Results of ILSI/HESI International Act Study

Bold: Unexpected responses

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		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

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

*XPA KO, XPA+p53KO, neonatal models

MacDonald et al: Toxicological Sciences 77, 188-194 (2004)

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Session 3

Alternative Mouse Model for Carcinogenicity Assessment

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

Chair-persons and Speakers

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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

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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