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Editorial:

CARCINOGENESIS AND GENOTOXICITY

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Carcinogenesis (Table 1A) and genotoxicity (Table 1B) are two of the most popular topics published in our partner journal Archives of Toxicology. A particular highlight was an article published in 2008 by Köhle et al. on hepatocarcinogenesis in humans and rodents. It is fairly well-accepted that major interspecies differences between human and rodents can compromise interspecies extrapolation in hepatocarcinogenesis. In their publication, Köhle et al. (2008) addressed the topic of interspecies extrapolation and concluded that a relatively high degree of similarity exists between humans and rodent for genotoxic-initiating carcinogens. However, remarkable species differences have been observed for nongenotoxic tumor promoters. Köhle and colleagues differentiated between two modes of action: (1) chronic cytotoxicity leading to replacement proliferation, which often occurs in both humans and rodents, and (2) sustained activation of orphan receptors such as CAR, PPAR alpha and the Ah receptor. Köhle et al. report that these mechanisms are much more relevant in rodents than in humans which may explain a considerable part of interspecies differences.

A second highlight is the novel classification of carcinogens by the SCOEL (Scientific Committee on Occupational Exposure Limits) reported by Bolt and Huici-Montagud (2008), where carcinogens are classified according to the possibility to establish either “practical” or “true” thresholds. Class A represents non-threshold genotoxic carcinogens where the linear non-threshold model appears appropriate. Class B comprises genotoxic carcinogens for which the existence of a threshold cannot be sufficiently supported. Therefore because of the scientific uncertainty, a liner non-threshold model should be used. Class C includes carcinogens with a practical threshold (as described by Hengstler et al., 2003) where exposure limits may be based on an established NOAEL. Class D are non-genotoxic and non-DNA-reactive carcinogens where a “true” or “perfect” threshold can be established.

An overview of the publications on carcinogenesis and genotoxicity is given in Table 1.

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Table 1A: Recent studies on **carcinogenesis**

Key message	Reference
Troglitazone, an insulin-sensitizing agent, shows a weak tumor-promoting effect in the rasH2/urethane mouse model.	Jin et al., 2008
Piperonyl butoxide activates c-Jun and ATF-2 in mouse hepatocytes, which may play a role in early stages of hepatocarcinogenesis.	Muguruma et al., 2008
This article focuses on interspecies differences of hepatocarcinogenesis in humans and rodents. While a high degree of similarity is often observed for genotoxic carcinogens, considerable species differences have been observed for the nongenotoxic carcinogens. Two modes of action are of particular relevance: (i) sustained activation of receptors such as CAR, PPARalpha and the Ah receptor, (ii) chronic cytotoxicity leading to replacement proliferation	Köhle et al., 2008
Dietary diphenyl diselenide delays chemically induced breast cancer in rats.	de Vargas Barbosa et al., 2008
2-Methylimidazole, which has been identified in food and is used in the manufacture of dyes and rubber, induces thyroid and liver tumors in rats and mice.	Chan et al., 2008a
The size of GST-P liver foci is associated with the rates of cell division and death.	Lu et al., 2008
The Scientific Committee on Occupational Exposure Limits (SCOEL) recommends consideration of four groups of carcinogens: (A) non-threshold genotoxic carcinogens, (B) genotoxic carcinogens for which the existence of a threshold cannot be sufficiently supported at present, (C) genotoxic carcinogens with a practical threshold, (D) non-genotoxic and non-DNA reactive carcinogens for which a true threshold can be derived.	Bolt and Huici-Montagud, 2008
4-Methlyimidazole causes alveolar and bronchiolar adenoma and carcinoma in rats.	Chan et al., 2008b

Table 1B: Recent progress in **genotoxicity research**

Key message	Reference
The Fast Micromethod is a 96-well microplate assay for identification of DNA strand breaks. The technique was further improved by omission of the cell lysis step and the time-consuming cell-counting.	Ullmann et al., 2008
Wastewater from a petrochemical plant, a petroleum refinery and a coke plant of the steel industry caused chromosomal aberrations in mononuclear blood cells.	Krishnamurthi et al., 2008
Vitamin B6 antagonizes the clastogenic effect of doxorubicin in rat bone marrow cells.	Takeuchi et al., 2008
The Ty1 assay detects a wide spectrum of genotoxic carcinogens based on induction of the transposition of a Ty1 retrotransposon in yeast cells.	Pesheva et al., 2008
Inhibition of poly (ADP-ribose) polymerase (PARP) can shift balances between apoptotic and necrotic cell death in HaCaT cells.	Kehe et al., 2008
Non-specific chromosomal genotoxicity can be predicted by physico-chemical properties, such as the relation of polar surface to the total molecular surface of compounds.	Dorn et al., 2008a
Anabolic doping steroids induce micronuclei in V79 cells.	Dorn et al., 2008b
This review discusses the mechanisms responsible for chomosomal instability in urothelial carcinomas.	Florl and Schulz, 2008

Key message	Reference
Panax ginseng extract reduces the genotoxicity of ethylenediamine-tetraacetic acid in rats.	Khalil et al., 2008
Phosphate fluoride is used by dental practitioners to prevent caries in children. However, this study has shown that phosphate fluoride induces DNA strand breaks in epithelial cells.	Tsai et al., 2008
Ginsenoside Rg(3) protects against cyclophosphamide-induced DNA damage in bone marrow cells of mice.	Zhang et al., 2008

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