

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Cresols TR 550

Comments of the
American Chemistry Council Cresols Panel
May 16-17, 2007
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The Panel wishes to comment in two areas:

- 1) Additional developmental and reproductive studies are available on cresols isomers
- 2) The panel urges NTP to consider the relevance of mouse forestomach tumors for human cancer

Repro & Developmental Cresol Toxicity Studies

- 9 Bioassays
- Rat and rabbit developmental toxicity
- 2-Generation rat reproductive toxicity
- Each cresol isomer tested separately
- Oral gavage administration
- GLP compliant, OPPTS protocols
- R. W. Tyl, PhD study director (BRRC)

IARC* on the relevance of rodent forestomach squamous cell papillomas to human cancer

Test conditions which lead to prolonged exposure and high local concentration of test material with forestomach epithelial tissue

Suggest a Mode-of-Action for forestomach squamous cell papilloma

* IARC Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans (2003)

Generalized Mode-of-Action for Rodent Forestomach Squamous Cell Papilloma Formation

- Non DNA-reactive agent
- Initial cytotoxicity (forestomach squamous epithelium)
- Sustained cell proliferation; hyperplasia

Evidence for MoA with m/p-Cresols

- Cresols have considerable contact irritation potential
- m/p-cresols did not exhibit mutagenic activity in NTP testing (draft report p 58, 63)
- Oral (feed) study; forestomach acts as food reservoir
- Mouse forestomach tumors were all papillomas, no carcinomas
- Tumors did not develop at any other site
- Promotes DMBA-initiated skin papillomas in mice

Mouse Forestomach Epithelial Lesions

Chronic dietary study

Forestomach lesion	Control	1000 ppm	3000 ppm	10000 ppm
hypertrophy	0/49	0/49	0/49	2/49
Papilloma	0/50	1/50	1/49	10/50

Evidence of m/p-Cresol Irritation

Hyperplasia (minimal) of forestomach squamous epithelium in 20% (1/5) high-dose mice in 28-day dietary study

Atrophy, regenerative changes and hypertrophy of nasal epithelium and lower respiratory epithelium

28-day dietary

90-day dietary

Chronic study

Consideration for additional language in Technical Report

IARC states “the relevance (of rodent forestomach papillomas) is probably limited for agents that have no demonstrable genotoxicity and that are solely carcinogenic for the forestomach squamous epithelium in rodents after oral administration, since the exposure conditions are quite different between the experimental animal and humans. Consequently, for these agents, the mode of carcinogenic action could be specific to the experimental animal.”

American Chemistry Council Cresols Panel

Dakota Gasification Company

Degussa Corporation

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Merisol, USA LLC

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