Model-Specific Illustrations

P53 +/- mouse on a C57BL/6 background strain

1. 6-month oral study in males; 15 animals per group. Findings: benign and malignant bladder tumors and evidence of crystals in the urine at the high dose. The chemical is positive in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	1/15	3/15	8/15
$p < 0.001$, survival adjusted trend test				
Historical control rate is 0/90				

2. 6-month study in females; 15 animals per group. Finding: malignant lymphoma. The chemical is positive in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	1/15	0/15	0/15	4/15
$p = 0.039$, survival adjusted trend test				
Historical control rate is 9/90 (range 0/15 to 3/15)				

3. 6-month oral study in males; 15 animals per group. Finding: kidney tubular cell tumors (one adenoma and one adenocarcinoma in different mice). Kidney tubular cell hyperplasia was diagnosed in 3 additional high dose mice. The chemical is positive in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	0/15	0/15	2/15
$p = 0.07$, survival adjusted trend test				
Historical control rate is 0/90				

4. A 6-month, oral study in males; 15 animals per group. Findings: all dose groups plus controls are negative for tumors. An MTD (minimally toxic dose) is achieved. The chemical is positive in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	0/15	0/15	0/15

5. A 9-month, oral study in males, 15 animals per group. Findings: 3 dosed groups plus controls are negative for tumors. An MTD (minimally toxic dose) is achieved. The chemical positive in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	0/15	0/15	0/15

rasH2 mouse: cross of C57BL/6 males with the transgene with BALB/cByJ females

6. 6-month oral study in females; 15 animals per group. Findings: alveolar/ bronchiolar adenomas and carcinomas. Alveolar bronchiolar hyperplasia was diagnosed in 5 additional high dose mice. The chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	1/15	1/15	3/15	9/15
$p < 0.001$, survival adjusted trend test				
Historical control rate is 7/90 (range 0/15 to 2/15)				

7. 6-month oral gavage study in males; 15 animals per group. Finding: thyroid adenomas. The chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	1/15	0/15	1/15	3/15
$p = 0.049$, survival adjusted trend test				
Historical control rate is 5/90 (range 0/15 to 2/15)				

8. 6-month, dosed feed study in males; 15 animals per group. Findings: 3 dosed groups plus controls are negative for tumors. The chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test. An MTD is achieved.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	0/15	0/15	0/15

Hemizygous Tg.AC: on an FVB/N background strain

9. 6-month dermal application study in females; 15 animals per group. Findings: multiple skin papillomas and several carcinomas. Multiple papillomas occurred in 5 mice in Dose Group 4 and in all mice in Dose Group 5. All of the nonneoplastic lesions were graded as minimal to mild. Chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test.

Skin	Dose Group					
	Control	1	2	3	4	5
Squamous cell papilloma	0	0	0	1	11*	15**
Squamous cell carcinoma	0	0	1	0	1	1
Inflammation	0	0	0	3	14**	12**
Hyperkeratosis	0	0	1	7**	14**	13*
Epidermal hyperplasia	0	0	1	4*	15**	15**

* $p < 0.05$, ** $p < 0.001$, survival adjusted test.

10. 6-month skin painting study in males; 15 animals per group. Findings: benign (papilloma and keratoacanthoma) and malignant (squamous cell carcinoma and spindle cell carcinoma) skin tumors (with increased multiplicity at the site of application). Multiplicity of keratoacanthomas, squamous cell carcinomas, and spindle cell carcinomas increased with dose. Inflammation is not observed. The chemical is positive in Salmonella.

Skin	Dose Group			
	Control	Low	Mid	High
Squamous cell papilloma	0	8**	15**	15**
Keratoacanthoma	0	7**	12**	15**
Squamous cell carcinoma	0	3	12**	15**
Spindle cell carcinoma	0	1	7**	15**
Hyperkeratosis	0	12**	15**	15**
Epidermal hyperplasia	1	12**	15**	15**

* $p < 0.05$, ** $p < 0.001$, survival adjusted test.

11. 6-month, skin painting study in males; 15 animals per group. Findings: 3 dosed groups plus controls are negative for tumors. The chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test.

	Controls	Low dose	Mid dose	High dose
Tumor incidence	0/15	0/15	0/15	0/15

Standard B6C3F1 mouse

12. 2-year study with dermal application in females; 50 animals per group. Finding: liver tumors. The chemical is negative in Salmonella and in the acute mouse bone marrow micronucleus test.

Liver	Dose Group			
	Control	Low	Mid	High
Hepatocellular adenoma	9 (18%)	18* (36%)	20* (40%)	33** (66%)
Multiple adenomas	0	3	7*	17**
Heptocellular carcinoma	6	8	4	5
Adenoma or carcinoma	12	23*	24*	34**

*p < 0.05, ** p< 0.01, survival adjusted test.

	Historical Control Incidence
Hepatocellular adenoma	144/954 (16%) range 7 to 28%
Hepatocellular adenoma or carcinoma	203/954 (23%) range 9 to 40%