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The Non-Linear Nasal Carcinogen Vinyl Acetate and Some Challenges of Tox21 for Non-Linear Dose-Response Assessment

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Outline

- Vinyl Acetate: Hypothesis driven research leads to an evidentiary basis for a threshold mechanism
  - MOA, intracellular pH, cell proliferation, genotoxicity
- Could systems biology have done as well?
  - Mode of action (Defines Dose-Response)
  - Dose-response—Silica Response Pathway Modeling
  - Genotoxicity
- Lingering Questions About Systems Toxicology Approaches
What Kind of Data do We Need to use A Non-Linear Approach to Risk Assessment?

- Mode of Action
- Genotoxicity data
- Dose-Response Data (genotox, and key processes in the MOA)
VAM is a synthetic organic ester used in the production of resins, polymers, adhesives and acrylic fibers.

High dose hazard assessment identifies target tissue:
- Nasal cavity tumors (≥200 ppm) in the rat olfactory and respiratory epithelium following chronic inhalation exposure.
- Olfactory tissue damage, respiratory metaplasia and regenerative cell proliferation.
Vinyl Acetate: A Case Study in Conventional Mode of Action Assessment

- Hypothesis driven, focused, systematic experimental work to reveal mode of action and its implications for human risk assessment
  - 20 year, $15 million product safety program
  - Sub-chronic exposure-response, metabolism, in vitro and in vivo DNA adducts, in vitro mutation dose-response, pharmacokinetic modeling in vitro and in vivo, and in vitro and other in vivo mechanistic work
Vinyl Acetate Metabolic Pathways

Vinyl acetate $\xrightarrow{\text{Carboxyelsterase}}$ Vinyl alcohol

$\text{Aldehyde dehydrogenase} \rightarrow$ Acetaldehyde

$\text{Vinyl alcohol} + \text{Acid} \rightarrow \text{Acetaldehyde}$

$\text{NADH} \rightarrow \text{NAD}^+$

10-May-04
Quantitative Fluorescence Image Microscopy

$pH_i = 6.20$

$pH_i = 6.80$

$pH_i = 7.49$

Hepatocytes

Vinyl Acetate Concentration (PM)

Regenerative or Mitogenic Cell Proliferation in the Rat Nasal Tissues at Higher Exposures

Cell proliferation following 20 exposures

Kuykendall and Bogdanffy et al. 1993, Bogdanffy et al., 2001)
TK Mutations Show a Threshold

Micronucleus Formation also show a Threshold

Micronucleus formation is Correlated to Cytotoxicity

Dosimetry Must be an Integral Part of the Gene Tox Test Systems (HTP, MTP, Omics…)

VA and acetaldehyde have important pharmacokinetic characteristics in vitro

Without dosimetry, the relevance of the test cannot be determined and results cannot be compared across test systems or to human exposures
Formaldehyde Adducts are below Endogenous levels at Carcinogenic Doses

Endogenous versus Exogenous DNA Adducts: Their Role in Carcinogenesis, Epidemiology, and Risk Assessment

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