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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM MAR 24 1982

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

DATE: March 17, 1982

SUBJECT: Carcinogenicity/Oncogenicity Assessment of Oryzalin 'Surflan'
Re: Lilly 2-Year Rat Feeding Study R167 & R177; Permanent Tolerance Action 6F1859; Registration #1471-96 & 1471-112; CASWELL#623A

FROM: Bertram D. Litt, Statistician
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TO: R. Bruce Jaeger, Section Head
Review Section I
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Toxicological review of the subject study identified large numbers of tumor bearing animals. Dr. Kasza, Branch pathologist, advised that statistical analyses be performed to determine the level of significance for the following groups of tumors: skin tumors (Fibroma and/or Fibrosarcoma; Keratoacanthoma and/or squamous cell carcinoma; papilloma; Basal cell and related tumors); Hepatic Adenoma; Mammary gland Fibroma, Adenoma or Adenocarcinoma as separate categories; Thyroid Follicular cell Adenoma and/or Carcinoma; thyroid C-cell Adenoma and/or carcinoma; Malignant Lymphoma; Pituitary Adenoma, Testicular Interstitial Cell Tumors. The toxicologist, Dr. Quaife, has prepared the data for analysis by abstracting and tabulating the tumors reported for each animal by dose and sex group and day and type of death. After noting the small number of apparently tumor-free rats the report sheets for these animals have been rechecked and some of them were found to have pancreatic and/or adrenal tumors and these findings are included in the following analyses of tumors bearing animals.

The initial consideration is the relative survival reported (see Table I.) It should be clear that there is a dose related reduction in survival of rats treated with Oryzalin ($P < .01$) in both sexes. Moreover, it is shown the there is a 20 percent reduction among the high dose (2700 ppm or 135 mg/kg/day) rats. This statistically significant reduction in high dose survival suggests that the maximum tolerated dose has been exceeded and that tumor finding may be biased among the high dosed groups.

Table I. Oryzalin Study 167 & 177 Rats: Survival

Survival of Male Rats

Dose (ppm)	Number of Survivors					Percent Survival			
	0 M	12 M	18 M	21 M	24 M	12 M	18 M	21 M	24 M
0	60	58	52	52	47	96.7	90.0	86.7	78.3
300	60	60	59	53	41	100.0	98.3	88.3	68.3
900	60	59	53	50	36	98.3	88.3	83.3	60.0
2700	60	59	49	43*	34**	98.3	81.7	71.7	53.3

Survival of Female Rats

Dose (ppm)	Number of Survivors					Percent Survival			
	0 M	12 M	18 M	21 M	24 M	12 M	18 M	21 M	24 M
0	60	60	55	49	44	100	90.0	81.7	73.3
300	60	60	58	51	40	100	96.7	85.0	66.7
900	60	60	56	47	37	100	93.3	78.3	61.7
2700	60	59	53	42[B]	31*	98.3	88.3	70.0	51.7

B: One-tail test $P = .1$
*: One-tail test $P < .05$
**: One-tail test $P < .01$

When the total number of tumor bearing animals was examined we found almost all males and the majority of all study rats had at least one tumor:

Dose Group	Tumor Free Proportion of Rats	
	Males	Females
Control	4/60	16/60
Low Dose	0/60	12/60
Mid Dose	1/60	3/60
High Dose	2/60	9/60

When, as suggested by the survival data, one deleted the high dosed group a statistically significant increase in tumor bearing animals is observed to be associated with increased Oryzalin exposure (or dose). At the suggestion of Dr. Kasza, the Tox Branch Pathologist we reexamined the total tumor incidence treating animals with a single tumor diagnosed as Interstitial Cell Tumor in males or a Mammary Tumor in females or a Pituitary Adenoma in either sex as if they were tumor-free, the proportion of tumor bearing rats was:

Dose Group	Males	Females
Control	33/60	25/60
Low-Dose	43/60*	30/60
Mid-Dose	43/60*	39/60*
High-Dose	53/60***	37/60*

(* One-tail Test $P < .05$; ***One-tail Test $P < .001$)

The increased proportion of tumor bearing rats is clear evidence of the need to look more closely at individual tumor types and particularly among the males.

Table II. Oryzalin Study 167 & 177 Rat Thyroid Findings

Thyroid: Follicular Cell Adenoma

Females 167&177	Interim	Terminal	Total
0 ppm	1/12	0/43	1/35
300 ppm	0/20	1/40	1/60
900 ppm	0/23	3/37	3/60
2700 ppm	3/26	6/29	9/55

Male 167&177	Interim	Terminal	Total
0 ppm	-----	------	1/59
300 ppm	-----	------	10/59
900 ppm	-----	------	5/57
2700 ppm	-----	------	6/56

C-Cell Adenoma

Females 167&177	Interim	Terminal	Total
0 ppm	1/12	4/43	5/55
300 ppm	0/20	2/40	2/60
900 ppm	2/23	3/37	5/60
2700 ppm	5/26	0/29	5/55

Males 167&177	Interim	Terminal	Total
0 ppm	----	----	6/59
300 ppm	----	----	8/60
900 ppm	----	----	1/60
2700 ppm	----	----	4/60

Thyroid tumors and more especially Follicular Cell Adenomas were identified by the toxicologist as a target tissue response. However, when the data are displayed as, in table II, we find that the principle response or high tumor rate, is observed among high dose females. This may easily be a spurious finding if the preceeding observations concerning bias in the high dose group and higher sesitivity for tumors among males are accurate.

Accordingly we next examined the proportion of animals with skin tumors of any of the 4 types listed below. The total number of skin tumor bearing animals is displayed in table III. The males are definitely more sensitive with respect to time of appearance of skin tumors although a higher level of statistical significance is seen among mid-dose females relative to controls: ($P = .0016$ for females vs .024 for males.) The sensitivity of the males is demonstrated by the highly significant dose response observed among the animals dying with tumor during the study - i.e. earlier onset; while females do not show an effect until the terminal kill.

When the individual or specific types of skin tumors are examined one at a time we find two tumor types of special interest. The keratoacanthoma and/or squamous cell carcinoma (see table IV) shows an increase in females and in males at the high dose but not significantly at mid or low doses; the basal cell and related adenomas or tricepithelioma group show a highly statistically significant increasing rate at low and mid-doses and a significant effect of the highest dose with the same patterns discussed for total skin tumors.

From these results we conclude that all statistical weight indicates that due to the increase in both sexes and earlier incidence of Basal cell type tumors in males that this tumor be used as the basis for quantitative risk assessment. The data were used as the basis for low-dose risk extrapolation after the dosage levels were adjusted to mg/kg/d by the constant showed in Lehman's tables, ppm $\simeq$ .05 mg/kg/day and adjusted to human exposure level equivalents using the surface area approximation of (human wt $\div$ animal wt)$^{1/3}$ i.e. divide animal dose by $5 \simeq (60000\text{ g} \div 500\text{ g})^{1/3}$. Thus the rat doses of 300 and 900 ppm were adjusted to 3 and 9 mg/kg/day respectively.

Models tested for goodness of fit for low dose extrapolation included:

Multi-Stage Model Males	P > .9
Multi-Stage Model Both Sexes	P > .9
Multi-Hit Model	P < .01
One-Hit Model	P > .05
Weibull with Additive Background	P < .01
Weibull with Independent Background	P < .01
Probit Model	P < .01

These findings plus sister chromatid study showing a potential for mutagenic response are consistent with the conclusion that the One-hit and Multi-stage models are the most logical but that the Multi-stage model provided a better fit to these data. Both of the Multi-stage models lead to approximately the same level of potency as estimated by the 95% Upper Confidence Bound on the slope or dose response as indicated by $Q_1^* = 3.375 \times 10^{-2}$ for the male plus the female data or $Q_1^* = 4.426 \times 10^{-2}$ for male data only. The estimate of potency, Q_1^*, when multiplied by individual exposures will provide an Upper 95% Confidence Bound on the expected risk of human cancer based on the finding of 11/120 basal cell tumors in control rats, 16/120 at 3 mg/kg/day human equivalent in food and 32/120 at 9 mg/kg/day human equivalent in the food of study rats.

Table III: Oryzalin Study 167&177 Rat Skin Tumors

Proportion of Animals with Skin Tumors

Sex	Dose	Interim # (%)	Terminal # (%)	Total # (%)
Males				
	0 ppm	3/13 (23.1)	15/47 (31.9)	18/60 (30.0)
	300 ppm	6/19 (31.6)	15/41 (36.6)	21/60 (35.0)
	900 ppm	15/22 (68.2)	15/36 (41.7)	30/58 (51.7)
	2700 ppm	18/25 (72.0)	25/34 (73.5)	43/59 (72.9)
Females				
	0 ppm	2/16 (12.5)	3/44 (6.8)	5/60 (8.3)
	300 ppm	4/20 (20.0)	6/40 (15.0)	10/60 (16.7)
	900 ppm	4/23 (17.4)	14/37 (37.8)	18/60 (30.0)
	2700 ppm	9/29 (31.0)	21/31 (38.7)	21/60 (35.0)

Table IV. Oryzalin Study 167&177 Rat Skin Tumors

Skin: Keratoacanthoma and/or Squamous Cell Carcinoma

Females 167&177	Interim	Terminal	Total	Statistical Sig.
0 ppm	0/16	1/44	1/60	-----
300 ppm	1/20	0/40	1/60	N.S.
900 ppm	1/23	3/37	4/60	<.05
2700 ppm	3/29	5/31	8/60	<.001

Males 167&177	Interim	Terminal	Total	Statistical Sig.
0 ppm	1/13	4/47	5/60	-----
300 ppm	0/19	3/41	3/60	N.S.
900 ppm	4/24	1/36	5/60	N.S.
2700 ppm	7/25	11/34	18/59	<.0001

Skin: Basal Cell, Preputial, Sebaceous or Zymbals' Gland Adenoma or Tricepithelioma

Females 167&177	Interim	Terminal	Total	Statistical Sig.
0 ppm	0/16	2/44	2/60	----
300 ppm	1/20	2/40	3/60	N.S.
900 ppm	3/23	10/37	13/60	<.001
2700 ppm	4/29	6/31	10/60	<.01

Males 167&177	Interim	Terminal	Total	Statistical Sig.
0 ppm	2/13	7/47	9/60	----
300 ppm	5/19	8/41	13/60	N.S.
900 ppm	9/24	10/36	19/60	<.02
2700 ppm	10/25	7/34	17/59	0.06

File last updated 3/22/02

ACCEPTABLE DAILY INTAKE DATA

Dog	ROEL	S.F.	ADI	DFI
mg/kg	ppm		mg/kg/day	mg/day(60kg)
18.750	750.00	2000	0.0094	0.5625

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	0.100	0.92	0.00138
Cottonseed (oil)(41)	0.050	0.15	0.00011
Avocados(6)	0.050	0.03	0.00002
Citrus Fruits(33)	0.050	3.51	0.00263
Figs(57)	0.050	0.03	0.00002
Kiwi Fruit(204)	0.050	0.03	0.00002
Nuts(101)	0.050	0.10	0.00008
Olives(104)	0.050	0.06	0.00005
Pistachio nuts(210)	0.050	0.03	0.00002
Pome Fruits(120)	0.050	2.79	0.00209
Pomegranates(186)	0.050	0.03	0.00002
Small Fruit,berries(140)	0.050	0.83	0.00062
Stone Fruits(151)	0.050	1.25	0.00094

DFI	TMRC	% ADI
0.5625 mg/day(60kg)	0.0082 mg/day(1.5kg)	1.46

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Unpublished, Tex Approved 82075,9D2219

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Sweet Potatoes(157)	0.50	0.40	0.00030
Peas(117)	0.050?	0.69	0.00052

DFI	TMRC	% ADI
0.5625 mg/day(60kg)	0.0091 mg/day(1.5kg)	1.61

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