
NTP Toxicology and Carcinogenesis Studies

Reviewed at the
February 17 & 18, 2004

Technical Reports Review
Subcommittee Meeting



Toxic Equivalency Factor (TEF) Initiative

- ♦ Dioxin-like compounds are environmental contaminants resulting from a number of sources including combustion and chemical manufacturing and processing, and from past production and release
- ♦ Humans are exposed to mixtures of these dioxin-like compounds
- ♦ Total exposure to mixtures of dioxins is determined by adding up all the dioxins in a mixture with each dioxin's contribution being weighted by its potency relative to the most potent dioxin, 2,3,7,8-TCDD
- ♦ The World Health Organization Dioxin Toxic Equivalency Factors (TEFs) are used for this potency adjustment
- ♦ The validity of the TEF approach for use in cancer risk assessment is uncertain

Study Objectives

- ◆ Determine the toxicity and carcinogenicity of the individual compounds and mixtures
- ◆ Determine potency factors of individual dioxin-like chemicals
- ◆ Test the validity of the TEF method for predicting the carcinogenicity of a simple mixture of dioxins
- ◆ Determine if non-dioxin-like PCBs antagonize the carcinogenicity of a dioxin-like PCB

Chemical	Levels of Evidence of Carcinogenic Activity
	Female SD-Rat
◆ TCDD and PCB-126	Clear Evidence (Liver; Lung; Oral Cavity) (TCDD- Uterus)
◆ PeCDF	Some Evidence (Liver; Oral Cavity)
◆ Mixture	Clear Evidence (Liver; Lung)

Malachite and Leucomalachite Green

- ♦ Malachite green - a dye used in the fish industry as an antifungal
- ♦ Leucomalachite green - formed by the reduction of malachite green chloride and persists in tissues of exposed fish
- ♦ Significant worker and consumer exposure
- ♦ Administered in the feed

Chemical	Levels of Evidence of Carcinogenic Activity			
	MR	FR	MM	FM
♦ Malachite Green	NT	EE	NT	NE
	(Thyroid; Liver; Mammary)			
♦ Leucomalachite Green	EE	EE	NT	SE
	(Thyroid)			(Liver)
	(Testes)	(Liver)		
♦ Anthraquinone	SE	CE	CE	CE
	<ul style="list-style-type: none"> ▪ Revisit- report and conclusions accepted ▪ Recommended that the title be changed to "Anthracene-derived Anthraquinone", and this made clear throughout the report 			

Carcinogenesis Studies in Guppies and Medaka

◆ A Test of Fish Models

- 2,2-Bis(Bromomethyl)-1,3-Propanediol mutagenic
- 1,2,3-Trichloropropane mutagenic
- Nitromethane non-mutagenic

Rationale for Models and Chemicals

- ◆ Savings in time and cost
- ◆ Larger numbers can be used (modeling)
- ◆ Reduced numbers of rodents used
- ◆ Low background incidence of cancer

- ◆ Mutagenic and non-mutagenic chemicals
- ◆ Clearly carcinogenic chemicals affecting multiple rodent tissues, and not necessarily the liver

Pathology Examination

- ◆ Whole fish fixed and embedded and 10 longitudinal sections examined
 - Two serial sections at each of five steps through whole fish
- ◆ Approximately 30 tissues examined per fish
- ◆ Early deaths usually not examined
- ◆ Modified pathology peer review with PWG

2,2-Bis(Bromomethyl)-1,3-Propanediol (Feed)

- ◆ **Male Rats**
 - Skin, Subcutaneous Tissue, Mammary Gland, Zymbal's Gland, Oral Cavity, Esophagus, Forestomach, Small and Large Intestine, Mesothelium, Urinary Bladder, Lung, Thyroid Gland, Seminal Vesicle, Mononuclear Cell Leukemia
- ◆ **Female Rats**
 - Oral Cavity, Esophagus, Mammary Gland, Thyroid Gland
- ◆ **Male Mice**
 - Harderian Gland, Lung, Kidney
- ◆ **Female Mice**
 - Harderian Gland, Lung, Subcutaneous Tissue

2,2-Bis(Bromomethyl)-1,3-Propanediol

- ◆ Male Rat - Clear Evidence (Multisite)
- ◆ Female Rat - Clear Evidence (Multisite)
- ◆ Male Mouse - Clear Evidence (Multisite)
- ◆ Female Mouse - Clear Evidence (Multisite)

- ◆ Male Guppy - Positive (Liver)
- ◆ Female Guppy - Inadequate Study
- ◆ Male Medaka - Positive (Liver)
- ◆ Female Medaka - Negative

1,2,3-Trichloropropane (Gavage)

- ◆ Male Rat
 - Oral Cavity, Forestomach, Pancreas, Kidney, Preputial gland, Zymbal gland
- ◆ Female Rat
 - Oral Cavity, Forestomach, Clitoral Gland, Mammary Gland
- ◆ Male Mouse
 - Forestomach, Liver, Harderian Gland
- ◆ Female Mouse
 - Oral Cavity, Forestomach, Liver, Harderian Gland, Uterus

1,2,3-Trichloropropane

- ◆ Male Rat - Clear Evidence (Multisite)
- ◆ Female Rat - Clear Evidence (Multisite)
- ◆ Male Mouse - Clear Evidence (Multisite)
- ◆ Female Mouse - Clear Evidence (Multisite)

- ◆ Male Guppy - Positive (Liver)
- ◆ Female Guppy - Positive (Liver)
- ◆ Male Medaka - Positive (Liver, Gallbladder)
- ◆ Female Medaka - Positive (Liver, Gallbladder)

Nitromethane (Inhalation)

- ◆ Male Rats
 - None
- ◆ Female Rats
 - Mammary Gland (Ca 2/50, 3/50, 3/50, 11/50; All 21-25-34-41)
- ◆ Male Mice
 - Harderian Gland, Lung
- ◆ Female Mice
 - Harderian Gland, Liver, Lung

Nitromethane

- ◆ Male Rat - No Evidence
- ◆ Female Rat - Clear Evidence (Mammary)
- ◆ Male Mouse - Clear Evidence (Multisite)
- ◆ Female Mouse - Clear Evidence (Multisite)

- ◆ Male Guppy - Inadequate
- ◆ Female Guppy - Negative
- ◆ Male Medaka - Negative
- ◆ Female Medaka - Negative

Selected Conclusions (3 chemicals)

- ◆ Cannibalism of early death animals poses a significant problem

- ◆ Studies are not inexpensive nor short
 - savings in pathology evaluation less than anticipated
 - Only 1/6 positive studies was positive at 9 months
- ◆ Guppies and Medaka are less sensitive than rodents; Medaka appear more sensitive than Guppies

- ◆ Limited response site(s) - liver appears to be the main target

- ◆ Static and short term studies are not good predictors for long-term studies

Studies to be presented in December, 2004

- ◆ PCB 118/126
- ◆ PCB 153
- ◆ Binary mixture

- ◆ Sodium Chlorate
- ◆ Bromodichloromethane

- ◆ Benzophenone
- ◆ Transplacental AZT-Swiss (CD-1) mouse

- ◆ Genistein dose range finding study