

Results of ILSI/HESI International Act Study

Bold: Unexpected responses



		rasH2	p53+/-	Tg.AC		XPA-/-	XPA/p53	Neonatal	SHE
				Gavage	Skin				
Human carcinogens	phenacetin	Positive	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	cyclophosphamide	Positive	Positive	Positive	Equivocal			Positive	Positive
	melphalan	Equivocal	Positive	Positive	Equivocal				Positive
Immunosuppressive human carcinogen									
	cyclosporin A	Equivocal	Positive	Equivocal	Positive	Positive	Positive	Negative	Positive
Human hormone carcinogen									
	diethylstilbestrol	Positive	Positive	Negative	Positive	Positive	Positive	Negative	Positive
	17-β -estradiol	Negative	Equivocal	Negative	Positive	Negative	Positive	Positive	Positive
Nongenotoxic rodent-only carcinogen									
based on Epidemiology	clofibrate	Positive	Negative		Positive	Negative		Negative	Positive
	phenobarbital	Negative	Negative			Negative	Negative	Negative	Positive
	reserpine	Negative	Negative	Negative	Negative	Negative	Negative		Positive
	dieldrin	Negative	Negative						Positive
	methapyrilene	Negative	Negative		Negative				Positive
based on mechanism	haloperidol	Negative	Negative			Negative	Negative	Negative	Positive
	chloroform	Negative	Equivocal						
	chlorpromazine	Negative	Negative					Negative	Positive
	metaproterenol	Negative	Negative					Negative	
	Wy-14643	Positive	Negative	Equivocal	Negative	Positive			Positive
	DEHP	Positive	Equivocal	Negative	Negative	Negative	Negative	Negative	Positive
	sulfamethoxazole	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive
Non-genotoxic non-carcinogen									
	sulfisoxazole	Negative	Negative	Negative	Negative			Negative	Negative
	mannitol	Negative	Negative			Negative	Negative		Negative
	ampicillin	Negative	Negative			Negative			Positive

Regulatory perspectives in USA, EU, and Japan

Model	USA: FDA	EU: CPMP	Japan: MHLW
rasH2	Accepted <i>Genotoxic and non-genotoxic</i>		
p53KO	Accepted <i>Clear or equivocal genotoxic</i>	Accepted <i>Genotoxic and non-genotoxic</i>	Accepted <i>Clear or equivocal genotoxic</i>
TG.AC	Accepted <i>Dermal applications only</i>		Not accepted <i>Unstable vector</i>
Others*	Partially accepted	Not accepted	

*XPA KO, XPA+p53KO, neonatal models

28th Annual Symposium of Society of Toxicologic Pathology



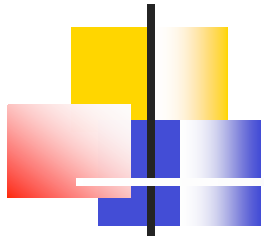
Session 3

Alternative Mouse Model for Carcinogenicity Assessment



(Washington, D.C., June 23, 2009)

Chair-persons and Speakers



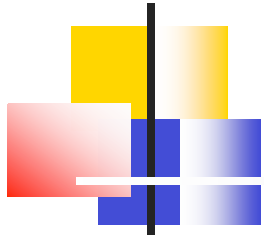
Session 3

Alternative Mouse Model for Carcinogenicity Assessment

Chairs: Daniel G. Morton (Pfizer) & James A. Swenberg (University of North Carolina)

- An Industry Perspective on Utility of Short-term Carcinogenicity Testing in Transgenic Mice in Pharmaceutical Development (Richard .D. Storer, Merck)
- Alternative Mouse Models for Carcinogenicity Assessment: Industry Use and Issues with Pathology Interpretation (Gerald G. Long, Eli Lilly)
- European Perspectives on Alternative Mouse Carcinogenicity Models (Bernard Leblanc, Pfizer)
- The Ito Medium Term Carcinogenicity Model (Hiroyuki Tsuda, Nagoya City University of Medical School)
- Genetically Modified Mouse Models for Hazard Identification and Risk Assessment in Toxicology and Carcinogenesis: Strength and Weaknesses (John E. French)

Carcinogenicity Alternative Mouse Models Working Group Survey



Preferred Selection of Models

- Replacement of 2 year mouse with rasH2
- p53 for potential genotoxicity
- Mechanistic studies

Generally rasH2

Single responses for other models

- CAMM acceptable for testing biologicals

Presented by Gerald G. Long of Eli Lilly & Company