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

JUN 12 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 3, 1981

Caswell # 623A

SUBJECT: TB/HED comments on Eli Lilly responses of 3/6/81 and 2/24/81 to the EPA letter of 2/4/81 to Lilly, Oryzalin (Surflan®).

FROM: Mary L. Quaife, Ph.D.
Toxicology Branch, HED (TS-769)

M.L. Quaife 6/4/81
RTS 6/11/81
Mfor WB

TO: Mr. R. Taylor, PM
Registration Division (TS-767)

THROUGH: Mrs. Christine F. Chaisson, Acting Chief
Toxicology Branch, HED

PP No. 6F1859
Reg. Nos. 1471-96 and 112

Eli Lilly and Company
Indianapolis, Indiana
46206

SUMMARY:

(Numbers and letters of major headings, underlined, correspond to those in the EPA letter of 2/4/81 to Petitioner.) PM, please see footnote, below.

1. Two-year rat (chronic) feeding (and oncogenicity) study, 2. a.

A. Petitioner's requested new tables show that time distribution of occurrence of skin tumors is roughly similar for control and test rats.

B. Therefore, we compiled detailed tables of occurrence of certain tumors (and non-neoplastic thyroid lesions) in individual rats, including time of every rat on test.

C. These tables await TB/HED statistical evaluation for significance of results and estimate of "risk."

*** D. Until this is accomplished, TB/HED can make no final conclusions as to oncogenic potential of oryzalin.

Note: For convenience' sake, we have placed asterisks in front of all statements which relate directly to regulatory status of these TOX studies.

E. This memo (pp. 5-10, inclusive) reviews some facets of tumor production by certain pesticide products, which - like oryzalin - are designated antithyroid agents.

Review is based on all Petitioner's cited references of this study; on certain "inhouse" documents, including WHO/FAO proceedings and R-PAR documents; and on results of a specific literature search made for us.

Following are points made, which relate to toxicology of oryzalin:

a. TB/HED agrees (with Petitioner), oryzalin causes thyroid follicular-cell tumors in the rat, probably, by indirect overstimulation of the thyroid gland.

b. Therefore, thyroid tumor "risk" estimates by a so-called one-hit model may be inappropriate.

c. We judge other (than thyroid) tumors rate inclusion when extrapolating oncogenic activity of oryzalin from test animals to man.

d. TB/HED finds (incidence of) certain non-neoplastic thyroid lesions in test rats important for (1) evaluating oryzalin's toxicologic potential in the rat and (2) extrapolating it to man.

e. We are unaware of any determination, experimentally, of the potency of oryzalin to affect thyroid function in the rat.

f. TB/HED finds this an important omission in Petitioner's studies on oryzalin, especially should this study be found to not support a clearcut "no-observed-effect" level (NOEL) with regard to thyroid (histopathologic) structure.

g. TB/HED judges that Petitioner's cited, indirect evidence (Refs. 5-14, inclusive) fails to establish the comparative antithyroid or oncogenic potencies of oryzalin in rat and monkey (or man).

h. Petitioner has not determined either comparative potency for oryzalin, experimentally.

i. TB/HED agrees, in the rat, thyroid tumor development due to oryzalin is probably reversible at an early stage (and before any such tumor appears).

2. Two-year rat (chronic) feeding (and oncogenicity) study, 2., b. and c.

A. TB/HED judges the newly identified impurities in technical oryzalin to be not of consequence in the trace amounts in which they occur.

B. [redacted] (as affirmed by RCB) [redacted] (a carcinogen and mutagen) does not require further "risk" evaluation (in regard to its presence), apparently, according to proposed Agency policy.

C. [redacted] nitrosamine impurity was present in the test oryzalin samples of chronic/oncogenicity and reproduction studies; therefore, its presence in commercial oryzalin products was adequately taken into account in such testing.

D. Content of active ingredient in technical oryzalin varies by a factor [redacted] that degree of variation is, accordingly, judged not of consequence to TB.

*** E. TB/HED finds, specific deficiencies (2.b. and 2.c.) of rat two-year study are resolved.

3. Three-generation rat (reproduction) study, 5.

A. We judge Petitioner's additional evidence as showing that effects on eyes in the rat reproduction study were not caused by oryzalin.

*** B. TB/HED concludes that deficiency 5 of the three-generation rat study is resolved.

C. The study is upgraded to CORE-MINIMUM

*** D. The NOEL is set at 250 ppm.

4. Rat dominant-lethal study, 2.

A. Petitioner's response is judged insufficient to allow upgrading of the study (as found by two other prior TB/HED reviewers).

*** B. TB/HED concludes that the deficiencies (2. and 3.) of the study are not (and cannot be) resolved.

C. Thereforefore, the study remains CORE-SUPPLEMENTARY.

5. Petitioner has promised to run a DNA repair study on oryzalin. TB/HED did not request or approve (and was not asked to approve) this action

6. Final conclusion, No. 4 (p. 4 of 2/4/81 EPA letter to Lilly).

A. Petitioner has concluded that, "A general metabolism study on oryzalin is needed," (while stating that three previous metabolism studies have been submitted) (cf. p. 3, 3/5/81 letter, Lilly - R. Taylor).

*** B. We agree with Petitioner's proposal to do a new general metabolism study (on oryzalin technical).

*** C. Submission of a protocol for the study, for TB/HED comment, is requested.

TB/HED COMMENTS OF PETITIONER'S REPLIES:

Two-year feeding study, 2., a.

As we have noted previously, Petitioner found oryzalin to be a rat oncogen, having caused thyroid follicular cell and mammary tumors, for example (memo of 1/7/81, this PP, p. 6). Although Petitioner noted increased skin tumor incidence in treated rats, he did not analyze this for statistical significance.

Per suggestion of Dr. L. Kasza, TB/HED Pathologist, we asked Petitioner for numbers of skin and thyroid tumors at 15, 18, 20, 22, and 24 months on test (corresponding to survivor figures in original report). Dr. Kasza pointed out that lesser survival of test rats (which is dose-related) might affect tumor occurrence.

Inspection of Petitioner's submitted tables indicates that time-distribution of skin tumors is roughly similar for control and test rats. Also, groups of skin tumors which are biologically similar show dose-related increase in incidence, frequently, in males and/or females.

Tumors of skin were grouped as suggested by Dr. Kasza. Recently, the International Agency for Research on Cancer (IARC) stated that....The experienced pathologist uses his knowledge of histogenesis and pathogenesis....in grouping lesions for statistical analysis....In general, it is accepted practice to group together tumours of the same general histological type that arise in the same type of tissue.... [Long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2, Lyon, France, 1980, p. 69.]

Although oryzalin is a rat oncogen, only analysis of appropriate data can provide basis for judgment as to the degree and biological importance of its oncogenicity in the rat - and to the degree realistically possible - to the human being.

EPA, including Toxicology Branch, Hazard Evaluation Division, is continually trying to improve its mode of statistical and "risk" analysis of oncogenicity data. Computer-based analyses are now - and since only recently - provided by Mr. Bert Litt, TB/HED Statistician, according to priorities set at Division level or higher.

We gave Mr. Litt (4/28/81) detailed tables of incidence of various lesions in individual rats, including time of each on test. Categories included were chosen with the kind assistance of Dr. Kasza. They are: a. Fibroma and/or fibrosarcoma, skin; b. Keratoacanthoma and/or squamous cell carcinoma, skin; c. Papilloma, skin; d. Basal cell adenoma, preputial gland adenoma, sebacious gland adenoma, Zymbal's gland adenoma, and/or tricoepithelioma, skin; e. Hepatic adenoma; f. Nodular hyperplasia, liver; g. Fibroadenoma, mammary gland; h. Adenoma, mammary gland; i. Adenocarcinoma, mammary gland; j. Follicular cell adenoma and/or carcinoma, thyroid gland; k. C-cell adenoma and/or carcinoma, thyroid; l. Cystic follicles in thyroid (non-tumor lesion described, p. 24 of original report, as "markedly enlarged follicles that closely resembled normal follicles except for their increased size and flattened epithelium "); m. Follicular hyperplasia, focal, thyroid gland; Malignant lymphoma, hemic-lymphatic system; Adenoma, pituitary gland; and Interstitial cell tumor tumor, testicle. Further comments on general oncogenetic implications of oryzalin are deferred pending receipt of Mr. Litt's findings.

A somewhat separate issue (cf. Petitioner's discussion, pp. 25-6, Acc. No. 099517) requires evaluation and HED response.

Petitioner seems to imply that the thyroid follicular tumors produced in oryzalin-fed rats do not have consequence for human beings because of (1) a "known mechanism" operating, (2) which is reversible before tumor formation, and (3) to which man is either unsusceptible or less susceptible than the rat.

We read all of Petitioner's citations which bear on the implied claim (Refs. 4-14, inc., copies of which were provided us) and a considerable number of other pertinent references at hand (Nos. 15-25, inc., and No. 26).

(1) Rat thyroid tumors may result from indirect effect on the thyroid, via the pituitary gland. So-called "antithyroid" substances, e.g., thioamides; aniline derivatives - especially, para-substituted ones; and polyhydric phenols, inhibit formation of the thyroid hormone, thyroxin. To compensate, the pituitary gland pours out more "thyroid-stimulating hormone" (TSH; thyrotropin), which causes the thyroid gland to make more thyroxin. The overstimulated thyroid may show hyperplasia and, on prolonged exposure, may develop tumors, e.g., follicular adenomas and/or carcinomas (8, 10, 11, 12, 13, 14, 15, 16, and 17).

We agree with Petitioner that this may be the mechanism by which the rat thyroid follicular tumors were produced in the present study by oryzalin, which is a para-substituted aniline derivative (as well as being a sulfonamide).

[It might explain the production of thyroid tumors (adenomas and/or carcinomas) produced in rats by ethylenethiourea (a breakdown product of certain bis-dithiocarbamate pesticides as zineb and maneb) (15, 16) and in mice by 3-amino-1,2,4-triazole (aminotriazole; amitrole) (19). Both are well-known antithyroid substances (11, 17).

[In the rat, such process seems to progress from hyperplasia to adenoma to carcinoma, depending on degree and length of exposure to the antithyroid. Rats fed ethylenethiourea (ETU) for two years showed some hyperplasia at 5 and 25 ppm, but not tumors; chiefly, adenomas at 125 ppm; and, chiefly, carcinomas at 250 and 500 pppm (15, 16).

[Somewhat parallel effects on thyroid function were shown by rats fed ETU in the diet (0, 1, 5, 25, 125, or 625 ppm) for 30 or 60 or 90 days. At 125 and/or 625 ppm, rats had lower serum thyroxin and triiodothyronine, increased serum TSH, and decreased uptake of I^{125}. At 60 days on 25 ppm, rats had increased serum thyroxin. [At 625 ppm, clinical evidence of poisoning occurred, and red thyroids and adenoma were seen. At 125 ppm, there were red thyroids and thyroid hyperplasia. At both levels, thyroid-weight to body-weight ratios were significantly increased. There were no effects at 25 ppm, except for thyroid hyperplasia, seen only at 60 days.] There were no effects at 5 ppm (20).]

Petitioner has not determined levels of oryzalin, specifically, which affect (and those which do not affect) thyroid function in the rat.

Determining which levels of oryzalin did or did not cause significant increase in adverse microscopic findings or tumors in thyroids of rats fed it for two years awaits Mr. Litt's statistical evaluation.

A factor in making that judgment might be two instances of recorded low occurrence of some spontaneous thyroid lesions in the Fischer 344 rat, which was used in Petitioner's present study:

Among 144 aged, male Fischer 344 rats, incidence of thyroid spontaneous lesions consisted of: 0.7%, thyroid adenoma, and 0.7%, diffuse thyroid hypertrophy, and 2.1%, medullary carcinoma of thyroid (4).

"....Follicular cell neoplasms are uncommon in untreated Fischer 344 rats..., 1.1% or less each....in male and female Fischer 344 rats (1,800 per sex) in the (National Cancer Institute) Carcinogenesis Testing Program.... (therefore, any)....follicular cell tumors found in (test) rats assume greater importance," (7).

(2) Referring to the rat, Petitioner finds that, "The thyroid hyperplasia induced by sulfonamides has been shown to be reversible," (13).

True, we believe, but thyroid tumors do not regress. E.g., "Thyroid hyperplasia was not noticeably reversible in those rats in each group (at 5 to 500 ppm) that were changed to control diet after 66 weeks on ETU diets," (16).

(3) According to Petitioner, a. Certain sulfonamides (para-aniline derivatives) which are antithyroid in rats are not clinically goitrogenic in man (9, 10, and 11) or in other animals (no reference cited), and, b. sulfamethoxazole (a para-aniline derivative) caused thyroid hyperplasia and neoplasia in rats but not in monkeys (12).

We note, a. It is true, in doses used clinically, sulfonamides are said to not be detectably antithyroid in man; however, the antituberculous drug, para-aminosalicylic acid (PAS), which like oryzalin is a para-substituted aniline, when given in doses of many grams daily for months, has caused hypothyroidism and goiter in man (9, 11), and antithyroid effects occurred in dog and mouse (and rat) in response to sulfonamides and thioureas (10), and, b. the sulfamethoxazole was given for a relatively much smaller fraction of the monkey's lifespan than the rat's (52 and 60 weeks, respectively) (12), a fact which, in itself, might preclude appearance of neoplasia in the monkey.

[Comparative potencies of the antithyroid compound, ETU, fed to monkeys for five to six months and to rats for three months, are indicated in the table:

PROPRIETARY: NO-OBSERVED-EFFECT DOSE LEVELS FOR ETU IN THE DIET BASED ON THYROID AND PITUITARY PARAMETERS, ppm.

Study	T-3(↓)[a]	T-4(↓)	^{125}I Uptake	Thyroid Weights(↑)	Thyroid Hyperplasia	Pituitary	TSH(↑)
Phase I (Rhesus)	250	50	10(↑)	50	<50	50	50
Phase II (Rhesus)	50(M) 150(F)	50	<50(↑)	50 <50(F)	<50	50	50

(table cont'd., next page)

(table continued from previous page)

Study	T-3(↓)[a]	T-4(↓)	^{125}I Uptake	Thyroid Weights(↑)	Thyroid Hyperplasia	Pituitary	TSH(↑)
Rats	125	25	125(↓)	25	5(60 d) 25(30 & 90d)	Not examined	25

(a) The arrows represent the trend of the parameter as higher doses of ETU are given.

Note. Data come from references 20 (rat) and 21 (monkey) - this table is Table 18 (21, p. 52).

[Quoting from p. 51 of the monkey ETU study (21), "The question as to whether the rat and rhesus monkey are similarly affected by the antithyroid agent, ETU, (has) not (been) answered in terms of its carcinogenic activity as judged by histopathological examination of thyroid tissue....Nor has (a no-effect level) been established for primates. Therefore, the relative sensitivity to the carcinogenic action of ETU in the two species is unknown.

["Similar sensitivities are observed in the two species to ETU for T-3, T-4, and TSH and thyroid weights. T-4 and TSH are both sensitive biochemical indicators of ETU toxicity, and could be monitored in intact animals. Thyroid hyperplasia occurs at dose levels below the no-effect levels for TSH and T-4 alterations. However, the hormonal alterations may still be accurate predictors of a neoplastic condition of the thyroid in experimental animals and perhaps human (beings)."]

We do not imply that relative antithyroid potencies of oryzalin in rat and monkey are similar (or dissimilar). We point out, however, that Petitioner has failed to determine these for oryzalin, specifically, with regard to either thyroid function or thyroid oncogenic activity.

In sum, regarding Petitioner's implied claim (Para. 2, p. 3 of this memo), we agree that oryzalin probably shows antithyroid activity in the rat by way of the proposed mechanism and that it is probably reversible at some early (but as yet undetermined) stage. However, in no way, do we find Petitioner's cited, mostly indirect evidence (Refs. 5-14) sufficient to establish the relative antithyroid or oncogenic potencies of oryzalin in rat and monkey (or man).

[The following brief discussion concerns choice of procedures for extrapolating thyroid oncogenic activity of an antithyroid substance, ETU, from rat to man.

ETU-induced rat thyroid neoplasms are said to result from excessive pharmacological stimulation, i.e., they occur because of excessive endocrine-organ stimulation and not because of the reaction of one molecule of carcinogen with one cell to initiate neoplasia (16).

The Midwest Research Institute (MRI) agrees (22) and adds that the "one hit model" is irrelevant to these thyroid tumors. As reasons, MRI notes (given in abbreviated form) (22, p. IV-14):

a. The thyroid gland in man has a large store of hormone and slow rate of nomral turnover, and functioning of the rat thyroid is not comparable to that of man.

b. In the rat thyroid, there is the "Wolff-Chaikoff effect," a phenomenon which is qualitatively different in the rat and man.

c. A sex difference in rat response (in thyroid tumor production) to ETU is shown (23). This indicates that such a tumor could be related to the rodent endocrine system, requiring consideration of its many variables before human extrapolation of the data is valid.

Thus, use of the one-hit model for human risk assessment in the ETU-induced thyroid tumor (based on rat data) is a "poor choice;" even though other (linear or one-hit?) mathematical model of risk determination may be adopted for most regulatory determinations (of liver tumor risk, for example) (MRI, 22).]

[We note, MRI (22) holds that, since thyroid effects (hyperplasia) are seen at lower doses than the tumors (in the rat, caused by ETU), thyroid toxicity is sufficiently important to be considered, itself, as a trigger area for RPAR.]

We believe that consideration of other possible target organs than the thyroid gland - below - is very germane to assessing the rat oncogenic potential of oryzalin.

Liver.

Antithyroid substances have caused liver tumors in mice, i.e., ETU and aminotriazole (19).

ETU caused biochemical effects on hamster liver, including increased hepatic glutamic-pyruvic transaminase and alkaline phosphatase (Gak (23), as quoted by MRI (22), p. II-23).

Although liver tumors (adenomas) occurred in approximately one per cent of rats (at FDA) in the authors' experience, yet the antithyroid compound, "thiourea, administered orally to (those) rats for a prolonged period of time, induce(d) liver tumors, without liver cirrhosis, in a large percentage of cases at concentrations which may be below those producing hyperplasia of the thyroid gland," (18).

Liver adenomas and hyperplastic nodules are not common spontaneous lesions in most rat strains (personal communication from Dr. L. Kasza, EPA Pathologist).

Following examples are taken from the NCI study on 2,4-diaminoanisole sulfate, a para-substituted aniline derivative, in the Fischer 344 rat (and mouse).

Skin and related glands (and thyroid).

Dietary administration of a para-substituted aniline derivative, 2,4-diaminoanisole sulfate, to the Fischer 344 rat increased the incidences of malignant tumors of the skin and its glands and malignant thyroid tumors in each sex (24).

The former include(malignant) squamous-cell carcinomas, basal-cell carcinomas, or sebaceous adenocarcinomas of the skin and associated glands (Zymbal's gland/ear canal and preputial/clitoral gland).

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The latter consist of various malignant follicular-cell, thyroid tumors (adenocarcinoma NOS, papillary adenocarcinoma, papillary cystadenocarcinoma, or follicular-cell carcinoma).

Male test rats had increased incidence of either a C-cell adenoma or a C-cell carcinoma, as well.

The incidence of integumentary neoplasms was increased, particularly in males, and the incidence of thyroid neoplasms was increased in rats of both sexes.

Mammary gland.

The response of the mammary gland to 2,4-diaminoanisole sulfate appears equivocal; since there was wide variation in the numbers of mammary tumors found in low-dose control females compared with high-dose control females.

Although the incidence of mammary fibroadenomas in low-dose females (35%) was significantly ($p = 0.011$) greater than in low-dose controls (10%), yet that for high-dose females (8%) was inversely related to that for high-dose controls (38%). Historical control incidence of spontaneous mammary fibroadenomas in untreated female rats, numbering 585, of this strain, Fischer 344, is 18%.

[We note that Handler et al. (25, p. 948) find that, "The status of thyroid functioning in man markedly influences the rates of metabolism" of estrogens, e.g., with respect to hydroxylation and conversion of hydroxy to keto groups. We do not know whether such a relation obtains in the rat.]

Other organs or tissues.

Incidence of testicular interstitial cell tumors in males was high (80 to 98%) and not different in control and test groups (24).

Incidence of pituitary tumors, adenomas or carcinomas, in test or control rats of either sex did not differ (24).

Incidence of malignant lymphoma was low in male and female test rats and not higher than in respective controls (24).

Other species.

In this study, dietary administration of 2,4-diaminoanisole sulfate, also, induced thyroid tumors in B6C3F1 mice of each sex (24). They were follicular adenomas in males; in females (45 in number) there were six rats with follicular-cell adenomas and two with follicular-cell carcinomas.

These female mice (24) showed possibly increased incidence of malignant lymphoma; males did not.

Discussion.

This study (24), then, seems to give a coherent picture of tumors produced in Fischer 344 rats (the strain used in the oryzalin oncogenicity study) by dietary administration of a para-substituted aniline derivative, 2,4-diaminoanisole sulfate (a chemical class to which oryzalin belongs), which is, demonstrably, an antithyroid substance.

Note that thyroid follicular tumors and tumors of skin and related glands (Zymbal's/ear canal, preputial/clitoral) were significantly increased in rats of both sexes and were malignant.

Without prejudicing evaluation of the oryzalin study (in the Fischer 344 rat), we note that numerical increases in thyroid follicular tumors and tumors of skin and related glands occurred in test rats. There were, also, dose-related increases in benign mammary fibroadenomas in females and some neoplastic lesions of liver in males at the high dose (only).

We suggest that tumors of any organ or tissue found in oryzalin-treated rats (which exceed in incidence that in the controls) are worthy of consideration in extrapolating oryzalin's oncogenic activity from rat to man.

Further, we suggest extrapolating the non-neoplastic, antithyroid activity of oryzalin from rat to man as a factor in making safety judgments of its use in agriculture or occurrence in the human diet.

To date (as noted), insofar as we are aware, Petitioner has (a) provided neither determination of activity of oryzalin on thyroid function in rat or monkey, yet (b) seemed to imply that man will be relatively insensitive to such effect.

Petitioner has cited lack of hyperplasia or neoplasia of the thyroid of monkeys - in contrast to presence of these in rats - fed sulfamethoxazole (a sulfonamide as oryzalin is) (12) [implying thereby that man is either less sensitive, or insensitive, to antithyroid effects of sulfonamides than the rat]. These are structural effects on the thyroid gland.

Therefore, it is of great interest to note that this same compound (sulfamethoxazole), when given to human, healthy adults for only 10 days, "Lowered serum T-3, T-4, and free T-4 indexes in both sexes....Thus, 10-day periods of drug administration do not cause hypothyroidism, but may reduce conversion of iodine to the organic form," (26).* These are functional effects on the human thyroid gland.

Conclusion:

To this reviewer, the desirable toxicologic characterization of oryzalin, for the purpose of extrapolating safety of proposed uses(s) to man, remains incomplete without determining its potency in affecting function of the thyroid gland - at least, in the rat and, preferably, in the monkey, too, in comparative studies.

This seems especially urgent, in case a clear cut "no-effect level" is found not to have been established in this two-year feeding study in the rat, with respect to adverse effects of oryzalin on thyroid gland structure.

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* To man, sulfamethoxazole was given in 5 to 1 combination with the drug, trimethoprim (26). To monkeys and rats, sulfamethoxazole was given either alone, or among various combinations, 5 to 1 with trimethoprim; antithyroid effects, when manifested, were unaffected by presence of trimethoprim (12) and, thus, must be ascribed only to the sulfamethoxazole. [Doses of sulfamethoxazole given are: To man, 13 mg/kg BW/day (if the adult weighed 60 kg), for 10 days (26). To rat, 25 to 600 mg/kg BW/day, for 60 weeks; to monkey, 50 to 300 mg/kg BW/day for 52 weeks (12).]

We thank Mr. R. Ceder of OPP User Service Center for locating (5/29/81) Ref. 26 for us.

Two-year Feeding Study, 2., b. and c.

In our memo of 1/7/81, this PP, we noted (under Summary) apparent discrepancies in composition of lots of test chemical (oryzalin) used in various toxicologic studies, including reproduction and chronic/oncogenic studies.

So-called Lots X28607 and 9SY47 were variously expressed as being 96.5 and 96.0% pure; 97.4 and 98.9 mole %, respectively, and Lot X28607 was also given as 99.0% pure.

In addition [redacted] were found present on analysis of oryzalin used in this 2-year feeding/oncogenicity study. We asked for their identity.

We wanted information as to whether the oryzalin which was tested in reproduction and chronic feeding/oncogenic studies is entirely typical of that produced commercially for uses in connection with this PP.

Because one impurity is acknowledged by Petitioner to be mutagenic in Ames-type testing (cf. our 1/23/81 memo, this PP, Summary, point 5) and because of the acknowledged presence in technical oryzalin [redacted] a known carcinogen and mutagen (personal communication of Dr. I. Mauer, TB/HED, 5/29/81), the question is important.

In reply of 2/10/81, Petitioner notes that, "Our chemists advise us using three different analytical methods on the same lot of material over a three-year period, one could expect [redacted] in assay results." Chemical identity of the impurities is provided.

In reply of 3/5/81, it is stated that results were determined by both [redacted] which is specific for oryzalin.

[redacted] Data sheets on each of the [redacted] are attached.

TB judges [redacted] impurities not of consequence in trace amounts.

Since RCB (memo of M. Nelson, 9/7/78, PP 8E2075) finds less [redacted] be present in 75% W Surflan (oryzalin tech., also) and based on EPA's proposed choice of 1 ppm as a practical limit of detection for analytical methods for nitrosamine contaminants in pesticides, as noted in the Federal Register, V. 45, No. 124, p. 42856, 6/25/80, concern as to presence of this impurity seems to be alleviated in accord with Agency policy.

Since the oryzalin used in diets of experimental animals in oncogenic and reproduction studies on it was found by chemical analysis to not have more than [redacted] then that test material corresponds to commercially marketed oryzalin (Surflan 75W, e.g) with respect to content [redacted] (cf. TB memos, this PP, of 1/7/81, p. 2, and 1/23/81, p. 5).

The mutagenic intermediate, [redacted] (TB memo of 1/23/81, this PP). [redacted]

The Nelson memo (of 9/7/78, PP 8E2075) notes, also, that purity of technical grade oryzalin may vary, typically [redacted] Therefore, we defer to RCB that this degree of variation is acceptable; since we regard known impurities acceptable, as noted in preceding paragraphs.

Conclusion: Our questions as to apparent discrepancies in composition of lots of technical oryzalin used in TOX studies are answered satisfactorily and our concern is satisfied. This "deficiency" is resolved.

Three-generation rat reproduction study, 5.

Because of the fact that oryzalin is a dinitro compound (and, thus, theoretically, possibly related to known cataract-causing chemicals), we asked for details of adverse eye effects noted in course of the rat reproduction study.

Petitioner has provided the information asked for.

Inspection of these tables provides assurance that the effects found were not related to exposure to the test chemical, oryzalin. Petitioner says (in 3/2/81 response), "The majority of the eye conditions noted in the multi-generation study were considered to be infectious in origin and were of short duration. The infection was not considered related to oryzalin treatment," and, "....findings at termination showed no evidence that the conditions were either dose or treatment-related....if result of in utero exposure, F_2 generation rats would have been similarly affected....(Instead) in the F_2 generation, the only eye opacity occurred in the control group."

Conclusion: Petitioner's response relieves the (point 5) deficiency with respect to the reproduction study. We now rate it as CORE-MINIMUM. Conservatively, we judge the NOEL to be 250 ppm. (There was borderline effect on pre- and post-weanling growth of rats in the 750-ppm group.)

Rat dominant-lethal study, points 1, 2, and 3.

We stated that this study is supplementary and cannot be upgraded to CORE (minimum or guideline).

Petitioner's defense of the conduct of the study is judged inadequate to change its status. In this view of it, we are joined by prior TB/HED reviewers, Dr. L. Anderson And Dr. M. Adrian Gross.

Conclusion:

Petitioner's response to points 1, 2, and 3 on the rat dominant-lethal study is judgedinsufficient to allow upgrading of the study to acceptable status. The dominant-lethal study (rat) on oryzalin remains CORE-SUPPLEMENTARY.

We note that Petitioner promises to run a DNA Repair Study, starting in mid-April and ending (final report to EPA) by June 15, 1981. [TB/HED did not request this study, and our opinion of the worth of carrying it out was not sought by Petitioner.]

Final conclusion, No. 4, p. 4, of the 2/4/81 EPA ltr. to Eli Lilly.

Petitioner concludes that, "A general metablism study on oryzalin is needed," (bottom of p. 3, 3/5/81 ltr., Lilly - R. Taylor), while stating that three previous metabolism studies have been submitted.

We are agreeable with Petitioner's intent to do a new general metabolism study (in accord with proposed guideline requirements, F. R., 8/22/75). We ask Petitioner to send TB/HED a proposed protocol before the study is done.

REFERENCES

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