

13 pp.

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Toxicology and Descriptive Biology

APFO

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Key Elements

Data Exists

Key Findings

Acute Toxicity

x

Low to moderate toxicity
oral/dermal/inhalation

Irritation potential defined

Not a sensitizer

Repeated Dose Toxicity

x

Oral/dermal/inhalation
rodent/non-rodent

Liver primary target organ

Potency defined

Developmental Toxicity

x

Oral/inhalation
rat/rabbit

Fetus not more sensitive than
maternal

Not associated with structural
anomalies

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Toxicology and Descriptive Biology

APFO

<u>Key Elements</u>	<u>Data Exists</u>	<u>Key Findings</u>
Reproductive Toxicity	-	Reproductive organs not a target Functional reproduction not defined
Genetic Toxicity	x	Point mutation - Ames negative Chromosomal effects - <i>in vivo</i> , <i>in vitro</i> - negative Not a genotoxic agent
Ecotoxicity - Acute	x	Not acutely toxic to fish - invertebrates (Daphnia) - algae

Toxicology and Descriptive Biology

APFO

Multi-generation Reproduction Study in Rats

- The objective of this study is evaluate the effect of APFO on the gonadal function, conception, parturition, and the growth and development of offspring of male and female rats over 2 generations involving the production of at least one set of litters in each generation.
- Work Plan - Initiated 11/00; first litters born and currently in lactational phase.
- Result - Dose levels 1, 3, 10, and 30 mg/kg.
Body weight effects - Males - 3 to 30 mg/kg
Females - No obvious effects

APFO Pharmacokinetic Studies

- ADME Mass Balance: Rats
- Protein Binding: Rat/Man
- PBK Modeling: Rat/Man

(Initiated 2Q 2001; estimated completion
all portions 4Q/2002)

APFO Pharmacokinetic Studies

Project Element: ADME/Mass Balance

Objective: To determine APFO absorption, distribution, metabolism and elimination following single and repeated doses in rats.

Product: GLP ADME/Mass Balance report

Payoff: Ability to use a scientifically defensible basis for development and validation of PBPK model

APFO Pharmacokinetic Studies

Project Element: Protein Binding

Objective: To determine the extent and type of APFO binding in rats and humans.

Product: Manuscript/report describing species and gender-specific binding to proteins.

Payoff: Ability to qualitatively and quantitatively compare APFO binding in rats and humans.

APFO Pharmacokinetic Studies

Project Element: PBK Modeling

Objective: To develop rat and human PBK models for APFO.

Product: Manuscript/report describing PBK model development and application to APFO kinetics in rats and humans.

Payoff: Ability to quantitatively relate APFO exposure to APFO concentration in the body. To understand how APFO effects in rats translated to man.

APFO Environmental Fate and Effects Studies

Focus on:

Physical Properties

Environmental Fate

Environmental Effects

Bioconcentration

APFO Environmental Fate and Effects Studies

Physical - Chemical Properties APFO

- | | |
|--|---|
| • Molecular Weight | x |
| • Boiling/Melting Point | x |
| • Vapor Pressure | In progress |
| • Water Solubility | In progress |
| • Log Kow (octanol - water partition) | To be determined
problematic,
3 plus phases |
| • Adsorption/Desorption onto glassware | Measure |

APFO Environmental Fate and Effects Studies

Environmental Fate

Biodegradation: Completed; not
biodegradable, OECD methodology

Adsorption/Desorption: Sediment/sludge
to be determined

APFO Environmental Fate and Effects Studies

Environmental Effects

Chronic Toxicity: 21 Day Daphnia - Complete
90 Day Early Life Stage
Study (Rainbow Trout) - to be conducted

Aquatic Chronic Toxicity Studies APFO

Objective:

The purpose of these tests is to determine the chemical concentrations that are associated with long-term chronic effects (NOEC, LOEC) on survival, growth and reproduction of a fish (rainbow trout) and an aquatic invertebrate (Daphnia) - Completed.

- Includes acute limit test
- Dose response, analytical confirmation of test concentrations

Results:

Assesses effects on survival, growth (length, weight), and Daphnid reproduction

SUMMARY OF WORK PLAN

- TOXICOLOGY
 - MULTIGENERATION REPRODUCTION 11/00 TO 3Q/02
- PHARMACOKINETICS
 - MASS BALANCE—RATS 2Q/01 TO 2Q/02
 - PROTEIN BINDING—RAT/MAN 2Q/01 TO 4Q/02
 - PBK MODELING—RAT/MAN 2Q/01 TO 4Q/02
- ENVIRONMENTAL
 - PHYSICAL PROPERTIES 1Q/01 TO 4Q/01
 - VAPOR PRESSURE
 - WATER SOLUBILITY
 - LOG K_{ow}
 - ADSORPTION TO SURFACES (GLASS)
 - SEDIMENT/SLUDGE—ADSORPTION/DESORPTION COMPLETED BY 4Q/02
 - EFFECTS—CHRONIC TOXICITY—TROUT COMPLETED BY 4Q/02
 - BIOCONCENTRATION—INITIAL ASSESSMENT 1Q/01 TO 2Q/01