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Addressing Genotoxic Impurities in Drug Development

The following white paper summarizes recent Guidances and the FDA / EMEA positions on potential genotoxic agents in your products.

ICH Q3A for Toxic Impurities

The ICH Q3A (R1) Impurities in New Drug Substances states: "*analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold*."

The problem is the following:

- Identification of "unusually potent" impurities not described
- No threshold of concern is given

EMEA Guidance on Genotoxins

- For impurities with genotoxic potential
- Applies *Threshold of Toxicological Concern* (TTC) concept to define acceptable risk
- 1.5 µg/day (registration limit) considered acceptable where compound specific tox data are not available

FDA Draft Guidance on Genotoxins[2]

- Mostly consistent with EMEA use of staged TT
- Impurities exceeding ICH thresholds should be assessed for genotoxic potential – Ames (sometimes chromo ab)
- If an impurity below ICH thresholds is identified it should be evaluated based on SAR relationships – *in silico* predicitions are acceptable, if positive, do Ames test

FDA and EMEA Staged TTC limits

The following tables summarize current allowable limits based on FDA and EMEA. The conclusion is that for a clinical trial of 1 month, no more than 120 ug/day (or 120 ppm assuming 1 g/day dose) of a potential genotoxic/mutagenic compound is allowed.

FDA

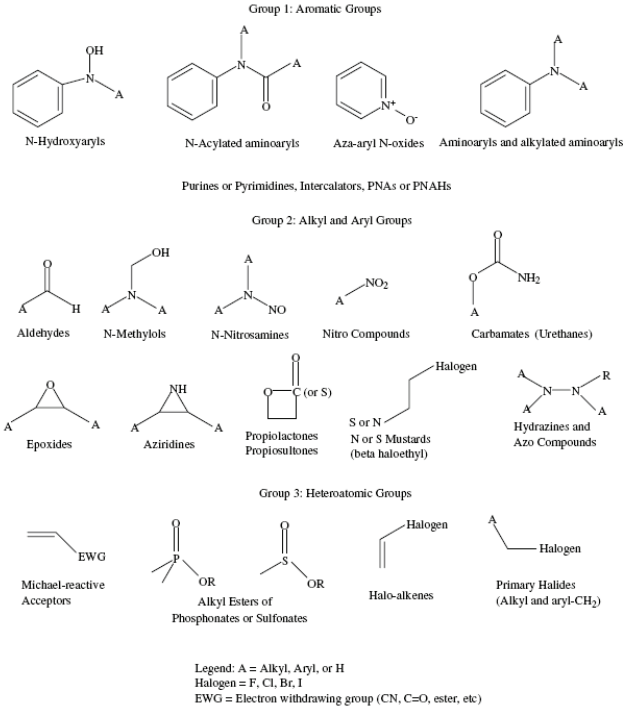
Duration	<14 d	14 d	1-3 mo	3-6 mo	6-12 mo
Threshold, µg/day	120	60	20	10	5

EMEA

Duration	Single dose	≤1 mo	≤3 mo	≤6 mo	≤12 mo
Allowable Daily Intake, µg/day	120	60	20	10	5

PhRMA – Structural Alerts is needed for Phase 1

The following is taken from Muller et al.[3] and represents the known structural features associated with common genotoxic agents.



Testing compounds with structural alerts for genotoxic

In addition to traditional "organic chemistry" "functional group" analysis you should also perform the following:

<u>*In Silico* methods</u>

- DEREK
- MCase
- TOPKAT

<u>Bacterial reverse mutagen test (Ames test)</u>

- Isolated compound or present in API - 250 µg/plate minimum
- Negative result puts compound in ordinary impurity class

Contact us today with your questions….

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[1] *Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: December 2008,* [2]*EMEA / CHMP "Guidelines on the limits of Genotoxic Impurities", CPMP/SWP/5199/02; EMEA/CHMP/QWP/251344/2006, London, UK, 28 June 2006.* [3]*The PhRMA Task Force White Paper:* Müller L, Mauthe RJ, Riley CM, Andino MM, De Antonis D, Beels C, DeGeorge J, De Knaep AGM, Ellison D, Fagerland JA, et al. "*A rationale for determining, testing and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity".* Regul. Toxicol. Pharmacol. (2006) 44:198–211.