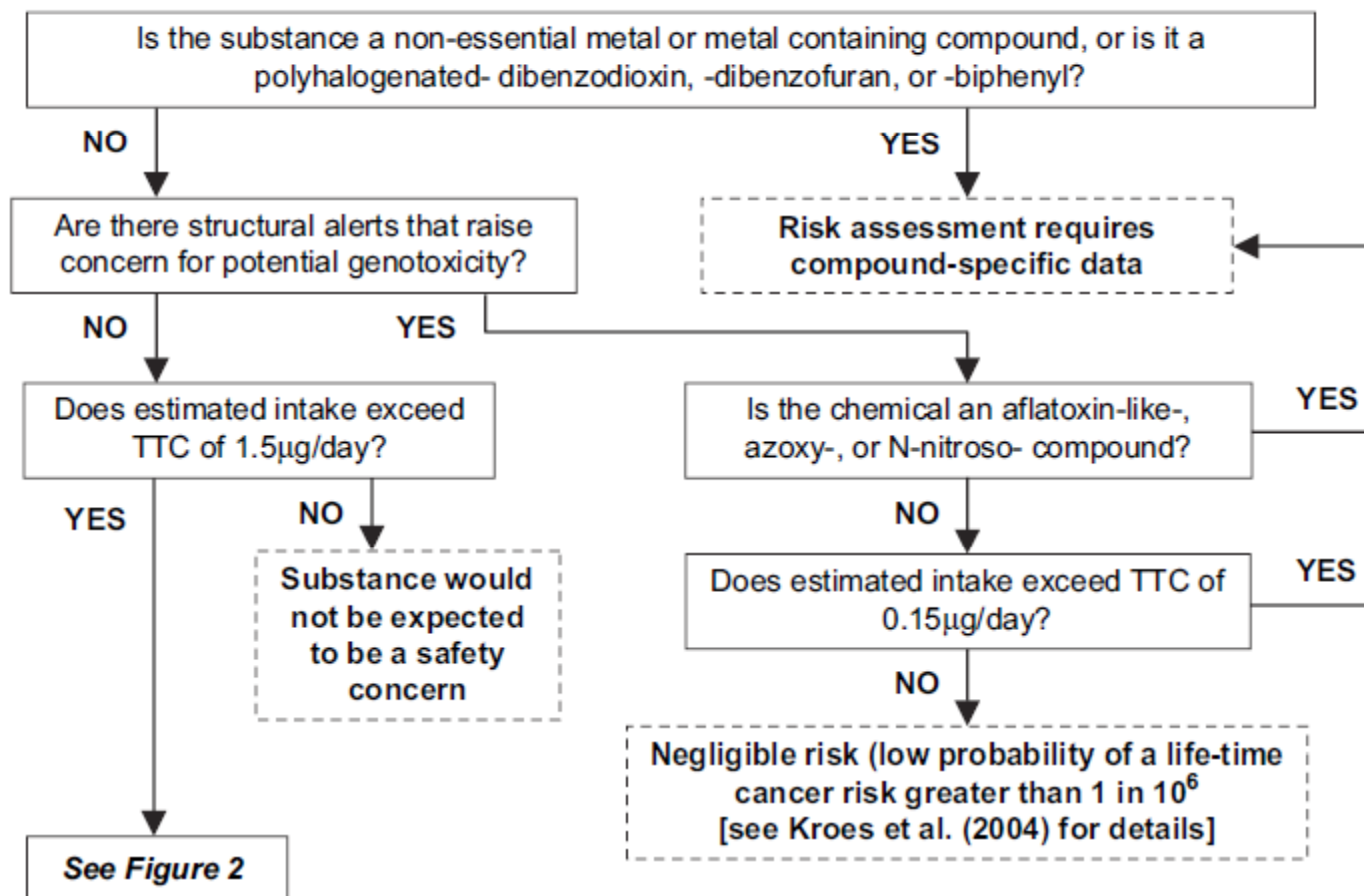
Class (µg/day)	Definition
1 (1800)	contains substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity
2 (540)	contains substances that are intermediate. They possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3
3 (90)	contains substances with a chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity.



TTC for genotoxic carcinogens

- Developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effect.
- TTC generally considered to be very conservative
 - simple linear extrapolation from the dose giving a 50% tumor incidence (TD₅₀) to a 1 in 10⁶ incidence, using TD₅₀ data for the most sensitive species and most sensitive site of tumor induction
- Acceptable limit of mutagenic impurities in drug substances and drug products, set at 1.5 µg/day (1 in 10⁵ excess lifetime risk of cancer)
- Special case structures where intake below the TTC associated with significant carcinogenic risk (cohort of concern)
 - aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds.

TTC Decision Tree

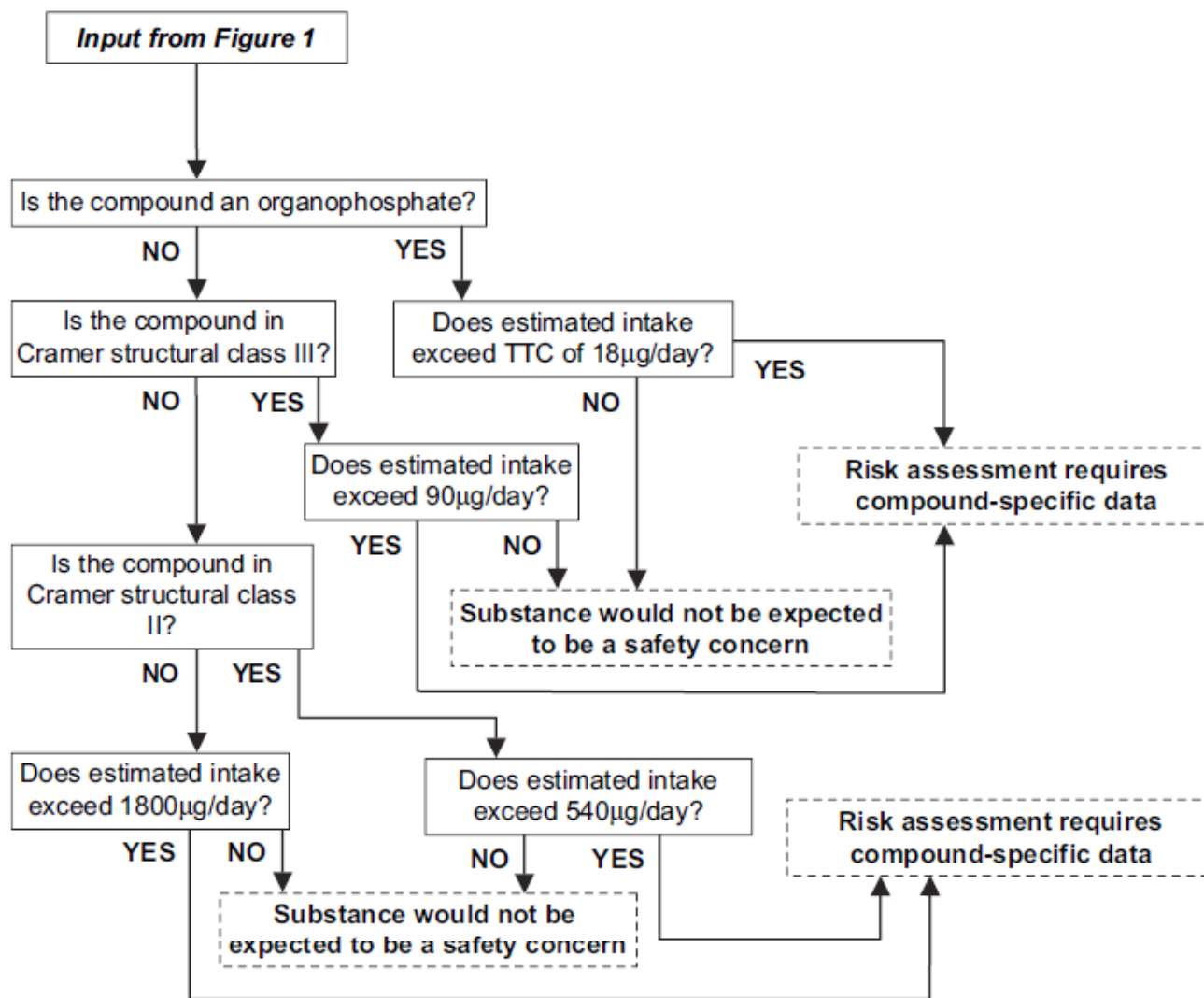


From Kroes, 2005



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TTC Decision Tree using Cramer Classification Levels



ICH M7 – Genotoxic Impurities

- Provides a practical framework that is applicable to the identification, categorization, qualification, and control of mutagenic impurities to limit potential carcinogenic risk
- Emphasizes considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk
- Outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use

ICH M7 Classification

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity



*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in *in vivo* gene mutation studies)

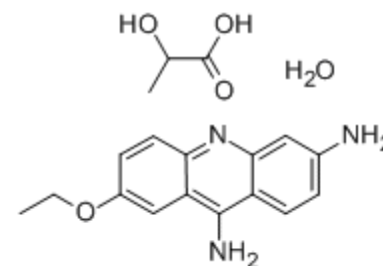
ICH M7 Limits for Genotoxic Impurities

Treatment Duration	≤ 1 Month	> 1-12 Months	>1 -10 Years	>10 Years
Individual Impurity (µg/day)	120	20	10	1.5
Multiple Impurities (µg/day)*	120	60	30	5

*When there are two Class 2 or Class 3 impurities, individual limits apply. When there are three or more Class 2 or Class 3 impurities specified on the drug substance specification, total mutagenic impurities limits apply

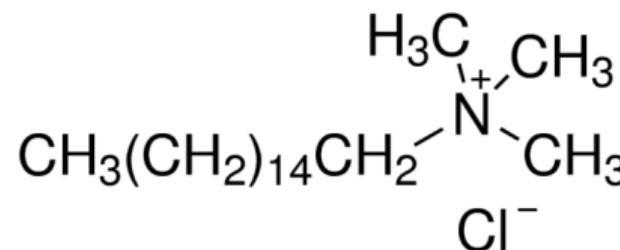
Case Example: Mutagen in intermittently dosed product

- Product dosage:
 - I.V. administration of 50 mg/mL sterile solution
 - 20 mg/kg/day X 21 days
 - Up to two treatment regimens
 - Total duration of dosing = 42 days
- Impurity: Acrinol present at 0.1 µg/mL
 - Bacterial mutagen
 - No carcinogenicity data for acrinol or related aminoacridine for compound-specific limit calculation
 - Apply less than lifetime TTC for intermittently dosed product
 - LTL TTC = 20 µg/day for >1-12 months
 - 20 mg/kg/day X 50 kg/ 50 mg/mL = 20 mL
 - 20 mL X 0.1 µg/mL = 2 µg/day



Case Example: Qualified by in silico assessment

- Cetyl trimethyl ammonium chloride (CTAC)
 - Levels of <0.025% in drug product given at ≤ 2 g/day
 - Derek (rule-based SAR) – no mutagenicity alerts
 - Sarah (statistical QSAR) – predicted negative
 - 8 other quaternary ammonium compounds tested in Ames assay; all negative
 - Per ICHM7, no genotoxicity tested needed unless above ICH qualification threshold (0.15%, or 1.0 mg/day; whichever is lower) and >1 mg/day



Container Closure System – Why the Concern

- Chemicals are known to migrate (leach) from the container closure
 - Leached chemicals may be at levels to cause either safety or quality issues with a DP
- FDA issues Container Closure Guidance - 1999
 - Identifies the DP of highest concern
 - Does not provide a process to qualify leachables in DP
- PQRI L&E team for OINDP Best Practices – 2006
 - Recommends a process for analytical and safety qualification
- PQRI L&E Team for PODP – 2009 to present
 - Developing best practices for parenteral and ophthalmic DP

Container Closure System Guidance (FDA, 1999)

Degree of Concern Associated with Route of Administration	Likelihood of Packaging Component-Dosage Form Interaction		
	High	Medium	Low
Highest	• Inhalation Aerosols and Solutions • Injections and Injectables • Suspensions	• Sterile Powders and Powders for Injection • Inhalation Powders	
High	• Ophthalmic Solutions and Suspensions • Transdermal Ointments and Patches • Nasal Aerosols and Sprays		
Low	• Topical Solutions and Suspensions • Topical and Lingual Aerosols • Oral Solutions and Suspensions	• Topical Powders; Oral Powders	• Oral Tablets • Oral Capsules



Why not ICH Q3B?

- OOS in the guideline
 - Impurities extracted or leached from the container closure system are not covered by Q3B
 - Extractables and leachables are not drug-related or process-related impurities
 - Therefore can not be qualified as a % or concentration based on concentration of API in the DP
 - Have differing toxicological profiles than that of the API
- However
 - PQRI OINDP and PODP follow the principles provided in ICH Q guidelines

PQRI Best Practices for L&E Qualification – Similarity to ICH Q3B

L&E Qualification	DP Impurity Qualification
Analytical Evaluation Threshold (AET) – based on the Safety Concern Threshold	Reporting Threshold – based on dose of API or % whichever is less
Safety Concern Threshold (SCT) – based on carcinogenic/genotoxic potential of a particular leachable	Qualification Threshold – based on dose of API or % whichever is less (ICH M7 now available to determine acceptable limits)
Qualification Threshold (QT) – based on noncarcinogenic potential of a particular leachable*	Qualification Threshold

*the PODP team further defines qualification into 3 classes, and applies ICH M7 for qualification of genotoxic leachables

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



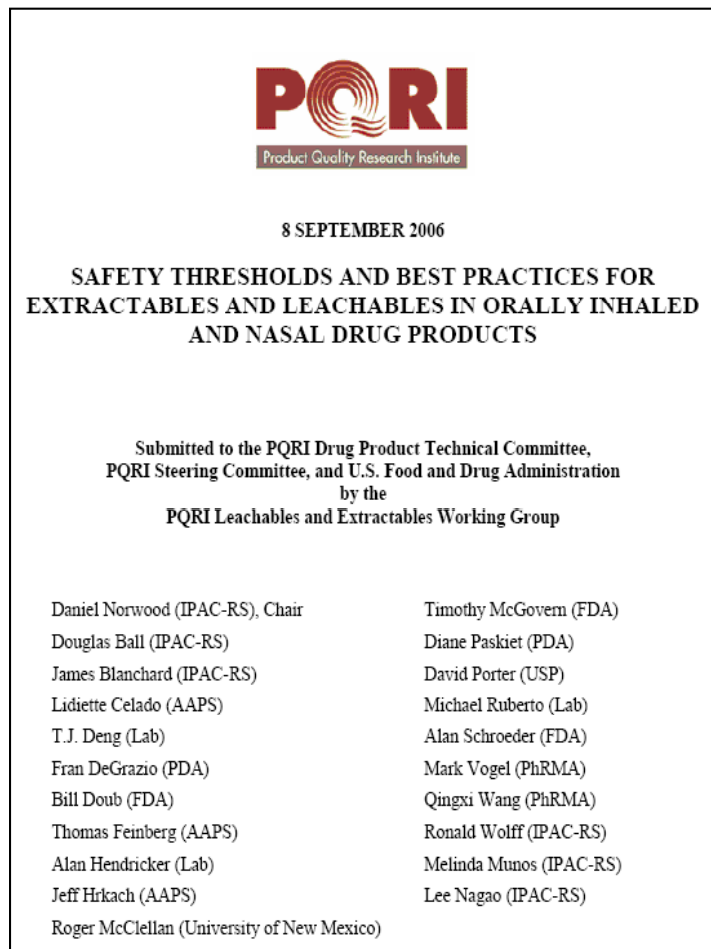
PQRI Best Practice Recommendations for OINDP

OINDP Outcomes

- Safety Concern Threshold (SCT)
 - Low Risk Leachables Not Identified
 - <0.15 ug/day
- Qualification Threshold (QT)
 - Assessment of Identified Leachable
 - non-carcinogenic >5 µg/day
- Best Practices for E&L studies
 - Analytical Evaluation Threshold (AET)
 - Identification threshold derived from SCT

Note:

- *Designed to reduce level of uncertainty within the pharmaceutical development of OINDP*
- *Not meant to be proscriptive*

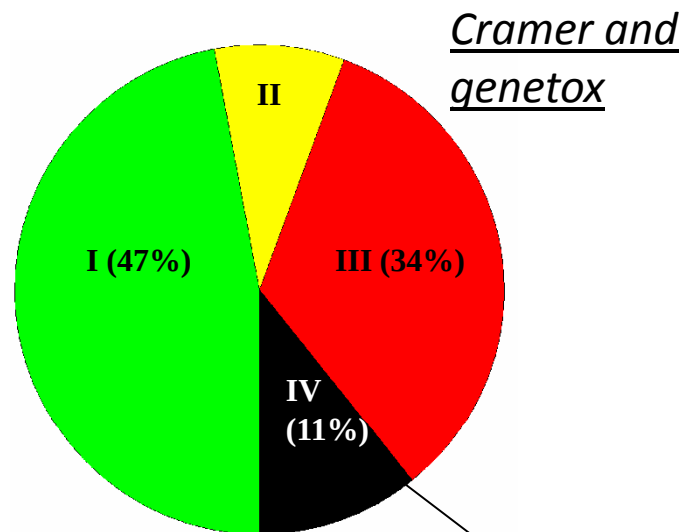
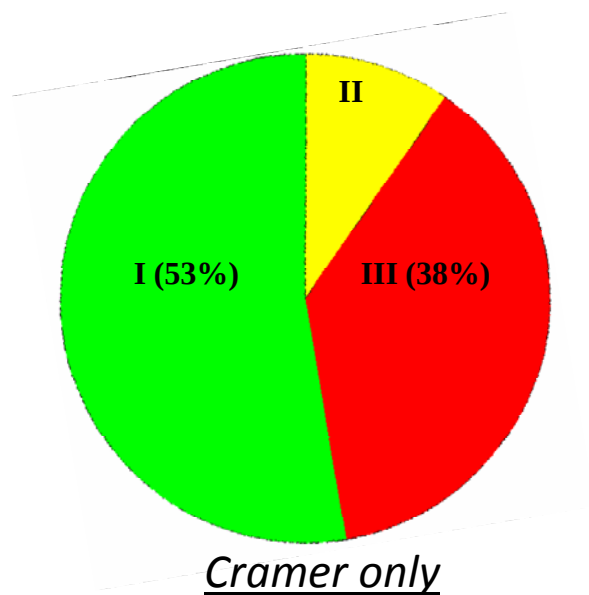


Thresholds in Parenteral DP

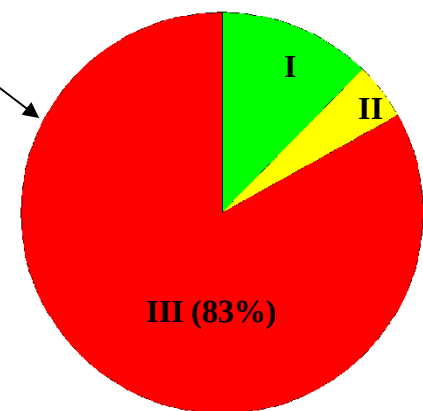
- The PQRI Toxicology Team developed a scientifically-justified classification strategy for leachables in parenteral drug products by taking the following approach:
 - Database of 606 chemicals (compiled by PQRI Chemistry team) that have been shown to potentially leach from container closure system materials
 - the database is representative of various chemical classes that have been observed in Controlled Extraction and/or Routine Leachable studies
 - The database was analyzed using in silico methods, then sorted into classes using a modified Cramer approach (ToxTree) that includes a class for genotoxicants (DEREK/Leadscope)
 - ~ 70 Class 2 and 3 (moderate and most toxic) ToxTree sorted chemicals underwent a risk assessment to calculate an acceptable dose based on ICH Q3C/D principles
 - Based on this process the classification strategy was developed



Classification Outcome



Class IV
Cramer Classification of
genotoxics



PQRI Classification Strategy

	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5-120*

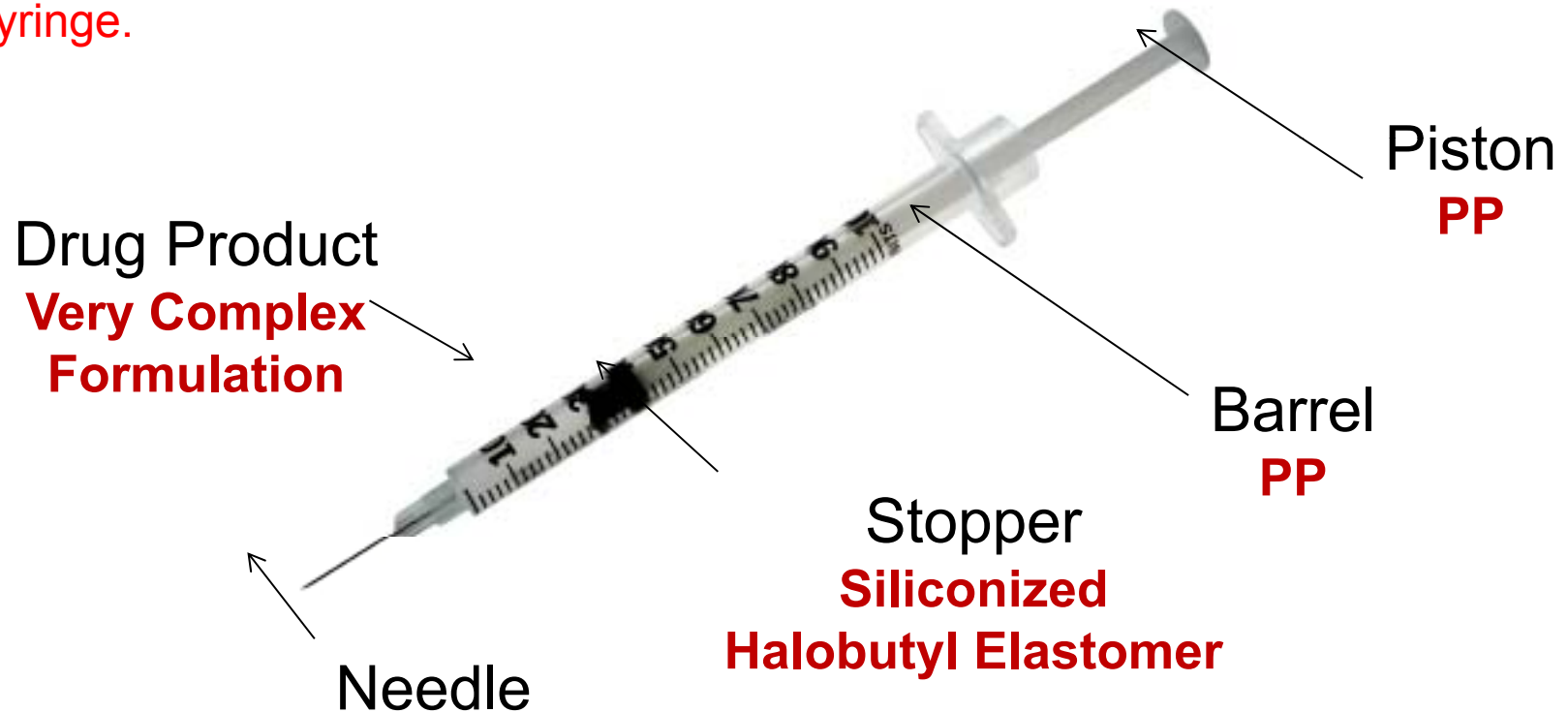
*The SCT is 1.5 µg/day. Identified leachables with mutagenic potential can be qualified up to 120 µg/day based on ICH M7 principles

- Classification based on a literature based risk assessment of 70 chemicals from database (Class 2 and 3), statistical assessment, and comments received from the regulators (FDA, HC, MHRA) on validation strategy



Parenteral DP Case Example

Leachables can arise from various parts of the pre-filled syringe.



Case Study

Toxicological Evaluation

- Pertinent details of drug product:
 - Pre-filled syringe (1 ml)
 - Once daily dosing every 8 weeks via intramuscular injection
 - Dose volume is 0.5 ml (based on 50 kg individual)
- These variables, along with a qualitative and quantitative description of the leachable profile, are required for conducting the toxicological assessment.

Case Study

Toxicological Evaluation

- The Leachable Profile, as provided by Chemistry, is evaluated based on individual leachables, concentration and estimated total daily dose, relative to the proposed thresholds for safety evaluation.

<u>Leachable</u>	<u>Concentration (µg/device)*</u>	<u>Estimated Daily Dose (µg)*</u>
2,4-Bis(1,1-dimethylethyl)-phenol, 1,1',1"-phosphate	0.09	0.045
2,4 Di t-butyl phenol	3.9	1.95
Erucamide	4.5	2.25
3-(3',5'-di-t-Butyl-1'-hydroxy-4'-oxacyclohexa-2',5'-dienyl) propanoic acid	0.05	0.025
Benzo(a)pyrene	0.03	0.015
Octadecane	0.06	0.03
2-Bromo-4-(1,1-dimethyl-propyl)-phenol	0.09	0.045
Hexamethylcyclotrisiloxane	0.08	0.04
Unknown A	3.3	1.65
Unknown C	0.05	0.025
Unknown E	0.07	0.035

*µg/device = µg/ml, since device is 1 ml; **Based on 0.5 ml once daily injection.

Case Study – Toxicological Evaluation

- Three leachable substances remain for further evaluation.
- Each of them exceed the most stringent threshold of 1.5 µg/day.
 - But are less than the proposed thresholds for substances structurally categorized as Class III or Class IV (sensitizers and irritants).

<u>Leachable</u>	<u>Concentration</u> <u>(µg/device)*</u>	<u>Estimated Daily</u> <u>Dose (µg)*</u>
2,4 Di t-butyl phenol	3.9	1.95
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*µg/device = µg/ml, since device is 1 ml; **Based on 0.5 ml once daily injection.

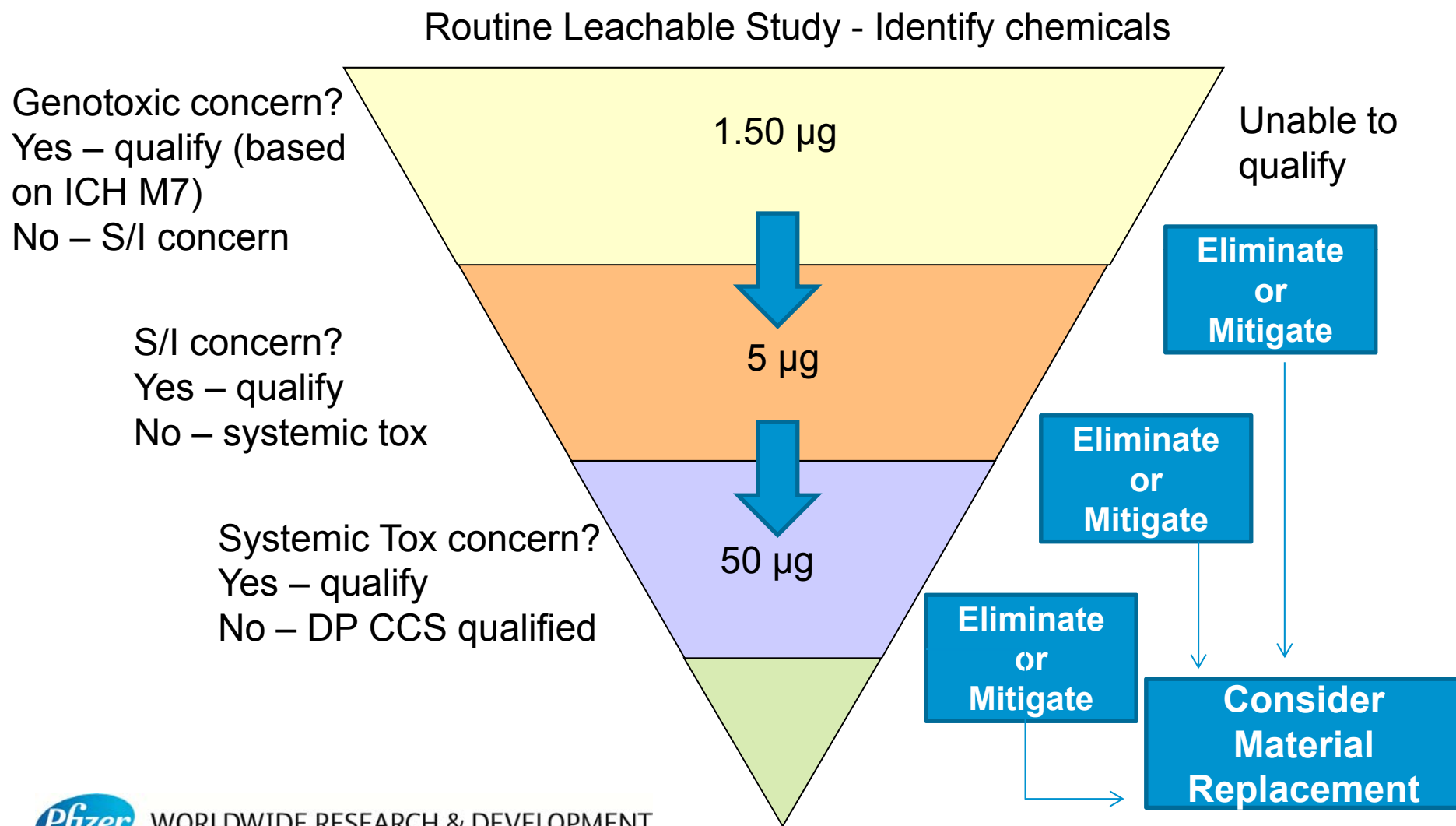
Case Study – Toxicological Assessment

Putting it all together

- Overall Evaluation:
 - Based on the results of the migration study, 11 substances were identified as actual leachables
 - Eight of these substances were present in the drug product at levels below the proposed threshold levels and are therefore considered qualified by virtue of the respective low estimated total daily intakes
 - Three substances required further evaluation, due to their respective estimated total daily intakes. These were 2,4 Di T-butyl phenol, erucamide, and “unknown A”
 - 2, 4 Di T-butyl phenol – Qualified based on ICH M7
 - Erucamide – Based on the estimated total daily intake and information in the literature, the levels of this leachable are considered qualified
 - Unknown A – The structure of this substance should be elucidated and submitted to Toxicology for further evaluation



Parenteral DP L&E Decision Tree



Conclusions

- TTC is a generally accepted method to evaluate and classify the toxicity of a chemical
 - Coupled with the Cramer Classification Tree, evaluation and chemicals can be classified for mutagenic and non-mutagenic endpoints
- ICH M7 defines acceptable doses for mutagenic impurities in DP based on duration of exposure
- PQRI adapted and modified the Cramer Classification Tree to qualify L&E in parenteral DP
 - ICH M7 principles can be applied to mutagenic leachables

References

- ICH:
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 - <http://journal.pda.org/content/67/5/430.full.pdf+html>



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