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

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SEP 18 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Paraquat

FROM: Esther Rinde, Ph.D. E. Rinde 8/26/86
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

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

The Toxicology Branch Peer Review Committee met on July 9, 1986 to discuss and evaluate the weight-of-the-evidence on Paraquat, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber	Theodore M. Farber
William L. Burnam	
Reto Engler	
Louis Kasza	
Bertram Litt	
Donald Barnes	
Diane Beal	
Robert Beliles	
Judith Hauswirth	
Esther Rinde	Esther Rinde

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2. Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Krystyna Locke (Reviewer) Krystyna Locke

Edwin Budd (Section Head) Edwin Budd

3. Peer review members in absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Stephen Johnson

Anne Barton

John A. Quest John A. Quest

B. Material Reviewed:

The material available for Committee review and cited in this report are:

Document 1. Evaluation of Combined Toxicity and Carcinogenicity Study in Rats. Life Science Research (LSR) (Stock, England. Oct. 27, 1983) EPA Regis. #239-2460. Report # 82/ILY217/328. K. Locke memo 10/30/85.

Document 2. Evaluation of Additional Requested data for Combined Toxicity and Carcinogenicity Study in Rats - LSR (Stock, England. Oct.27,1983) Access.#: 25372-252384. K. Locke memo 6/9/86.

Document 3. Evaluation of a Rat Chronic Feeding/Oncogenic Study: Histopathology of the Lung. Record #169741. K. Locke memo 6/24/86.

Document 4. Evaluation of Mouse Oncogenic Study. Report # CTL/P/556 (6/22/81). EPA Accession #246504. K. Locke memo 2/9/83.

Document 5. Evaluation of a 1-year Feeding Study in Dogs. Imperial Chemical Industries, England. April 20, 1983. Report #CTL/P/734. K. Locke memo 7/22/85.

Document 6. Mutagenic Profile of Paraquat (from Registration Std., Dec.20, 1985.)

Document 7. "One-Liners" " "

C. Background Information:

Paraquat is a non-selective herbicide and desiccant. Two products are most frequently associated with the term "paraquat": 1,1'-dimethyl-4,4'-bipyridinium dichloride ($C_{12}H_{14}N_2Cl_2$; mol.wt. 257.2) or 1,1-dimethyl-4,4-bipyridinium dimethyl sulfate ($C_{12}H_{14}N_2$ $(CH_3SO_4)_2$; mol.wt. 408.5). The dissociated paraquat ion is the active moiety which determines the product's toxicity and herbicidal properties (salts readily dissociate). Paraquat dichloride is the salt most commonly used as a herbicide.

Paraquat, discovered in 1882, has been used as an oxidation-reduction indicator ("methyl viologen") since 1932. Imperial Chemical Industries Ltd. produced the first commercial paraquat formulation (registered) for agricultural use (England, 1962 and U.S.A., 1964).

In the U.S.A., paraquat is a restricted use pesticide and is used as a weed killer, harvest aid chemical (desiccant and defoliant) and a plant regulator in pine trees to increase resin content in the treatment area. In 1984, about 4.2 million pounds of paraquat (a.i.) were utilized in the U.S.A., mostly (95%) for agricultural use.

D. Evaluation of Oncogenicity Evidence for Paraquat:

1. Rat chronic feeding study, Life Science Research - Report No. 82/ILY217/328, Oct.27,1983. [Documents A, B and C]

Paraquat (cation) was fed in the diet to 70 male and 70 female Fisher 344 rats at concentrations of 0, 25, 75, and 150 ppm for 113-117 weeks (males) and 122-124 weeks (females).

Pulmonary Lesions

The interpretation of lung lesions in the rat was difficult, ultimately involving 5 pathologists. Drs. J.P. Finn (LSR), J. Ishmael (ICI-sponsor), and W.M. Busey (EPL) examined a complete set of lung slides for all animals in the study.

The original report* on the study contains data obtained by Dr. Finn, who was Director of Pathology when that laboratory conducted the study. According to his findings, there was a dose-related increase in the incidence of pulmonary neoplasms (adenomas and carcinomas, especially adenomas) in the male and female rats.

Dr. Ishmael, who subsequently examined the same slides, found that paraquat was not oncogenic in the lungs of rats. A third opinion was then provided by Dr. Busey, who also examined the same set of slides. According to his assessment of the rat lung tissue, the incidence of adenomas and carcinomas did not show a relationship to treatment with paraquat.

A summary of the findings by the above 3 pathologists is given in Table 1 [Document 3].

The Committee concluded that paraquat was not oncogenic to the rat lung, based on the findings of the 2 out of 3 pathologists who had looked at the complete set of slides: Drs. Ishmael and Busey. The difficulties experienced by all 3 pathologists, in the assessment of the histopathology of these rat lung lesions is summed up in the following comment by Dr. Busey:

> "The differentiation of these proliferative lesions from primary neoplasms of the lung was particularly difficult in this study. The adenomatous hyperplasia involved the same cell type that is involved in primary lung neoplasms, i.e., bronchioalveolar adenomas and carcinomas, and, in some respects resembled these neoplasms. However, the adenomatous hyperplasia rather than being a part of a neoplastic process was probably a reactive hyperplasia associated with the alveolar wall fibrosis and other inflammatory changes resulting from the administration of paraquat".

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*Since it was difficult to differentiate between neoplastic and non-neoplastic pulmonary lesions - representative lung slides were re-examined independently by 4 pathologists: Dr. Finn, Dr. Ishmael, Dr. Robert A. Squire (consultant). and Dr. Donald Dungworth (Univ. of California, School of Vet. Med.). Their diagnoses are shown in Appendix A . It should be noted that the diagnosis of neoplasia (adenoma, adenocarcinoma or carcinoma) was made by Drs. Finn and Dungworth for 14 of these 21 slides (by Dr. Ishmael, for 6 and Dr. Squire, for 9) and that there were 9 slides for which 3 out of 4 pathologists diagnosed neoplasia. The Committee, however, gave less weight to these findings, because 2 of the pathologists did not look at all of the slides.

Table 1. Incidence of pulmonary adenomas and carcinomas in male and female rats, as reported by Drs. Finn, Ishmael and Busey after examining the same set of slides

Test Group	1,2M	3M	4M	5M	1F,2F	3F	4F	5F
Paraquat Cation (ppm)	0	25	75	150	0	25	75	150
	J. P. Finn							
Number of lungs examined	139*	70	70	69*(1)	139*	70	70	70
Adenoma	3	3	5	4	0	1	2	8(2)
Carcinoma(3)	1	1	1	3	0	1	1	2
Total neoplasms	4	4	6	7	0	2	3	10(2)
Percent neoplasms	2.9	5.7	8.6	10.1	0	2.8	4.3	14.3
	J. Ishmael							
Number of lungs examined	139*	70	70	69*	139*	70	70	70
Adenoma	0	2	1	1	0	0	1	0
Carcinoma(4)	2	2	1	3	0	1	1	0
Total neoplasms	2	4	2	4	0	1	2	0
Percent neoplasms	2.9	5.7	2.8	5.8	0	1.4	2.8	0
	W. H. Busey							
Number of lungs examined	139*	70	70	69*	140	70	70	70
Adenoma	2	2	0	0	0	0	1	1
Carcinoma(5)	2	2	3	4	0	1	1	1
Total neoplasms	4	4	3	4	0	1	2	2
Percent neoplasms	2.9	5.7	4.3	5.8	0	1.4	2.8	2.8

*No tissue section was available for one rat in these groups. However, Dr. Busey had all of the slides for the females in the control group.

(1) In this groups, one rat had carcinoma and separate adenoma, and each is recorded.

(2) Significantly different from combined controls ($P < 0.001$).

(3) This term includes:

- °Bronchioloalveolar carcinomas (single rats in groups 3M, 5M, 3F and 4F, and two rats in group 5F).
- °Squamous cell carcinomas (single rats in groups 4M and 5M).
- °Bronchioloalveolar carcinomas and squamous cell carcinomas in the same mass (single rats in 1M and 5M).

(4) According to Dr. Ishmael, "Carcinomas showed a variety of forms. Most frequent were adenocarcinomas showing proliferation of abnormal epithelium, with glandular or acinar formation, bizarre nuclei with frequent mitoses, obliteration of the normal architecture and invasion of surrounding structures. There was a variable degree of stromal fibrosis and some tumours showed areas of necrosis and dystrophic calification. Some squamous cell carcinomas were seen also, while other carcinomas appeared to be of mixed glandular and epidermoid (adenosquamous) type."

Historical Control Data for Pulmonary Neoplasias

The incidence of pulmonary adenomas and carcinomas in Fisher 344 rats is given in Table 2 [Document 3].

Other Tumor Types

The predominant neoplasms (other than pulmonary) considered by the Committee were pituitary adenomas and carcinomas, thyroid parafollicular adenomas and follicular adenomas, adrenal benign pheochromocytomas, and tumors of the skin and subcutis. The incidence of these neoplasms is summarized in Appendices B and C[1].

The increased incidences of tumors of the pituitary, thyroid and adrenal glands, were all within the range reported for historical controls (Appendix D [Document 2]).

The incidences of pancreatic islet cell adenomas (mid-dose), mammary gland benign fibroepithelial and testis interstitial cell tumors (high dose) were increased (not statistically significant) over concurrent controls in male rats. Malignant lymphomas were also increased in males, however "it was a relatively small elevation and there was a discrepancy between low and high dose" [L. Kasza]. Historical control data on these 4 tumor types were not available. According to Dr. Kasza, these tumors could not be related to the compound.

Skin Tumors:

At the high dose, in male rats, the incidence of lipomas was significantly increased over concurrent controls, and also exceeded that in historical controls, however this was not seriously considered, "because it is a common tumor of benign character, furthermore there were other skin tumors (squamous neoplasias) which were more important" [L. Kasza]. Basal cell tumors appeared to be compound-related at low and mid-level, but according to Dr. Kasza, since the incidence drops down to near control level at the high dose, it was difficult to relate this tumor to the compound.

There was an increase in the incidence (over concurrent controls) of fibromas at the high dose in males, which was within the range reported for historical controls.

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[1]Appendix B contains the data for skin and subcutis neoplasias, based on Supplementary information on numbers of protocol tissues examined and is from Document 2; Appendix C lists other tumor types and is taken (in part) from Document 1 - refer to section B. "Material Reviewed" for complete citations.

Table 2. Historical incidence of pulmonary adenomas and carcinomas in Fisher 344 rats: 8 studies, 5 conducted in Essex and 3 conducted in Suffolk*

Neoplasms	Percent incidence(a)		No. of studies(b)	
	Essex	Suffolk	Essex	Suffolk
	MALES			
Number of lungs examined	50-60	45-60		
Adenoma	1.7-2.0	1.7-4.4	3	3
Carcinoma	1.7	4.0	1	1
Adnoma and carcinoma	2.0-3.4	1.7-6.0	3	3
	FEMALES			
Number of lungs examined	50-60	50-63		
Adenoma	1.7-1.9	4.0	2	1
Carcinoma	0	0 4.0	0	0
Adenoma	1.7-1.9		2	1

*These data were obtained from a document entitled "Attachment 3. Historical control data for selected neoplastic lesions in studies using Fisher 344 rat at Life Science Research" October 28, 1985. Accession No. 260281; TB Project No. 1083.

a. Number of lungs with adenomas or carcinomas x 100/Number of lungs examined.

b. Number of studies in which adenomas or carcinomas were observed.

The above data indicate that Dr. Ishmael's and Dr. Busey's observations fall within the historical incidence of adenomas and carcinomas. However, the incidence of these neoplasms reported by Dr. Finn for the mid-dose and high-dose females is higher than that reported for the historical controls.

Detailed observations reported by Drs. Finn, Ishmael and Busey are summarized in Tables 3-12.

Squamous cell carcinoma was a predominant tumor in the head region of the male and female rats. This uncommon tumor occurred in 51.6% of all rats having tumors of the skin and subcutis in the head region.

In high-dosed males (150 ppm) the incidence of this tumor was significantly increased over concurrent controls (p=0.01).

The % incidence of squamous cell carcinoma [Appendix B[1]] was:

	Males		Females
historical controls	0-2.0		1.9-4.0
concurrent controls	2.14	(3/140)	0
low-dose	4.29	(3/70)	0
mid-dose	0		4.28
high-dose	8.57	(6/70)	2.86

When squamous cell -carcinoma and -papilloma, and papilloma of the skin and subcutis (including the head region) were combined, the incidence of these tumors exceeded historical controls only in the high-dose male rats.

The % incidence [Document B] of these combined tumors was:

	Males	
historical controls	2.0-10.0	(Papilloma/Squamous papilloma)
	0-2	(Squamous cell carcinoma)
concurrent controls	6.43	(9/140)
low dose	10.0	(7/70)
mid dose	7.14	(5/70)
high dose	20.0	(14/70)

[1]Note: Several tables of data, which varied in the use of diagnostic terminology and expression of incidence, were presented (in Documents 1-3) to the Peer Review Committee. In Documents 1 and 2, there appear to be discrepancies in the listing of tumors of the skin and subcutis. According to Drs. Kasza and Locke, the table given in Appendix B (from Document 2) more accurately represents this data, and was the one used by the Peer Review Committee.

The Committee agreed that the increased incidence of squamous cell papillomas and carcinomas in high-dose males were treatment-related, however the data was considered to be confounded by the following:

- °Animals were group housed (five to a cage)[1], which tends to lead to scratching and fighting, especially among males.
- °The product is corrosive.
- °The site for these tumors was mainly in the head region, suggesting a direct effect on skin through contact, rather than through internal dosing.

Information on whether or not historical controls were similarly group-housed was not available to the Committee at the time of the meeting. This was thought to be a critical issue for the skin tumors, since for reasons mentioned above, exposure was probably mainly via dermal or intradermal routes. Thus, it was not clear whether these tumors were compound-induced or could be attributed to the effects of intra-dermal impaction of food particles alone, due to increased fighting among the treated animals (supported by the higher incidence of tumors in males).

From the clinical signs: hypersensitivity, piloerection or respiratory distress (Appendix E), it does not appear that the paraquat treated animals were more active or distressed than the concurrent controls, which were similarly housed. This information, which was not available to the Committee at the meeting, helps to assuage the concern regarding increased fighting among the treated males leading to increased impaction of food particles.

As far as the other concerns, corrosivity of the product, and that this was not a true oral exposure - it was felt that these same conditions would prevail during actual use of the product.

The Committee acknowledged these concerns and agreed that the study was possibly flawed, based on its design. Nevertheless, the conclusion was that the data were not invalidated.

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[1]Subsequent to the meeting, the housing of control animals was submitted as shown in Table 3. Thus the majority of the historical control groups were group-housed (5/cage), as were the animals in this study; in view of this information and the above noted clinical observations, it now appears unlikely that the tumors can be attributed to increased impaction of food particles alone.

Housing of the historical control rats (males and females)*: data submitted for the rat chronic feeding/oncogenic study with paraquat (Report NO. 82/ILY 217/328; Life Science Research; 10/27/83)

Study ID	Number of rats housed per cage	Study was conducted in:
FSR 1	5	Suffolk
FSR 4	5	Essex
FSR 6	5	Suffolk
FSR 7	5	Suffolk
FSR 9	1	Essex
FSR 11	1	Essex
FSR 13	5	Essex
FSR 14	1	Essex

* This information was related to me today (7/17/86) by telephone, by Dr. Zimmerman (Toxicologist at Chevron in Richmond, California). Dr. Zimmerman obtained this information from Life Science Research (testing laboratory) through ICI (sponsor). A hard copy containing these data will be delivered to the Branch by Dr. Nancy Radman, in a day or two.

PS The above rat chronic feeding/onco study was conducted in ESSEX and rats, including the controls, were housed 5 per cage. R.R. Locke 7/17/86

In summation, of all tumor-types, which occurred in the rat feeding study and were considered by the Committee, only the squamous cell neoplasias of the skin and subcutis were determined to be treatment-related - albeit with some reservations due to the study-design.

The MTD was probably reached in this study at the high dose as evidenced by the statistically significant changes in organ weights, dose-related statistically significant increase in the incidence of degeneration of sciatic nerve fibers in male rats and of hydrocephalus in female rats.

2. Mouse Oncogenic Feeding Study. Report # CTL/P/556 6/22/81 EPA #246504

Paraquat was fed in the diet at 0, 12.5, 37.5 and 100/125* ppm to 60 male and 60 female SPF Swiss-derived mice. The study was classified as Core-Minimum. Tumor incidences are given in Table 4 [Document 4].

The Committee agreed that under conditions of this test, paraquat was not oncogenic.

The MTD was probably approached in this study because of increased mortality in the females at the high dose and renal tubular degeneration in males at the mid-dose.

Historical control data were not obtained for these mice.

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*The dose was increased to 125 ppm at week 36, because no adverse effects were seen after 35 weeks at 100 ppm.

TABLE 4

Data summarized below show the incidence of the most prevalent neoplasma, both benign and malignant.

DISTRIBUTION OF THE MOST FREQUENTLY OCCURRING TUMORS

Paraquat ion (ppm) ----->	0	0	12.5	37.5	100/125	0	0	12.5	37.5	100/125
	Percent of animals examined									
Benign tumors	Males					Females				
Lung adenoma[a]	13	18	12	15	18	13	8	8	7	17
Harderian gland adenoma[b]	8	12	19	12	13	3	3	14	7	7
Pituitary adenoma[c]	0	4	7	4	0	20	25	32	31	23
Liver nodules (Type A)[a]	12	17	15	13	5	3	0	2	3	2
Kidney adenoma[d]	3	3	3	2	10	0	0	0	0	0
Adrenal cortical adenoma[d]	2	3	5	2	2	0	0	0	0	0
Malignant tumors										
Lymphosarcoma[a]	27	18	27	22	27	40	38	37	17	38
Liver nodules (Type B)[a]	10	8	10	12	7	3	2	5	2	2
Lung adenocarcinoma[a]	0	3	2	0	5	2	0	3	0	0
Pituitary carcinoma[c]	0	0	0	0	0	2	3	2	0	0
Kidney carcinoma[d]	2	2	2	0	0	0	0	0	0	0
Mammary gland adenocarcinoma[d]	-	-	-	-	-	0	0	5	0	2

Numbers of mice examined in each group: a = 60; b = 58 or 59; c = 50-60; and d = 56-60.

These data show the following:

1. Lung adenomas, Harderian gland adenomas, liver nodules (Types A and B), and pulmonary adenocarcinomas occurred more frequently in the male mice than in the female mice, but the incidence was not dose-related.

2. Lymphosarcomas and pituitary adenomas were more prevalent in the females than in the males, especially pituitary adenomas. However, the incidence of pituitary adenomas in the females was similar in the control and the paraquat-fed groups.

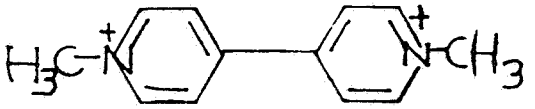
3. Kidney adenomas and carcinomas and adrenal cortical adenomas were observed only in the males, whereas pituitary carcinomas were observed only in the females. The incidence of these tumors was low and was not dose-related.

4. At the 100/125 ppm level (highest tested), females had a higher incidence of lung adenomas and Harderian gland adenomas, and the males had a higher incidence of kidney adenomas and lung adenocarcinomas than did their controls, but these increases were statistically insignificant. There was also no evidence of a dose response.

5. At the 12.5 ppm level (lowest tested), males and females had a higher incidence of Harderian gland adenomas than their controls. This increase was statistically significant in the females ($p = 0.015$). However, as mentioned above, there was no evidence of a dose response.

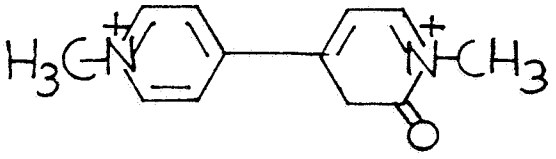
E. Additional Toxicology Data on Paraquat:

1. Metabolism:

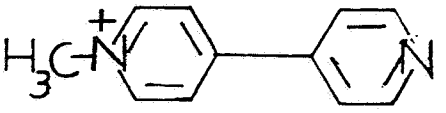


Paraquat Cation

Paraquat -dichloride or -dimethyl sulfate is poorly absorbed from the GI tract of mammals. In the rat, after oral administration (gastric intubation) of these labeled salts, paraquat (unchanged) was excreted mainly in the feces (69-96% of the dose), whereas after subcu. injection of these compounds, parquat appeared mostly in the urine (70-90% of the dose). In a Fresian cow, 95.6% of an orally administered dose was excreted unchanged in feces (89% during the first 3 days). Only 0.7% of the dose was excreted in urine, mostly as unchanged paraquat and some monopyridone and monoquat.



Monopyridone



Monoquat

Rhesus monkeys injected i.m. with paraquat dichloride eliminated 58.6% of the dose in urine within 7 days (47% of the dose was excreted in 24 hours).

The distribution of a radioactive dose was studied in the pig and goat. Most of the radioactivity was found in the lungs, kidneys and liver. With the exception of liver and peritoneal fat, the radioactivity in all tissues studied was associated with unchanged paraquat. In the liver, 3-7% of the dose was in the form monopyridone and/or monoquat. Peritoneal fat contained about 6.5% monoquat. Similar findings were repoarted in studies with rats. Paraquat accumulates in the lungs of goats and rats, but not in the lungs of pigs.

Labeled paraquat dichloride applied to forearms, hands and legs of adult male human volunteers was poorly absorbed.

Neat paraquat (28.6% a.i., 20.7% ion) is moderately corrosive to rabbit skin and dilutions as small as 1:200, when applied to the base of the tongue, were slightly irritating.

2. Non-Oncogenic Toxicological Effects

The oral LD_{50} in:

Rat	from 100 to 189	mg paraquat ion/kg.
G.pig	from 22 to 30	" "
Cat	35	" "
Monkey	50	" "
Hen	262	" "

The dermal LD_{50} in Rabbit = 59.5 " "
in Rat = 80 to 90 " "

The inhalation LC_{50} in rats ranged from 0.6 to 3.5 ug paraquat ion/liter, depending on particle size (0.3 to 23 u, respectively).

The LD_{50} obtained i.p. in Rat = 16 to 18 mg paraquat ion/kg.

Paraquat is poorly absorbed when administered orally, as evidenced by the large difference between the oral and i.p. LD_{50} in the rat, although the toxic symptoms by the 2 routes are similar (eg: cyanosis, tachycardia, hepatic and renal tubular necrosis, pulmonary changes - including fibrosis, etc.)

Paraquat is also very toxic to man and cases of poisoning (from deliberate or accidental ingestion) have been described in the literature. The symptoms of toxicity are similar to those reported for various species: initially burning of the mouth and throat, nausea and vomiting, followed (after 1-2 weeks delay) by respiratory distress, progressive fibrosis and epithelial proliferation in the lungs, convulsions and death.

In a one-year feeding study in dogs the major effect of paraquat cation was a dose-related increase in the severity and extent of chronic pneumonitis in mid and high dose males and females.

In the rat chronic feeding study, paraquat enhanced the development of ocular lesions in all of the treated groups (lenticular opacities and cataracts).

3. Mutagenicity:

Paraquat has been extensively tested in a number of assays, the results of which are summarized in Table 5 and below.

Paraquat was not mutagenic in S. typh. TA 98, 100, 1535, 1537 or 1538 either with or without metabolic activation with S9. It was also negative in the dominant-lethal test with both CDI and Swiss-Webster mice.

In the mouse (L5178Y) lymphoma gene mutation test, paraquat was weakly positive, both with and without S9, when analytical grade paraquat dichloride (99.6% a.i.) was tested; when technical grade (45.7% a.i.) was tested, a positive response was obtained only when S9 was added.

Paraquat (dichloride) did not cause bone marrow cell chromosomal aberrations in the rat at levels up to 19 mg/kg b.w./day of test material.

In DNA Damage/Repair assay (unscheduled DNA synthesis) with Alderley Park male rat hepatocytes, paraquat dichloride was negative at concentrations of 10^{-2} to 10^{-9}, however, the same assay was positive with human embryo epithelial cells. Positive or weakly positive results were also obtained in DNA Damage/Repair assays with S. typh. TA 1978 and 1538 and with Sacch. cerevisiae D4 and JDI strains.

Paraquat was positive, both with and without S9, in sister chromatid exchange assay in CHO lung fibroblasts.

* * * * * * *

Paraquat is largely negative in bacterial and chromosomal aberration assays, but it has shown activity in DNA Repair/Damage assays in mammalian systems, and in the mouse-lymphoma and sister-chromatid exchange assays. It appears that paraquat has mutagenic activity, however questions have arisen as to the interpretation of some of these studies. These are being looked into, however, the outcome of this re-evaluation is not expected to materially change the categorization of paraquat.

Mutagenic Profile of Paraquat

Assay	Reference	Test Material	Results Metabolic activation** Without	With	Classification of data
GENE MUTATION ASSAYS					
S. typhimurium TA 1538, 1535, 100 and 98	Anderson, D.; ICI Report No. CTL/P/243; 7/8/77.	Paraquat dichloride 99% pure	-	-	Acceptable*
S.typhimurium TA 1538, 1537, 1535, 100 and 98	MacGregor, D.; IRI Report No. 877; 10/77.	Paraquat dichloride 99% pure	-	-	Acceptable*
S.typhimurium Strains not specified	Andersen, K.J. et al.; J. Agric. Food Chem. 20: 649-656; 1972.	Techn. 90-99% pure	-	-	Supplemental
S.typhimurium TA 1538, 1537, 1535, 100 and 98	Benigni, R. et al.; Mutat. Res. 68:183-193; 1979	Paraquat (Purity not stated)	-	-	Acceptable*
S.typhimurium TA 1535 and 92, and his G 46 (Induction of 8-AG-resistant mutants)	Ibid	Paraquat (Purity not stated)	+	-	Not Acceptable*
A. nidulans Strain 35 (Induction of 8-AG-resistant mutants)	Ibid	Paraquat	+ weak		Not Acceptable*
Strain P3 (Detection of recessive lethal mutation in chromosome 1, 3 or 5)			+		Not Acceptable*
L5178Y mouse lymphoma cells in culture	Clay, P. and Thomas, M.; ICI Report No. CTL/P/1398; 9/24/85.	Techn. paraquat dichloride; 45.7% a.i.	-	+ weak	Acceptable
L5178Y mouse lymphoma cells in culture	Cross, M.; ICI Report No. CTL/P/1374; 9/17/85.	Anal. grade paraquat dichloride; 99.6% a.i.	+ weak	+ weak	Acceptable
STRUCTURAL CHROMOSOME ABERRATION ASSAYS					
Dominant lethal (Charles River CD1 mice); by gavage	Anderson, D. et al; Mut. Res. 40:349-358; 1976; or Mc. Gregor, D.B.; IRI Report No. 145 (Date not given).	Paraquat dichloride; 23.8% ion	-		Acceptable*
Dominant lethal (Swiss-Webster mice); i.p. injection	Pasi, A. et al.; Mut. Res. 26:171-175; 1974.	Anhydrous paraquat dichloride	-		Supplemental*
Cytogenic (Wistar male rats; bone marrow); by gavage	Anderson, D. et al.; ICI Report No. CTL/P/367; 7/5/78	Paraquat dichloride 100% pure	-		Acceptable
Cytogenic (human lymphocytes	Sheldon, T. et al.; ICI Report No. CTL/P/1351; 9/3/85	Anal.grade paraquat dichloride; 99.6 a.i	+ weak	+ weak	Acceptable
Micronucleus test in mice	Sheldon, T. et al.; ICI Report No.CTP/P/1369; 9/4/85	Techn. paraquat dichloride; 30% a.i.	-		Not Acceptable
DNA DAMAGE/REPAIR ASSAYS					
S.typhimurium TA 1978 and 1538	Benigni, R. et al.; Mutat. Res. 68: 183-193; 1979.	Paraquat (Purity not stated)	+	+ weak	Acceptable*
Human embryo epithelial cells (unscheduled DNA synthesis)	Ibid	Paraquat (Purity not stated)	+		Supplemental*
Sacch. cerevisiae D4 (mitotic gene conversion)	Siebert, D. and Lemperle, E.; Mut. Res. 22:111-120; 1974	Gramoxone***	+ weak		Not Acceptable*
Sacch. cerevisiae (mitotic gene conversion)	Parry, J.M.; Mut. Res. 21:83-91; 1973.	Gramoxone	+		Supplemental*
Sacch. cerevisiae JD1 (Mitotic gene conversion)	Parry, J.M.; Mut. Res. 46: 165-176; 1977.	Gramoxone	+		Supplemental*
Rat hepatocytes in culture (unscheduled DNA synthesis)	Trueman, R.W. et al.; ICI Report No. CTL/P/1339; 9/4/85.	Anal. grade paraquat dichloride; 99.6% a.i.	-		Acceptable
Sister chromatid exchange in Chinese hamster lung fibroblasts	Howard, C.A. et al.; ICI Report No. CTL/P/1392; 9/24/85.	Anal. grade paraquat dichloride; 99.6% a.i.	+	+	Acceptable

*These studies were included in the Decision Document (1982); MRID GS-0262-001.

**Refers to assays performed in the presence of a microsomal fraction S9, obtained from livers of the Aroclor 1254-treated rats; plus appropriate cofactors.

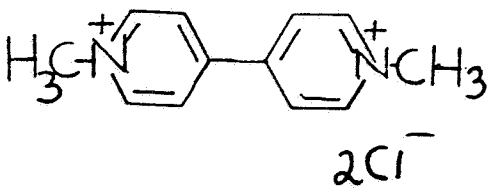
***It was stated in the protocol that Gramoxone (containing paraquat dimethyl sulfate) was tested. However, according to the FARM CHEMICALS HANDBOOK (1985), Gramoxone contains the dichloride salt of paraquat.

Abbreviations:

ICI	Imperial Chemical Industries (England)
CTL	Central Toxicology Laboratory
IRI	Inveresk Research International (Scotland)
8-AG	8-Azaguanine

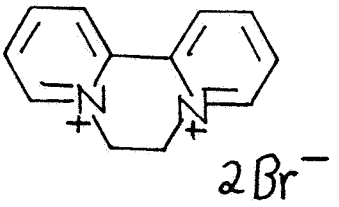
4. Structure-Activity Correlations:

Paraquat is structurally related to diquat, morfamquat and to 1-methyl-4-phenyl-pyridinium ion (MPP^+).



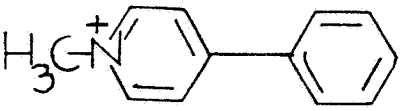
$2Cl^-$

Paraquat

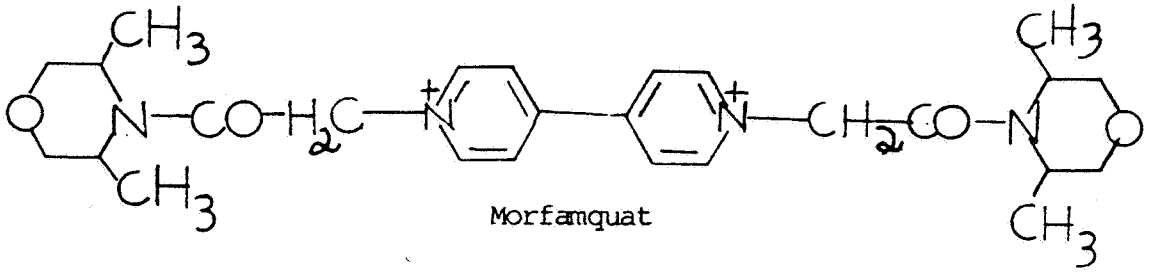


$2Br^-$

Diquat

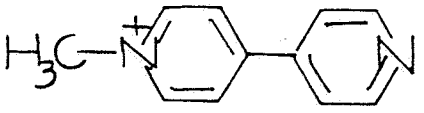


MPP^+

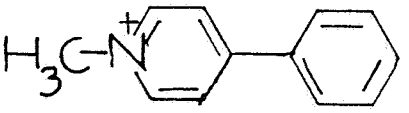


Morfamquat

Monoquat, a metabolite of paraquat is even more closely related (structurally) to MPP^+:



Monoquat



MPP^+.

However there are no data on the oncogenicity of any of these analogs, except diquat which was evaluated as negative in rats and tentatively negative in mice [K. Locke]. Both were ICI studies and were by the oral route (in the diet).

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding toxicology data on paraquat to be of importance in a weight of evidence determination of oncogenic potential.

I. Rats

Paraquat was tested at Life Science Research for oncogenicity in Fisher 344 rats. An MTD appeared to be achieved at the highest dose. The predominant tumor types considered by the Committee in Peer Review were of the lungs, endocrine glands (pituitary, thyroid, adrenal), and of the skin and subcutis.

1. Lung - adenomas and carcinomas - The Committee concluded that paraquat was not oncogenic to the rat lung, based on the findings of Drs. Ishmael and Busey - 2 of 3 pathologists (the third was Dr. Finn) who examined the complete set of slides. The incidences of pulmonary adenomas and carcinomas reported by these 2 pathologists were within the range of historical controls for Fisher 344 rats at Life Science Research.

2. Incidences of tumors of the pituitary, thyroid and adrenal glands were all within the range reported for historical controls.

3. Tumors of the Skin and Subcutis:

   a) Squamous cell carcinoma was a predominant tumor in the head region. It was noted that the study was possibly flawed based on its design, because the animals were group-housed. The Committee agreed, nevertheless, that the data were not invalidated and that the increased incidence of squamous cell papillomas and carcinomas in the high dose males was treatment-related.

      Additional data received subsequent to the Peer Review Meeting, assuaged some of the concerns (see discussion, D.1-page 11).

   b) The incidences of other tumor types were either not considered to be treatment-related (lipomas) or fell within the range reported for historical controls.

4. Paraquat appears to have mutagenic activity, however the interpretation of some of the studies is being re-evaluated.

5. Although one analog (diquat) was negative when tested in the rat (and tentatively negative) in the mouse, there is no information on the carcinogenicity of even more closely-structurally related analogs.

II. Mice

Paraquat was tested at ICI for oncogenicity in SPF Alderley Park Swiss-derived mice, at or near the MTD.

The Committee concluded that under conditions of this test, paraquat was not oncogenic.

G. Classification of Oncogenic Potential:

Criteria contained in the proposed EPA Guidelines [Draft Jan.7, 1986] for classifying a carcinogen were considered. These Guidelines state that -

For Group C - Possible Human Carcinogen:

"Limited evidence of carcinogenicity .... means that the data suggest a carcinogenic effect but are limited because:

a) The studies involve a single species, strain, or experiment and do not meet the criteria for sufficient (see section B.1.c which says: ..to an unusual degree in a single experiment with respect to high incidence, unusual site or type of tumor, or early age of onset.);
b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or
c) an increase in the incidence of benign tumors only."

For Group D - Not Classifiable as to Human Carcinogenicity

"Inadequate Evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect."

The Committee concluded that the data presently available for paraquat places it in the "C Category" - limited evidence for oncogenicity in animals, in that there was only one study with positive findings (rat). Although the type of tumor was considered to be uncommon, it was not of high incidence, nor did it appear early, thus the higher B2 category was not warranted. This conclusion was based primarily on the findings of squamous cell carcinoma in male rats, even though it was recognized that the study was probably of inadequate design (as described in D.1). The Committee also decided that a quantitative estimation of the oncogenic potential of paraquat would not be developed.

Category D (inadequate evidence) was also considered, based on the study design (as discussed in D.1) however it was decided that despite possible flaws in the study eg: animals were group-housed (5/cage[1]), the data obtained were not invalidated and the squamous cell neoplasias could in fact be interpreted as treatment-related.

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[1]Information obtained subsequently indicated that historical control animals were also similarly housed.

TABLE 20

Diagnosis by four pathologists of a series of representative lung slides

Group, sex and rat number	Finn	Ishmael	Squire	Dungworth
1 M 393	Adenoma	Adenomatosis	Adenomatosis Broncho-alveolar adenoma	Bronchiolo-alveolar tumours (adenoma and early carcinoma?).
2 M 57	Adenoma	Adenomatosis Adenocarcinoma	Adenomatosis Broncho-alveolar adenoma Broncho-alveolar adenocarcinoma	Bronchiolo-alveolar Carcinoma (early).
2 M 67	Adenoma	Adenomatosis and Leukaemia	Adenomatosis (lymphoma)	Bronchiolo-alveolar tumours (early carcinoma?).
3 M 100	Adenoma	Adenoma Adenomatosis	Chronic bronchiolitis and alveolitis; adenomatosis; Broncho-alveolar adenoma.	Bronchiolo-alveolar adenoma (possibly early carcinoma).
3 M 101	Bronchiolitis	Adenocarcinoma	Broncho-alveolar adenocarcinoma; adenomatosis.	Bronchiolo-alveolar carcinoma (prominent epidermoid component).
4 M 513	Adenoma	Adenomatosis	Bronchio-alveolar adenocarcinoma; adenomatosis	Bronchiolo-alveolar carcinoma (adeno-squamous) (mixed adenoma and epidermoid pattern). Bronchiolo-alveolar carcinoma.
5 M 148	Adenoma/ carcinoma/ squamous cell carcinoma	Carcinoma and incipient leukaemia	Adenomatosis; Broncho-alveolar adenoma; focal interstitial pneumonia	
5 M 162	Epithelialization	Pneumonitis	Interstitial pneumonia with adenomatosis.	Interstitial pneumonia segmental. Bronchiolo-alveolar. Hyperplasia.
5 M 159	Epithelialization	Adenomatosis	Interstitial pneumonia with adenomatosis	Interstitial pneumonia patchy, severe, early chronic in most active areas. (Bronchiolo-alveolar hyperplasia present).
5 M 564	Adenoma	Adenoma Adenomatosis Incipient leukaemia.	Broncho-alveolar adenoma	Bronchiolo-alveolar tumour (early carcinoma?).

TABLE 20 - continued

Diagnosis by four pathologists of a series of representative lung slides

Group, sex and rat number	Finn	Ishmael	Squire	Dungworth
1 F 592	Epithelialization	Adenomatosis	Focal chronic bronchiolitis and alveolitis	Bronchiolo-alveolar tumour (adenoma), early.
2 F 233	Epithelialization	Adenomatosis	Adenomatosis	Epithelial hyperplasia and squamous metaplasia, inflammatory.
3 F 253	Adenoma	Adenomatosis	Adenomatosis; focal chronic bronchiolitis and alveolitis	Bronchiolo-alveolar tumours - although the smaller is not obviously malignant (therefore adenoma) the larger has sufficient foci of distortion and encroachment on the peribronchial fascia to qualify for early carcinoma. a) chronic centriacinar inflammation. b) Excess of proliferation over inflammation in these foci indicates neoplastic process. The three foci are bronchiolo-alveolar tumours which are not obviously malignant at this stage, but might eventually have become so.
3 F 660	Epithelialization	Adenomatosis and pneumonitis	Adenomatosis, multifocal chonic bronchiolitis and alveolitis	Bronchiolo-alveolar tumours (adenoma possibly pre-malignant.
4 F 672	Epithelialization	Adenomatosis	Focal chronic and alveolitis; focal interstitial pneumonia	Inflammatory hyperplasia/metaplasia (interstitial pneumonal, segmental.
4 F 690	Adenoma	Adenoma	Broncho-alveolar adenoma	Bronchiolo-alveolar adenoma
5 F 316	Adenoma	Adenomatosis	Adenomatosis	Bronchiolo-alveolar carcinoma (early).
5 F 336	Adenoma	Adenomatosis	Interstitial pneumonia with adenomatosis	Interstitial pneumonia, segmental with prominent epithelial proliferation in some regions.
5 F 715	Adenoma	Adenomatosis	Adenomatosis; broncho-alveolar adenoma	Bronchiolo-alveolar carcinoma (early).
5 F 721	Adenoma	Adenomatosis	Adenomatosis	Bronchiolo-alveolar carcinoma (early).
5 F 728	Adenoma	Adenomatosis	Adenomatosis	Bronchiolo-alveolar tumour (adenoma). I cannot see cell characteristics well enough to decide whether it might be potentially malignant.

APPENDIX B

Table III. Incidence of tumors found in the skin and subcutis, including the head

Paraquat ion (ppm) Group	0 1+2 M	25 3M	75 4M	150 5M	0 1+2F	25 3F	75 4F	150 5F
Number of rats examined*	140	70	70	70	139	70	70	70
Tumor type	Number of rats with tumors							
Papilloma	5	2	4	8	3	2		
Squamous papilloma	1	2	1					
Squamous carcinoma	3	3		6			3	2
Basal cell tumor	4	3	4	2	3	1	1	1
Fibroma	12	8	14	7	5	4	3	3
Fibrosarcoma	2	1	1	2	2	3	1	1
Keratoacanthoma		1	1			1		
Leiomyoma			1					
Lipoma	2	3	3	5	1	1		
Sarcoma	2		1		2			
Sebaceous adenoma	2							
Skeletal leiomyosarcoma					1			
Undifferentiated carcinoma		1		1				
Histiocytic sarcoma							1	
	Percent of rats with tumors**							
Papilloma	3.57	2.86	5.71	11.43	2.16	2.86		
Squamous papilloma	0.71	2.86	1.43					
Squamous carcinoma	2.14	4.29		8.57	6		4.28	2.86
Basal cell tumor	2.86	4.29	5.72	2.86	2.16	1.43	1.43	1.43
Fibroma	8.57	11.43	20.00	10.00	3.60	5.71	4.29	4.29
Fibrosarcoma	1.43	1.43	1.43	2.86	1.44	4.29	1.43	1.43
Keratoacanthoma		1.43	1.43			1.43		
Leiomyoma			1.43					
Lipoma	1.43	4.29	4.29	7.14	0.72	1.43		
Sarcoma	1.43		1.43		1.45			
Sebaceous adenoma	1.43							
Skel. leiomyosarcoma					0.72			
Undif. carcinoma		1.43		1.43				
Histiocytic sarcoma							1.43	

*Number of rats examined = number of organs/tissues examined. However, ears, tongue and turbinates were not examined in all of these animals. Details appear in Table I.

APPENDIX C

Table XXVI. Incidence of predominant neoplasms in male rats: Summary[a]

Test Group	1M and 2M				3M				4M				5M			
Paraquat cation (ppm)	0				25				75				150			
Neoplasms	S	D	Total	Percent[b]	S	D	Total	Percent[b]	S	D	Total	Percent[b]	S	D	Total	Percent[b]
	80	60	140		33	37	70		35	35	70		43	26	69	
Adrenal: benign pheochromocytoma	8	4	12	8.6	4	5	9	12.9	5	3	8	11.4	9	3	12	17.4
	80	58	138		33	37	70		35	35	70		43	25	68	
Pancreas: islet cell adenoma	6	2	8	5.8		3	3	4.3	4	2	6	8.6	2	1	3	4.4
	74	56	130		33	35	68		31	34	65		41	27	68	
Pituitary: adenoma	11	11	22	16.9	5	13	18	26.5	6	12	18	27.7	7	4	11	16.2
carcinoma		1	1	0.8					1	2	3	4.6				
TOTAL	11	12	23	17.7	5	13	18	26.5	7	14	21	32.3	7	4	11	16.2
	80	55	135		33	32	65		35	31	66		43	26	69	
Thyroid: parafollicular adenoma	9	5	14	10.0	4	2	6	9.2	4	2	6	9.1	11	2	13	18.8
parafollicular carcinoma	2		2	1.5	3		3	4.6	2		2	3.0				
TOTAL	11	5	16	11.9	7	2	9	13.8	6	2	8	12.1	11	2	13	18.8
follicular adenoma	3	1	4	3.0		1	1	1.5	1	1	2	3.0	2	1	3	4.3
	80	60	140		33	37	70		35	35	70		43	27	70	
Mammary gland: benign fibroepithelial tumor	11	1	12	8.6	3	1	4	5.7	4	1	5	7.1	5	2	7	10.0
	80	59	139		33	37	70		35	35	70		43	27	70	
Testis: interstitial cell tumor	59	45	104	74.8	21	31	52	74.3	25	26	51	72.9	33	21	54	77.1
	80	60	140		33	37	70		35	35	70		43	27	70	
Preputial gland: adenoma	4	4	8	5.7	1	1	2	2.9		2	2	2.9				
	80	60	140		33	37	70		35	35	70		43	27	70	
Lymphoreticular system																
Malignant lymphoma		1	1	0.7	1	1	2	2.9	1		1	1.4	1		1	1.4
Monocytic leukemia	11	25	36	25.7	8	12	20	28.6	5	13	18	25.7	4	9	13	18.6

Table XXVII. Incidence of predominant neoplasms in female rats: Summary[a]

Test Group	1F and 2F				3F				4F				5F			
Paraquat cation (ppm)	0				25				75				150			
Neoplasms	S	D	Total	Percent[b]	S	D	Total	Percent[b]	S	D	Total	Percent[b]	S	D	Total	Percent[b]
	78	62	140		39	31	70		39	31	70		39	31	70	
Adrenal: benign pheochromocytoma	2	1	3	2.1					1		1	1.4	1		1	1.4
	78	61	139		39	30	69		39	31	70		39	30	69	
Pancreas: islet cell adenoma	6	1	7	5.0	1		1	1.4	3		3	4.3	1		1	1.4
	74	56	130		36	29	65		37	31	68		39	28	67	
Pituitary: adenoma	33	26	59	45.4	16	17	33	50.8	11	22*	33	48.5	16	18	34	50.7
carcinoma	3	5	8	6.1	2	4	6	9.2	3	2	5	7.4	1	4	5	7.5
TOTAL	36	31	67	51.5	18	21	39	60.0	14	24	38	55.9	17	22	39	58.2
	78	62	140		39	31	70		39	30	69		39	29	68	
Thyroid: parafollicular adenoma	9	5	14	10.0	1	5	6	8.6	3	1	4	5.8	7	3	10	14.7
parafollicular carcinoma	2		2	1.4	3		3	4.3	1		1	1.4	1		1	1.5
TOTAL	11	5	16	11.4	4	5	9	12.9	4	1	5	7.2	8	3	11	16.2
follicular adenoma	3	1	4	2.9		2	2	2.9	2		2	2.9		3	3	4.4
	78	62	140		39	31	70		39	31	70		39	31	70	
Mammary gland: benign fibroepithelial tumor	34	23	57	40.7	16	13	29	41.4	17	12	29	41.4	18	9	27	38.6
	78	62	140		39	31	70		39	31	70		39	31	70	
Lymphoreticular system																
Malignant lymphoma		3	3	2.1	1	1	2	2.9	1	1	2	2.9	1	1	2	2.9
Monocytic leukemia	7	14	21	15.0	6	4	10	14.3	3	3	6	8.6	2	7	9	12.9

a. This table is based on TABLES 19A, 19B and 19C of the submission and on Amended Supplement to LSR Report No. 82/ILY217/328; August 23, 1985. For each organ or tissue, the top line represents the numbers of tissues examined and the remaining lines the numbers of neoplasms observed. Pulmonary and ocular lesions were considered separately.

b. Of total tissues examined.

S = Scheduled sacrifices (interim and final).
D = Moribund sacrifices and deaths.
* Significantly different from controls ($P<0.05$).

APPENDIX D

Table VI. Historical incidence of selected neoplastic lesions in Fisher 344 rats: 8 studies, 5 conducted in Essex and 3 conducted in Suffolk*

Neoplasms	MALES				FEMALES			
	Percent incidence[a]		No. of studies[b]		Percent incidence[a]		No. of studies	
	Essex	Suffolk	Essex	Suffolk	Essex	Suffolk	Essex	Suffol
SKIN AND SUBCUTIS	50-60[c]	50-60[c]			50-60[c]	50-63[c]		
Papilloma/Squamous papilloma	1.9-10.0	2.0-10.0	4	3	2.0-3.8	1.6-4.0	3	3
Squamous cell carcinoma	2.0	0	1	0	1.9-4.0	0	2	0
Fibroma	5.0-25.0	16.0-30.0	5	3	1.7-4.0	1.6-6.0	3	3
Fibrosarcoma	1.7- 4.0	4.0-16.0	4	3	1.9-2.0	8.0-6.0	2	2
Lipoma	2.0-3.3	1.7	2	1	0	0	0	0
Liposarcoma	0	4.0	0	1	0	0	0	0
Basal cell tumor[d]	1.7-2.0	0	2	0	2.0	0	1	0
Basal cell carcinoma	2.0	2.0-4.0	1	2	2.0	0	2	0
Keratoacanthoma	0	6.0-8.0	0	2	2.0	2.0	1	2
Sebaceous gland adenoma	4.0	0	1	0	0	0	0	0
Hemangioma	0	0	0	0	0	0	0	0
Hemangiosarcoma	2.0	2.0	1	1	0	0	0	0
Rhabdomyosarcoma	4.0	0	1	0	0	0	0	0
Zymbal gland adenoma	0	0	0	0	0	0	0	0
Zymbal gland carcinoma	1.7	0	1	0	0	0	0	0
Osteoma	2.0	0	1	0	0	0	0	0
HEAD	50-60[c]	50-60[c]			50-60[c]	50-63[c]		
Squamous carcinoma	1.9-2.0	2.0	2[e]	2[e]	1.7-2.0	2.0	3	2
ADRENAL GLAND	49-60[c]	47-60[c]			50-60[c]	40-63[c]		
Cortical adenoma	1.7-4.0	2.1-4.0	2	2	1.9-8.0	0	3	0
Cortical carcinoma	2.0	2.0	1	1	0	0	0	0
Pheochromocytoma	19.2-38.8	6.7-34.0	5	3	2.0-12.0	3.2-20.0	5	3
Ganglionneuroma	0	0		0	0	0	0	0
PITUITARY GLAND	48-60[c]	47-60[c]			47-59[c]	49-63[c]		
Adenoma	17.6-53.3	12.8-40.0	5	3	51.9-63.3	32.7-42.9	5	3
Carcinoma	1.7-2.0	6.4-24.0	4	2	2.0-7.7	12.0-30.6	4	2
Adenoma and carcinoma	19.6-55.0	19.2-64.0	5	3	55.3-65.3	42.9-63.3	5	3
THYROID GLAND	48-60[c]	43-60[c]			49-60[c]	47-63[c]		
Parafollicular cell adenoma	16.7-30.8	13.0-20.7	5	3	11.7-20.4	1.6-8.5	5	3
Parafollicular cell carcinoma	1.9-10.4	4.7-6.5	3	2	1.7-8.2	1.6-8.2	2	3
Parafollicular cell adenoma & carcinoma	16.7-35.4	13.3-24.8	5	3	13.4-28.6	3.2-16.4	5	3
Follicular cell adenoma	1.9-8.0	1.7-2.3	4	3	1.7-3.8	1.6-6.1	2	2
Follicular cell carcinoma	2.0-3.3	2.3-8.7	2	2	1.7-4.1	2.0-4.3	3	2
LUNGS	50-60[c]	45-60[c]			50-60[c]	50-63[c]		
Pulmonary adenoma[f]	1.7-2.0	1.7-4.4	3	3	1.7-1.9	4.0	2	1
Pulmonary carcinoma[g]	1.7	4.0	1	1	0	0	0	0
Pulmonary adenoma and carcinoma	2.0-3.4	1.7-6.0	3	3	1.7-1.9	4.0	2	1

a. Number of tissues or organs with a neoplasm X 100 / Number of tissues or organs examined.

b. Number of studies in which a neoplasm was observed. (Historical control data were obtained from eight studies, 5 conducted in Essex, as was the rat chronic feeding/oncogenic study No. 82/ILY/217/328, and 3 conducted in Suffolk).

c. Number of tissues or organs examined per study.

d. Figures derived from reported incidences of basal cell tumor, basal cell epithelioma and tricholepithelioma.

e. In one study squamous carcinoma was found on the neck.

f. Figures derived from reported incidences of pulmonary adenoma and lung adenoma.

g. Figures derived from reported incidences of pulmonary carcinoma and lung carcinoma.

APPENDIX E

TABLE 3A

Distribution of clinical signs† recorded for animals dying during the treatment period

Group	1	2	3	4	5
Compound	Control		---	Paraquat	---
Level (ppm)	0	0	25	75	150

Signs	Group and sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Genito-urinary staining	15	14	15	18	8	22	15	17	12	19
Anal staining/diarrhoea	12	6	8	12	7	0	2	1	4	0
Nasal staining	7	6	8	5	10	8	8	11	7	9
Necrotic/ulcerated mass	8	9	9	7	8	4	3	4	4	1
Pallor	18	17	18	19	8	13	16	10	6	11
Discharge from eye	14	10	19	11	13	22	23	19	21	18
Yellow colouration	6	4	13	7	4	4	2	1	2	5
Lack of muscle tone	5	5	5	5	1	6	1	5	6	7
Abdominal mass/distension	8	7	9	6	2	4	7	3	1	7
Opacity of eye	1	1	2	1	7	1	1	1	4	8
Hypothermia	8	8	14	8	6	11	8	11	4	7
Lethargy	10	12	17	15	8	13	15	17	13	18
Piloerection	1	0	2	3	2	1	6	1	2	5
Blood from penis	1	1	0	1	1	-	-	-	-	-
Vaginal discharge	-	-	-	-	-	6	9	4	11	8
Suspected middle ear infection	1	0	1	0	1	3	1	3	3	1
Hypersensitivity	3	0	3	0	0	0	1	1	1	0
Flaking skin on feet	1	1	0	0	0	1	2	1	0	1
Ptosis/swollen eyelids	0	2	2	2	1	2	2	2	2	3
Salivation	0	1	0	0	0	1	0	3	0	1
Respiratory distress	2	2	7	5	7	8	8	8	6	7
Kyphosis	0	1	0	4	0	0	4	1	4	3
Scabs	0	0	0	0	0	0	0	1	1	1
Numbers of animals examined	31	29	37	35	27	32	30	31	31	31

† Signs tabulated are those considered to be of potential toxicological significance; non-specific observations such as bodyweight loss, wheezing and localised hair loss are not included. The values in the body of the table are the numbers of rats showing a given sign at any time during the treatment period.

TABLE 3B

Distribution of clinical signs† recorded for animals sacrificed at termination

Group	1	2	3	4	5
Compound	Control		---	Paraquat	---
Level (ppm)	0	0	25	75	150

Signs	Group and sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Genito-urinary staining	11	8	1	4	7	12	14	12	16	18
Anal staining/diarrhoea	8	8	9	5	6	2	5	2	1	0
Nasal staining	4	3	4	7	3	2	7	3	5	5
Necrotic/ulcerated mass	2	6	2	5	7	3	0	0	3	2
Pallor	3	6	2	0	7	2	4	4	1	3
Discharge from eye	8	9	8	3	9	15	12	15	17	10
Yellow colouration	1	1	0	1	1	1	2	2	0	0
Lack of muscle tone	1	0	0	1	2	0	0	0	1	3
Abdominal mass/distension	4	5	3	5	3	2	4	1	2	5
Opacity of eye	3	0	1	4	15	2	4	5	10	27
Hypothermia	1	0	2	0	2	0	0	0	1	1
Lethargy	1	0	1	2	2	1	2	4	4	3
Piloerection	0	0	0	0	0	0	1	2	0	0
Blood from penis	0	0	0	0	0	-	-	-	-	-
Vaginal discharge	-	-	-	-	-	10	8	6	8	11
Suspected middle ear infection	0	0	1	2	1	3	0	3	1	1
Hypersensitivity	0	0	0	0	0	0	1	0	0	1
Flaking skin on feet	0	0	0	0	0	1	0	0	0	1
Ptosis/swollen eyelids	0	1	0	0	0	2	2	1	3	4
Salivation	0	0	0	0	0	0	0	0	0	0
Respiratory distress	0	1	0	1	0	0	0	0	0	1
Kyphosis	0	0	1	1	0	0	0	0	0	0
Scabs	0	0	0	0	0	2	2	1	1	0
Numbers of animals examined	29	31	23	25	33	28	30	29	29	29

† Signs tabulated are those considered to be of potential toxicological significance; non-specific observations such as bodyweight loss, wheezing and localised hair loss are not included. The values in the body of the table are the numbers of rats showing a given sign at any time during the treatment period.