10-21-85

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Paraquat: Additional Data for the 3-Generation Rat Reproduction Study (No. CTL/P/719; December 22, 1982; Accession Numbers 249911 and 249912) and the Rat Chronic Feeding/Oncogenic Study (No. 82/ILY217/328; October 27, 1983; Accession Numbers 252372-252384).

Tox. Chem. 634
Project No. 413

10/17

FROM: Krystyna K. Locke, Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Krystyna K. Locke

TO: Robert Taylor, Product Manager 025
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 10/21/85

and

Theodore Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

In September 1984 and in August 1985, Toxicology Branch/Hazard Evaluation Division requested additional data for the 3-generation rat reproduction study and the rat chronic feeding/oncogenic study, respectively, in order to finalize the evaluations of these studies. The current submission (Record No. 158397) includes the following data:

1. "Chevron Response to EPA Comments on the Rat Reproduction Study." Volume II; Accession No. 259284.

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2. "Paraquat: Three-Generation Reproduction Study in Rats - Individual Animal Data." Parts I and II; Volume I; Accession Nos. 259285,.259297 and 259298.

3. "Chevron Response to EPA Comments on the Rat Chronic/Oncogenicity Study." Volume III; Accession No. 259299.

Data concerned with the reproduction study were examined and found satisfactory. (Please see ADDENDUM TO THE REVIEW OF A 3-GENERATION RAT REPRODUCTION WITH PARAQUAT; attached). Data submitted for the rat chronic feeding/oncogenic study were also satisfactory.

Regarding the rat chronic/oncogenicity study, only a listing of the numbers of organs/tissues examined in each group was submitted. These data were requested in point 1 of the memorandum dated August 15, 1985 (attached). Data requested in points 2 and 3 of the same memorandum have not yet been submitted.

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ADDENDUM TO THE REVIEW OF A 3-GENERATION RAT REPRODUCTION STUDY WITH PARAQUAT

Tox. Chem. No. 634
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In September 1984, Toxicology Branch/HED completed an evaluation of a reproduction study entitled "Paraquat: Multigeneration Reproduction Study in Rats--Three Generations" Report No. CTL/P/719; December 22, 1982. EPA Accession Nos.: 24991 and 249912; Record No. 16071. The NOELs and Core Classification of that study were as follows:

Provisional reproduction NOEL: 150 ppm (highest tested)
Reproductive LEL effects: Not determined.

Provisional systemic NOEL: 25 ppm
Provisional systemic LEL: 75 ppm (alveolar histiocytosis in male and female parents).

Core Classification: Supplementary

The following comments were also made in that review (p. 31):

"Toxicology Branch accepted the NOELs as provisional because of absence of individual data and because of deficiencies and/or ambiguities which were detailed in the review. The provisional NOELs and core classification will be updated upon the receipt and evaluation of the following data:

"1. Summary table showing number of males mated and siring live young; number of females mated, killed or died, nonpregnant and those rearing young to weaning; and number of females with total resorption and total litter loss. The data should be separated for each level and generation.

"2. Table(s) showing number of offsprings, stillbirths and live births for each female.

"3. Distribution of sex between litters.

"4. Individual body weight or body weight gain data showing adjustments for missing values.

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"5. Data showing when, in which test group(s), and for how many animals adjustments were made in the food consumption data.

"6. Gross necropsy findings for adult rats (and their ID numbers) and for the offsprings.

"7. Clarification of data by supplying footnotes and/or explanations. Details appear in the review."

The current submission (Record No. 158397) contains the requested data. It includes the following documents:

1. "Chevron Response to EPA Comments on the Rat Reproduction Study." Volume II; Accession No. 259284.

2. "Paraquat: Three-Generation Reproduction Study in Rats - Individual Animal Data." Parts I and II; Volume I; Accession Nos. 259285, 259297, and 259298.

These data were examined and found satisfactory. Therefore, the above NOELs are no longer provisional and the Core Classification is now changed to that of Guideline.

10/17/85

Raymona R. Loche

Brad 10/21/85

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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Request for Additional Information from the Registrant (Chevron Chemical Company) with Respect to the Following Study: Paraquat: Combined Toxicity and Carcinogenicity Study in Rats. Report No. 82/ILY217/328; Life Science Research, Stock, England; October 27, 1983.

Tox Chem. # 634

FROM: Edwin R. Budd, Section Head
Section 2, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 8/16/85

TO: Robert Taylor, Product Manager #25
Registration Division (TS-767)

THRU: Theodore M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

In order to complete the Toxicology Branch review of the subject study, additional information described below under items 1, 2 and 3 is absolutely essential. Please request this information from the registrant (Chevron Chemical Company) immediately. This information is urgently needed as soon as possible in order to meet critical Agency time commitments on this chemical.

In order to avoid possible misunderstandings regarding technical specifics of this request, it is strongly recommended that a copy of this memorandum, in its entirety, be sent to the registrant.

1. With respect to the reporting of histopathological findings, a listing of the total numbers of organs/tissues actually examined, on an animal by animal basis, for each organ/tissue with individual listings for each dosage level group and sex. This listing should be comprehensive, include all animals in the study and clearly indicate for each organ/tissue, how many animals in each group were actually histopathologically examined. The data previously presented, with the exception of eyes, only lists numbers of animals in each group. The requested information is absolutely essential for proper interpretation of study results.

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Due to severe time constraints, the above information is requested to be submitted immediately for the specific organs/tissues listed below. The remainder of the information, for all other organs/tissues, should be submitted as soon as possible thereafter.

For All Animals In All Groups

Lungs
Adrenal gland
Pituitary gland
Thyroid gland
Skin and subcutis
"Head region" (including skin, middle ear, "head tissue" hard palate and any other part in which squamous cell carcinomas were observed)

NOTE: This information (item 1) was previously requested to be submitted to the Agency in a memorandum, dated March 8, 1985, from Krystyna K. Locke (Toxicology Branch) to Robert Taylor (PM #25) and subsequently in a letter, dated April 25, 1985, from Robert J. Taylor (EPA) to L. R. Stelzer (Chevron). As of this date, no response has been received from Chevron.

2. For all animals identified in the study as having skin tumors of epithelial origin (including papilloma, squamous papilloma and squamous carcinoma) and all animals identified as having squamous cell carcinomas in the head region (including skin, middle ear, "head tissue" and hard palate), an individual listing for each animal, including identification number, describing the specific type and location of all skin tumors of epithelial origin (including those described above). This information should be submitted immediately.

3. Historical control data for neoplastic lesions for the strain of rat used in this study. Data for animals from the same supplier and which were studied in the same laboratory as this study should be submitted if feasible. The submitted data should cover consecutive long-term studies in this laboratory for at least the past 5 years and earlier if possible. Pertinent data for each individual study should be submitted, i.e., results from different studies should not be pooled and presented in only that form. For each individual study, the following information should be included.

a. Strain and source of experimental animals.

b. Laboratory performing the study.

c. Date of initiation of study.

d. Duration of study.

e. Number of male and female animals in the control groups.

f. A listing of types, locations and incidences of all neoplastic lesions noted during histopathological examination for the male and female groups separately.

g. If available, for neoplastic lesions in each organ/tissue, the numbers of animals in each group that were actually histopathologically examined.

Due to severe time constraints, the above information is requested to be submitted immediately for the specific neoplastic lesions listed below. The remainder of the information, for all other neoplastic lesions, should be submitted as soon as possible thereafter.

Lungs	-	Bronchio-alveolar adenoma/carcinoma
Adrenal gland	-	Benign/malignant pheochromocytoma
Pituitary gland	-	Adenoma/carcinoma
Thyroid gland	-	Parafollicular adenoma/carcinoma
	-	Follicular adenoma/carcinoma
Skin and subcutis	-	Fibroma, fibrosarcoma, mesenchymal fibrosarcoma
	-	Papilloma, squamous papilloma, squamous carcinoma
	-	Lipoma, basal cell tumor, unidentified carcinoma
"Head region"		(Including skin, middle ear, "head tissue" and hard palate)
	-	Squamous cell carcinoma