Regulation of Genotoxic and Carcinogenic Impurities in Pharmaceuticals

Impurities in Drugs:
Monitoring, Safety and Regulation
The Israel Chapter of PDA

July, 15 – 16, 2008

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Food and Drug Administration

Relevant guidelines, publications and promises on impurities

- ICH Q3A(R) Impurities in New Drug Substances, 2002
- ICH Q3B(R) Impurities in New Drug Products, 2003
- ICH Q3C Impurities: Guideline for Residual Solvents, 1997
- EMEA, Guideline on the Limits of Genotoxic Impurities, 2006
- EMEA, Questions and Answers on the CHMP Guideline on the limits of genotoxic impurities, 2008
- Establishment of Allowable Concentrations of Genotoxic Impurities in Drug Substance and Product, 2005, PhRMA position paper.
- FDA draft: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches and Acceptable Limits

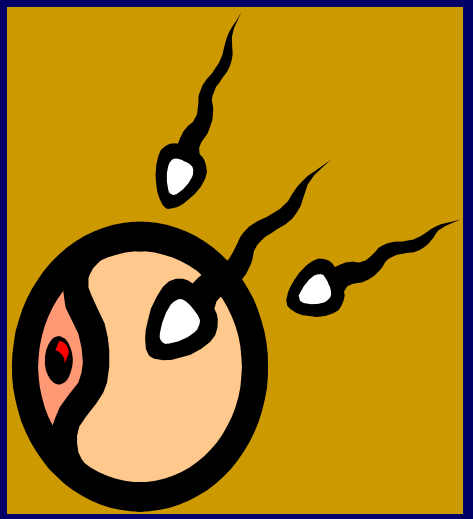
Mutations in Somatic Cells

- Cancer
- Heart disease
- Aging

Mutations in Germinal Cells

- Genetic diseases

  eg. achondroplasia



Mechanisms of Activation/Inactivation of Cancer-Associated Genes

- Point Mutations
- Chromosomal Deletions
- Chromosomal Translocations
- Gene Amplification

Tests for qualifying impurities in drug substance

- Genotoxicity studies (point mutation, chromosomal aberration-- Ames assay, *in vitro* cytogenetics or mouse lymphoma assay)
- General toxicity studies (one species usually 14 to 90 days)
- Other specific toxicity endpoints as appropriate

What if impurity is found to be genotoxic and cannot be completely removed?

- ICH guidelines are not explicit in this regard
- Quantitative risk assessments for cancer are based on lifetime exposures of animals. What about drugs in clinical trials for relatively short periods? Should permissible levels of genotoxic impurities be higher?

Calculating thresholds for effects without thresholds- virtually safe doses, or TTCs

- Concept first proposed by CFSAN as a “threshold for regulation” of food contact materials.
- TTC refers to a dose of a material that does not pose a **significant** risk of cancer or other toxic effects.

Fed. Regist. 60, 36582-36596, 1995

European Medicines Agency
Evaluation of Medicines for Human Use

London, 28 June 2006
CPMP/SWP/5199/02
EMEA/CHMP/QWP/251344/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE LIMITS OF GENOTOXIC IMPURITIES

Deals only with marketed products

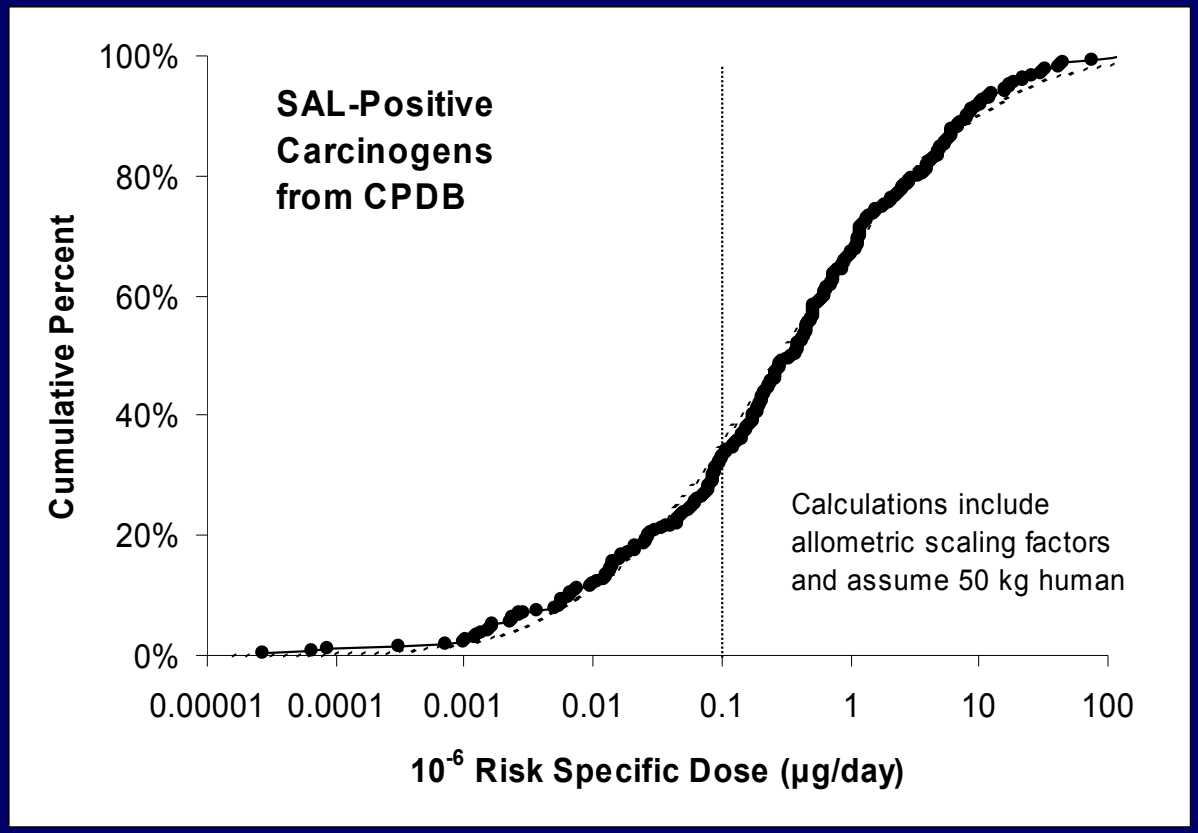
EMEA guideline on limits of genotoxic impurities

Some genotoxic chemicals may have thresholds because of known mechanism of action, e.g. spindle poisons, topoisomerase inhibitors.

- Linear extrapolation may be not be justified for all DNA reactive chemicals.

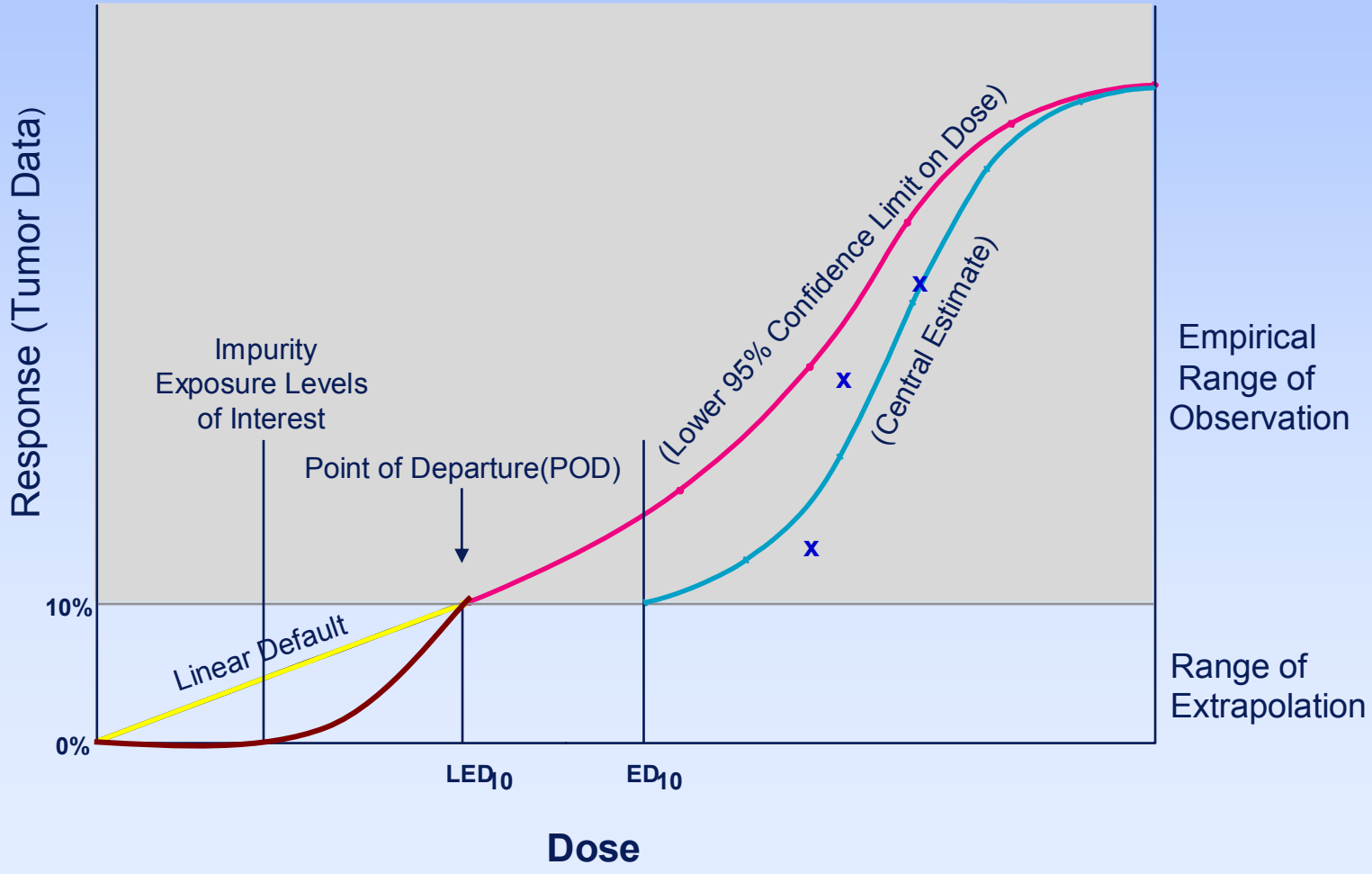
EMEA guideline on limits of genotoxic impurities

- In most cases mechanistic data on impurity will not be available. May have structural alerts for genotoxicity and/or carcinogenicity.
- Applies a Threshold of Toxicological Concern (TTC)—exposure to an unstudied chemical that will not pose a significant risk of cancer or other toxic effect
- TTC of 1.5 µg/person/day derived from a data base of over 700 carcinogens (from the Carcinogenic Potency Data Base)
- Implies that daily exposure to this level of the average carcinogen increases the upper bound lifetime risk of contracting cancer by less that one in one million. Considered "virtually safe dose" and commonly used by EPA for environmental contaminants.



Distribution of estimated human 10^{-6} risk specific doses for 276 SAL-positive carcinogens from Carcinogen Potency Database (CPDB). From: Justification of Thresholds for Leachables in Orally Inhaled and Nasal Drug Products. Ball et al., In preparation.

Carcinogen Risk Assessment



Risks from carcinogenic exposures

- Subset of highly potent carcinogens (generally those that are mutagens) suggest a lower TTC. These could be considered on a case-by-case basis.
- What is "virtually safe dose"
  - EPA generally uses 10^{-6} lifetime risk for cancer
  - State of California uses 10^{-5} lifetime as their "no significant risk level."
  - EMEA proposes 10^{-5} lifetime risk for cancer for pharmaceuticals since unlike environmental contaminants, they provide benefit
  - ICH Q3C uses 10^{-5} lifetime risk for cancer as the criterion for setting acceptable levels of solvents in marketed drug products

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London 26 June 200
Doc. Ref. EMEA/CHMP/SWP/131994/200

CHMP SAFETY WORKING PARTY (SWP)

Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities

Food and Drug Administration

Major points in EMEA's June 2008 Q&A

- Guideline is NOT applied retrospectively unless there "cause for concern" e.g. mesylate salt drugs.
- If the level of a mutagenic impurity is below TTC (<1.5 µg/day) it is not necessary to apply ALARP (as low as reasonably possible) unless structure is of high concern, e.g. N-nitroso or azoxy compounds.
- Negative result in an Ames assay qualifies an impurity with a structural alert.
- Absence of structural alerts is sufficient to regard impurity a "not genotoxic."
- It is sufficient to reduce impurities with structural alerts to TTC levels without an actual test (assume it's positive).

Major points in EMEA's June 2008 Q&A

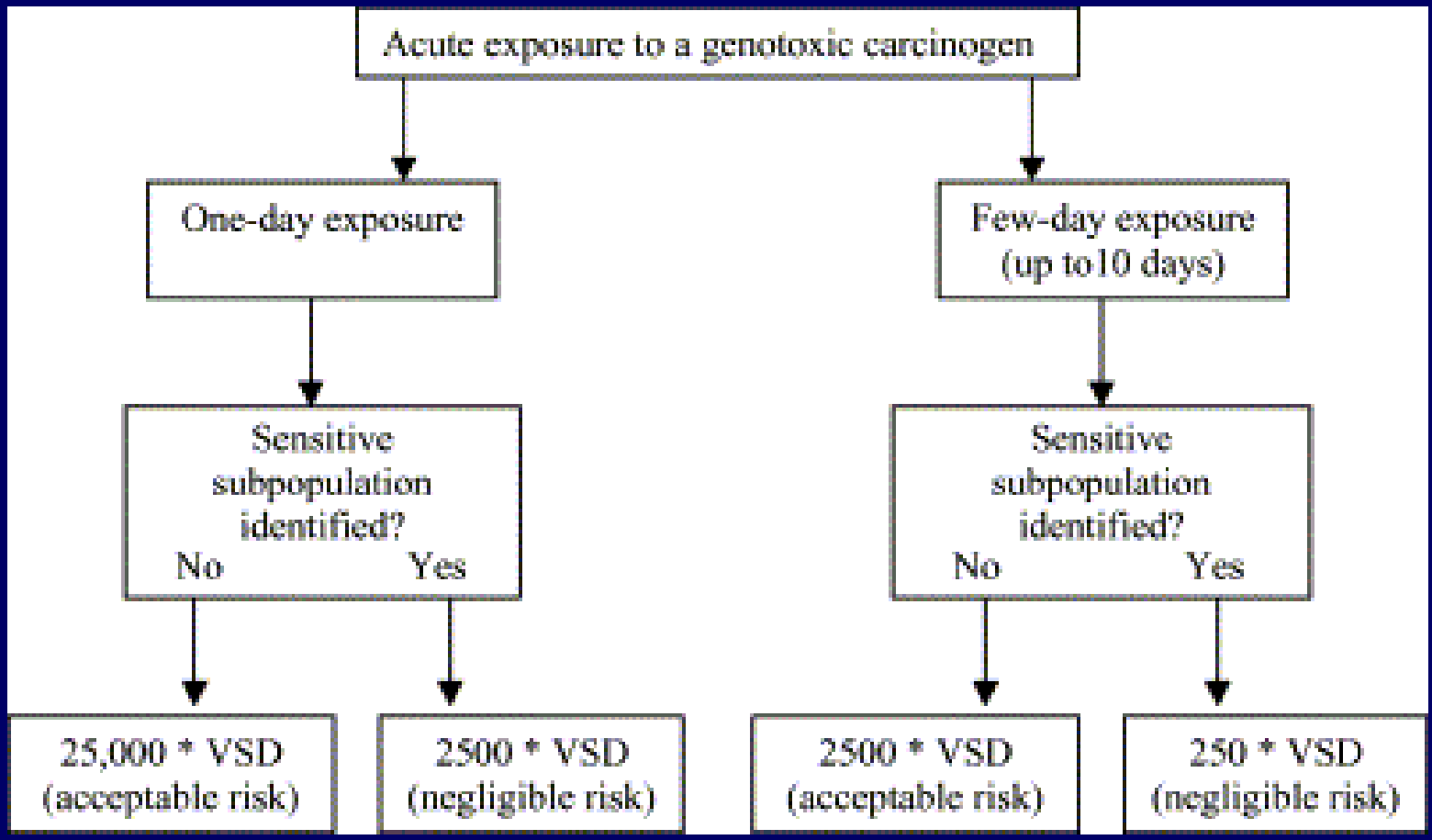
- No action is required for a new unidentified impurity found at levels below the ICH identification threshold.
- When an impurity is found above the ICH identification threshold, but below the qualification threshold and it has a structural alert, this can be qualified with an Ames test on the API containing the impurity as long as the impurity is tested up to 250 µg/plate.
- EMEA accepts the notion of a "staged TTC."

Major points in EMEA's June 2008 Q&A

- When more than one genotoxic impurity is present in the drug substance, the TTC value of 1.5 µg/day can be applied to each impurity if they are structurally unrelated. If structurally similar, MOA expected to be the same and they are summed.
- May not always be achievable:
  - Maximum daily dose of API
  - Indication
  - Step of synthesis at which impurity arises
  - Capability to eliminate by purification
  - Capability of analytical procedures

Risk assessment of peak exposure to genotoxic carcinogens: a pragmatic approach

Peter M. J. Bos, Bert-Jan Baars and Marcel T. M. van Raaij
Toxicology Letters 151: 43 – 50, 2004



Staged TTC during drug development

From EMEA Q & A, June 2008

	Duration of Exposure				
	Single dose	≤1 mo.	≤3 mo.	≤6 mo.	> 12 mo.
Allowable Daily Intake (μg/day)	**120**	**60**	**20**	**10**	**5**

Acceptable limits in ug/day based on Allowable Daily Intake calculations using a staged TTC approach*

*Müller et al. Jour. of Regulatory Toxicology and Pharmacology, 2006.

	Duration of Exposure				
	≤1 mo.	>1-3 mo.	>3-6 mo.	>6-12 mo.	> 12 mo.
Proposed Allowable Daily Intake (μg/day) for all Phases of development	**120**	**40**	**20**	**10**	**1.5**
	or	or	or	or	
Alternative maximum based on percentage of impurity in API	0.5%	0.5%	0.5%	0.5%	

10^{-6} cancer risk – extra conservatism during shorter duration trials (e.g. for volunteers)

10^{-5} cancer risk – risk used by ICH for carcinogenic residual solvents and CHMP draft for genotoxic impurities

A few typical daily exposures to carcinogens

Source of carcinogen	Carcinogen	Average daily human exposure
Indoor air	Formaldehyde Benzene	598 µg 155 µg
Tap water	Bromodichloro-methane chloroform	13 µg 17 µg
Celery	8-methoxy psoralen	4.9 µg
Coffee	Catechol Hydroquinone Caffeic acid	1.3 mg 333 µg 23.9 mg
Lettuce	Caffeic acid	7.9 mg
Brown mustard	Allyl isothiocyanate	62.9 µg