PC 061601 Record No. 227707, 227721

SEP - 2 1988 Caswell No(s). 634 **CASWELL FILE** 12

To: R.J. Taylor / V. Walters, PM Team 25, Registration Division (TS-767 C)

Registration No(s).: 10182-103

Pesticide Petition No(s).: 7F1910 (ICI Americas Inc.)

Chemical(s): Paraquat, formulated as GRAMOXONE SUPER Herbicide (23.2% paraquat dichloride (a.i.))

Requested Action(s): Section 3 registration of the above formulation for use as harvest aid on dry beans and establishment of a tolerance (0.3 ppm) on/in rac dry beans.

Recommendation: Approval is recommended. (The above petition was rejected by Tox. Branch in 1980 because of data gaps, but these no longer exist).

Inert(s) cleared 180.1001: Yes

% of ADI occupied: Existing: This information Resulting:

Resulting % increase in TMRC: is now provided for RD by RCB.

Data considered in setting the ADI: One-year dog feeding study and Uncertainty (Safety) Factor of 100 (see TAS printout from RCB for details).

Attached (?): ADI printout: YES (NO); TOX "one-liner": YES (NO); DER: YES (NO)

Existing regulatory actions against registration: No

Special Review Status: No

New Data: No

Data gaps: None

Comments: Until recently, paraquat was classified as Category C oncogen. However, based on additional data and reassessment of the previously submitted data, the Peer Review Committee changed this category to Category E or not an oncogen (Memorandum from R. Engler to R. Taylor; 7/28/88). Secondary residues and food additive tolerances are not associated with this petition. Label modification (attached) is acceptable to TB. The issue of toxicological significance of paraquat metabolites, raised by RCB (see memo from B.J. Kaminski to R.J. Taylor; 5/9/88) has already been addressed by Tox. Branch (see attachment).

Reviewer: Krystyna Kylocheg Date: 8/23/88

Section Head: Ed Budd 8/31/88 Branch Chief:

(28597, 28598, 28599)

PROPOSED GRAMOXONE® SUPER
DRY BEAN HARVEST-AID LABEL

Dry Bean Harvest-Aid - Apply 1½ to 2½ pints per acre in 20 to 40 gallons of water with ground equipment or in a minimum of 5 gallons of water with aerial equipment. Add Spreader (non-ionic) at 1 quart per 100 gallons of spray mix. For vining-type beans or bush-type beans with lush and vigorous growth, use a single application of the higher rate. May also be applied as a split application. Do not make more than 2 applications or exceed a total of 2½ pints per acre. The split application method may improve vine coverage. Do not harvest within 7 days of the last application.

Apply when the crop is mature and at least 80% of the pods are yellowing and mostly ripe with no more than 40% (bush-type beans) or 30% (vine-type beans) of the leaves still green in color.

Do not apply when weather conditions favor spray drift. A drift control agent may be included to reduce spray drift. Do not use on Faba beans.

050388SFP109

RESTRICTED USE PESTICIDE.

Gramoxone® SUPER

HERBICIDE

A WEED AND GRASS KILLER – HARVEST AID CHEMICAL

KEEP OUT OF REACH OF CHILDREN

DANGER POISON

ONE SWALLOW CAN KILL!

SYMPTOMS ARE PROLONGED AND PAINFUL. ONSET OF SYMPTOMS MAY BE DELAYED FOR UP TO 3 DAYS AFTER SWALLOWING

PELIGRO

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... ingles, no use este producto hasta que la ... haya sido explicada ampliamente.

ICI

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DO NOT REMOVE CONTENTS EXCEPT FOR IMMEDIATE USE.

NEVER PUT INTO FOOD, DRINK OR OTHER CONTAINERS.

READ DANGER STATEMENTS AND WORKER SAFETY RULES ON BACK PANEL.

REFER TO BACK PANEL FOR STATEMENT OF PRACTICAL TREATMENT.

Active Ingredient:	By Wt.
Paraquat dichloride (1,1'-dimethyl-4,4'-bipyridinium dichloride)	29.1%
Inert Ingredients:	70.9%
Total	100.0%

Contains 1.5 lbs. Paraquat cation per gallon.
Contains Stench (Odor) and Emetic

ICI Americas Inc.
Agricultural Products
Wilmington, Delaware 19897

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS AND DOMESTIC ANIMALS

DANGER POISON

WORKER SAFETY RULES

STATEMENT OF PRACTICAL TREATMENT

ENVIRONMENTAL SAFETY CAUTIONS

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2½ GALLONS
(9.46 LITERS)
EPA Reg. No. 10182-103

DIRECTIONS FOR USE

RECOVERY STATEMENTS

STORAGE AND DISPOSAL

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Toxicological Significance of the Following Metabolites of Paraquat: Monoquat, QINA, Monopyridone, Dipyridone, and Methylamine (See Table 1 for Structures)

TB Project No.:
TOX Chem. No.: 634

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

TO: Robert J. Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (TS-767C)

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

and

William Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

This is a reply to the memorandum from RCB, dated April 17, 1987 (attached).

Current scientific literature and data submitted by the registrants indicate that unchanged paraquat, and not the above metabolites, is the only compound of toxicological concern for the following reasons:

I. Following oral administration of paraquat to cows, goats, pigs, and hens, the concentrations of the above metabolites in milk and/or tissues were too small to be of toxicological

significance, as follows (See RCB Chapter for the Paraquat Registration Standard; selected pages attached):

A. In one study with cows (MRID 00114422; dose: 233 ppm), total radioactivity recovered in feces, urine, and milk over the 9 days of feeding ^{14}C-methyl-labeled paraquat dichloride was 95.6%, 0.7%, and 0.0032%, respectively, of the administered dose. Of the radioactivity detected in milk (highest concentration was equivalent to 0.005 ppm expressed as paraquat ion), 14% was associated with unchanged paraquat, 8% with monopyridone, 19% with monoquat, and 28% with lactose. It was suggested, but not identified, that the uncharacterized radioactivity might have been dipyridone of paraquat.

Of the radioactivity recovered in urine, about 40% was attributed to QINA and monopyridone and dipyridone of paraquat, and the remainder to unchanged paraquat.

Feces contained more that 95% of the radioactivity as unchanged paraquat (Attachment A, pages 17 and 18).

B. In a study with goats (MRID 00028597; dose: 103 ppm), the highest radioactivity in milk was equivalent to 0.0092 ppm, expressed as paraquat ion, after 7 days of feeding ^{14}C-ring-labeled paraquat dichloride. Of that concentration, 75.5% was unchanged paraquat and the remaining 24.3% was uncharacterized.

Monopyridone of paraquat and monoquat were the only metabolites identified in 2 of the 10 different tissues examined (Attachment A, page 24). Liver contained radioactivity equivalent to 0.56 ppm of paraquat ion. Of that concentration, 48.1% was associated with unchanged paraquat, 3.2% with monopyridone, 3.4% with monoquat, and the remaining radioactivity was uncharacterized.

Peritoneal fat contained radioactivity equivalent to 0.03 ppm of paraquat ion. Of that concentration, 49% was attributed to unchanged paraquat, 6.5% to monoquat and the remainder was uncharacterized.

C. In studies with pigs (MRID 00028598 and 00028599; dose in each study: about 48 ppm), of the 10 different tissues examined, only liver contained a metabolite (monoquat) after 7 days of feeding either ^{14}C-methyl-labeled or ^{14}C-ring-labeled paraquat (Attachment A, pages 25 and 26). In each study, liver contained radioactivity equivalent to 0.20 ppm of

paraquat ion. Of that concentration, 69.6% or 73.0% was associated with unchanged paraquat and 3.6% or 7.0% with monoquat. The remaining radioactivity was uncharacterized.

D. In a study with hens (MRID 00028596; dose: about 30 ppm), 99% of the administered radioactivity was recovered in feces after 10 days of feeding ^{14}C-ring-labeled paraquat dichloride. Of that radioactivity, 97% was unchanged paraquat, 0.25% monopyridone of paraquat, and 0.4% monoquat (Attachment A, pages 27 and 28).

The remaining radioactivity (1.0%) was distributed throughout the tissues. Of the eight tissues examined, including eggs, a metabolite (monoquat) was identified only in the liver and kidneys. Liver contained 80.1% of the radioactivity as unchanged paraquat, and 3.6% as monoquat, whereas 16.3% was uncharacterized. Kidneys contained 86.0% of the radioactivity as unchanged paraquat and 4.1% as monoquat, whereas 9.9% was uncharacterized.

II. Toxicology Branch has a limited amount of toxicity data and information on these metabolites, but available data indicate that the above metabolites possess little biological activity of concern, as is indicated below:

A. Acute and subchronic toxicity of QINA:

Acute oral LD_{50} > 5000 mg/kg; rat (5);

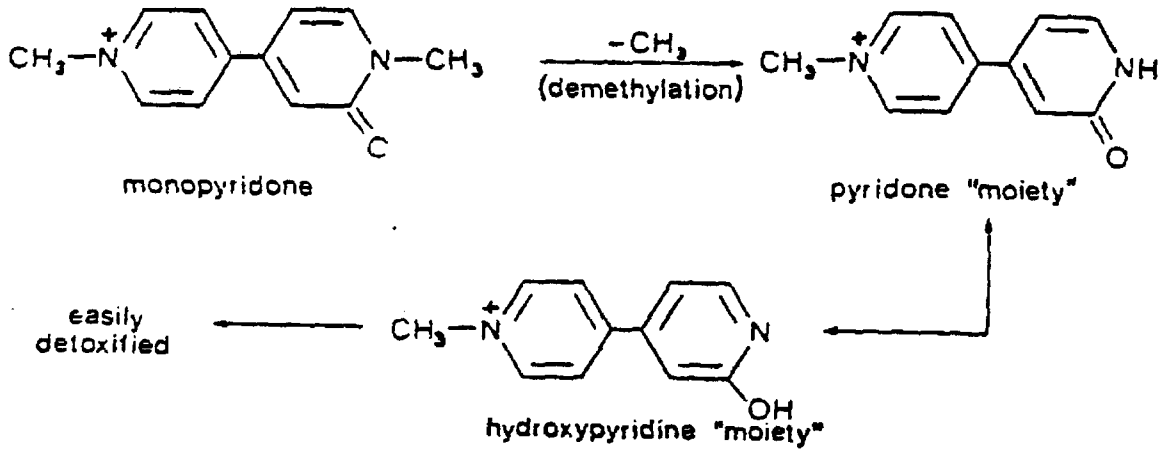
Dose levels of 5000 to 20,000 mg/kg were not toxic in a 90-day rat feeding study (1, page 30).

B. The subcutaneous lethal dose for methylamine was 2500 mg/kg; mouse (2).

C. Monoquat has very little herbicide activity and apparently very little mammalian toxicity (3; page 165). In in vivo and in vitro studies with ^{14}C-methyl-labeled paraquat dichloride, monoquat did not affect several metabolic reactions of rat liver mitochondria (4). Only intact paraquat altered these reactions.

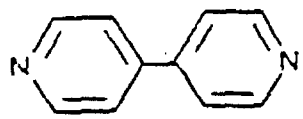
D. Monopyridone of paraquat would be expected to be less toxic than paraquat because, following demethylation of the pyridone-containing portion of the molecule, the resulting pyridone moiety would be in equilibrium with a hydroxypyridine moiety, making

the latter easily detoxified by conjugation through the hydroxyl group. This sequence of reactions appears below.



The above reasoning applies also to the dipyridone of paraquat. This compound would be expected to be less toxic than monopyridone of paraquat because two hydroxyl groups would be available for detoxification by conjugation.

E. The presence of radioactive galactose in cow's milk indicates that some of the ^{14}C-methyl-labeled paraquat was demethylated, probably by microorganisms in the gut, and the methyl groups were incorporated into many organic compounds, including galactose. In this case, paraquat contributed methyl groups to the "metabolic pool" for the synthesis of biological compounds. The demethylated paraquat, known as 4,4'-bipyridyl, has no pesticidal activity and is not toxic (4).



4,4'-bipyridyl

It should be noted that the above metabolites are not presently regarded as true metabolites, that is, those formed enzymatically in the liver or other organs, or by the plant enzymatic systems. Rather, they are regarded as photodegradation products and products of microbial degradation on soil surfaces and in the GI tract of animals and fowls (3, page 175; 5, 6). When paraquat is used agriculturally as a defoliant or desiccant, these products can be ingested by domestic animals in the feed and then they can be absorbed from the GI tract and distributed throughout the animal body.

In conclusion, Toxicology Branch does not, at this time, intend to require any additional toxicity tests on these metabolites, due to their low residue levels in food and their low levels of biological activity. For the same reasons, Toxicology Branch does not believe that there is any need to include these metabolites in the tolerance expression for paraquat.

References

(1) World Health Organization (WHO); Paraquat and Diquat, Environmental Health Criteria 39 (Geneva 1984); page 29.

(2) Merck Index, Tenth Edition (1983); page 5891.

(3) Summers, L.A. The Bipyridinium Herbicides (1980) Academic Press.

(4) Locke, K.K. (1977) In vitro and in vivo effects of paraquat on rat liver mitochondria. In Biochemical Mechanisms of Paraquat Toxicity, Anne page Autor (ed.). New York, Academic Press, pages 93-115.

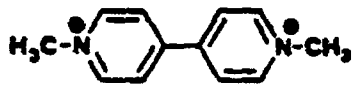
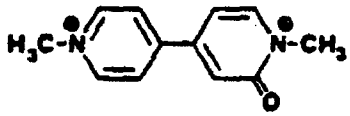
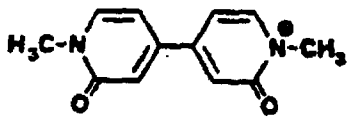
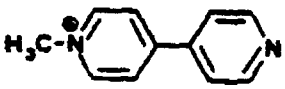
(5) Bus, J.S.; Praeche, M.M.; Cagen, S.Z.; Posner, H.S.; Eliason, B.C.; Sharp, C.W.; Gibson, J.E. (1975) Fetal toxicity and distribution of paraquat and diquat in mice and rats. Toxicol. Appl. Pharmacol. 33, 450-460.

(6) Funderburk, H.H. (1969) Diquat and paraquat. In Degradation of Herbicides, pageC. Kearney and D.D. Kaufman (eds.). New York, Marcel Dekker, Inc., pages 283-298.

(7) Menzie, G.M. (1974) Paraquat. In Metabolism of Pesticides, Office of Environmental Assistance, Special Scientific Report--Wildlife #184. Washington, DC, pages 172-176.

Attachments

Table 1. Paraquat and its degradates and metabolites.

CODE	STRUCTURE	CHEMICAL NAME	ABBREVIATION
I		1,1'-dimethyl-4,4'-bipyridinium ion	Paraquat
II		4-carboxy-1-methyl pyridinium ion	QINA
IIIp	$CH_3NH_3^{\oplus}Cl^{\ominus}$	methylamine hydrochloride	Methylamine
IVA		1,2-dihydro-1,1'-dimethyl-4,4'-bipyridylium ion	Monopyridone of Paraquat
VA		1,1'-dimethyl-4,4'-bipyridyl-2,2'-dione	Dipyridone of Paraquat
VIA		1-methyl-4,4'-bipyridiylium ion	Monoquat

P- Found in plants only. A- Found in animals only.

Attachment A

Pages from RCB Paraquat Registration Standard chapter

the activity is concentrated in the tips and peripheries of the leaves. Based on the data from the previous experiment which suggest that ^{14}C uptake by seedlings grown in treated soil might largely be due to the use $^{14}CO_2$ released from the soil itself, we conclude that the residues given in Table 4 are upper limits, and that actual residues of paraquat and QINA are less than indicated.

In addition to the studies discussed above, Chevron Chemical Co. (MRIDs 00065602 and 00065604) also submitted two published review articles concerning degradation, uptake, and mode of action of paraquat in plants. Because these are review articles, they contain no data. However, they support and extend the conclusions reached by the studies discussed above.

The nature of the residue in plants is adequately understood. Paraquat is not measurably metabolized by plants. It is degraded by ultraviolet light into QINA, which undergoes further degradation to methylamine hydrochloride. No additional data are required.

NATURE OF THE RESIDUE IN ANIMALS

Conclusions:

The metabolism of paraquat [1,1'-dimethyl-4,4'-bipyridinium ion] in animals is adequately understood. The terminal residue of concern is considered to be paraquat per se. In addition however, to the parent molecule the metabolites 1,2-dihydro-1,1'-dimethyl-4,4'-bipyridylium ion (monopyridone of paraquat, IV), and 1-methyl-4,4'-bipyridylium ion (monoquat, VI) have been identified in milk and in the liver of goats, pigs, and poultry. Also, the monopyridone of paraquat, 4-carboxyl-methylpyridinium ion (QINA, II), and 1,1'-dimethyl-4,4'-bipyridyl-2,2'dione (dipyridone of paraquat, V) have been found in urine. [Refer to Table 1 on page 3a for a depiction of the molecular structure of paraquat and its metabolites.] The percentages of each of these metabolites as they occur in tissues, eggs and milk are given in Tables 5,8,9,10, and 11 (Note: All of the radioactivity observed in egg yolk was characterized as paraquat.).

TOX Branch should be apprised of the fact that the metabolites listed above occur in animal commodities along with paraquat. If TOX concludes that any of these metabolites are of concern, additional methodology as well as revision of the tolerance regulations for meat, milk, poultry and eggs will be required.

References (used):

00028596. Hendley, P.; Leahey, J.P.; Spinks, C.A. 1976. Paraquat: Metabolism and Residues in Hens: AR 2676A. (Unpublished study received Mar. 25, 1980 under 239-2186; prepared by ICI, submitted by Chevron Chemical Co.; CDL:099330-B.)

00028597. Hendley, P.; Leahey, J.P.; Spinks, C.A.; et al. 1976. Paraquat: Metabolism and Residues in Goats: AR 2680A. (Unpublished study received Mar 25, 1980 under 239-2186; prepared by ICI, submitted by Chevron Chemical Co.; CDL:099330-C.)

00028598. Leahey, J.P.; Hendley, P.; Spinks, C.A. 1976. Paraquat: Metabolism and Residues in Pigs Using ^{14}C-Methyl Labelled Paraquat: AR-2694A. (Unpublished study received Mar. 25, 1980 under 239-2186; submitted by Chevron Chemical Co.; CDL:099330-D.)

00028599. Spinks, C.A.; Hendley, P.; Leahey, J.P.; et al. 1976. Paraquat: Metabolism and Residues in Pigs Using ^{14}C-Ring Labelled Paraquat: AR 2692A. (Unpublished study received Mar. 25, 1980 under 239-2186; prepared by ICI, submitted by Chevron Chemical Co.; CDL:0993330-E.)

00089748. Stevens, M.A.; Walker, G.H.; Walley, J.K. 1964. The Excretion of ^{14}C-Paraquat by the Cow: Report No. THR/164. (Unpublished study recieved Aug 30, 1965 under 239-1994; prepared by Imperial Chemical Industries, Ltd., England, submitted by Chevron Chemical Co.; CDL:050874-E.)

00114414. Chevron Chemical Co. 1967. Name, Chemical Identity and Composition of the Pesticide Chemical: Paraquat. (Compilation; unpublished study received Apr. 3, 1967 under 7F0592; CDL:092880-A.)

00114422. Chevron Chemical Co. 1975. The Results of Tests on the Amount of Residue Remaining, Including a Description of the Analytical Method Used: Paraquat. (Compilation; unpublished study received Feb. 24, 1975 under 5F1598; CDL:094362-B.)

00117783. Chevron Chemical Co. 1970. The Results of Tests on the Amount of Residue Remaining, Including a Description of the Analytical Methods Used: Paraquat. (Compilation; unpublished study received June 17, 1970 under 0F0986; CDL:091698-B.)

References (not used):

[The following references are duplicates of references cited above, or are irrelevant to animal metabolism.]

00028595. Chevron Chemical Co. 1976. Paraquat Residue Tolerance Petition No. 7F1910 (Dry Beans): Part 1 (Metabolism and Residue Studies in Hens, Goats and Pigs). Summary of studies 099330-D through 099330-E. (Unpublished study received Mar. 25, 1980 under 239-2186; CDL:099330-A.)

00036296. Daniel, J.W.; Edwards, M.J.; Slade, P.; et al. 1971?. Milk Residues Arising from the Ingestion of ^{14}C-Paraquat by the Cow: Report No. AR 2282 A. (Unpublished study received Feb. 1, 1975 under 5F1598; prepared by Imperial Chemical Industries, Ltd., submitted by Chevron Chemical Co.; CDL:095986-K.)

00036297. Leahey, J.P.; Hemingway, R.J.; Davis, J.A.; et al. 1972. Paraquat: Metabolism in a Cow: Report No. AR 2374 A. (Unpublished study received Feb. 1, 1975 under 5F1598; prepared by Plant Protection, Ltd. in cooperation with Veterinary Surgery, submitted by Chevron Chemical Co.; CDL:095986-N.)

00081830. Stevens, M.A.; Walker, G.H.; Walley, J.K. 1964. The Excretion of ^{14}C-Paraquat by the Cow: Report No. IHR-164. (Unpublished study received Feb. 23, 1965 under 5G0440; prepared by Imperial Chemical Industries, Ltd., England, submitted by Chevron Chemical Co.; CDL:090478-I.)

Discussion of the Data:

Cows: Chevron Chemical Co. (MRID 00114422) submitted data prepared by Plant Protection, Ltd., concerning metabolism of ^{14}C-methyl-labeled paraquat dichloride in a cow. Paraquat was administered orally to a 475 lb cow in a packet containing 5.41 g unlabeled paraquat and 3.91 g labeled paraquat, for an equivalent of 233 ppm paraquat in the the diet. Urine and feces were collected daily, and milk was collected twice daily (4:30 pm and 7:30 am) for nine days. Total radioactivity in the samples was determined by liquid scintillation counting. Samples were fractionated by acid extraction and chromatography, and the components of the fractions determined by chromatography or reverse isotope dilution. Total radioactivity recovered in the feces, urine, and milk over the nine days of the experiment was approximately 96% of the original dose. Feces contained 95.6%, urine 0.7%, and milk 0.0032% of the dose. Total ^{14}C-activity (expressed as paraquat ion equivalents) in the milk was greatest (0.005 ppm) the day after dosing, and decreased daily thereafter. Chromatography and reverse isotope dilution (Table 5) characterized 60 to 80% of the total radioactivity present in the milk samples collected 1 to 3 days after dosing. Paraquat accounted for about 14% of the activity, the monopyridone of paraquat (IV) about 8%, and monoquat (VI) about 19%. Radiolabeled lactose, however, accounted for about 28% of the activity.

The authors suggest that the incorporation of radioactivity into lactose results from the demethylation of paraquat to give monoquat, and the uptake of the labeled methyl group in the formation of lactose. They also suggest that the uncharacterized portion of the radioactivity in the milk might be the dipyridone of paraquat (V), but offer no evidence to support this supposition. Of the radioactivity in the feces, more than 95% was identified as paraquat, but the rest was uncharacterized. In the urine, as much as 40% of the activity found was identified as metabolites II, IV, and V. The proportion of paraquat in the urine decreased from 90% on day 1 to 62.5% on day 5. (40 % of 0.7 % radioactivity recovered in milk)

A second study, prepared by Imperial Chemical Industries, Ltd. (ICI) and submitted by Chevron Chemical Co. (MRID 00114422), concerns the metabolism of ^{14}C-methyl-labeled paraquat dichloride in cows. Two cows were dosed for three days with 4 g [^{14}C]paraquat at a specific activity of 2.3175 µCi for an equivalent dose of 100 ppm paraquat in the diet. The doses were administered as a liquid via a stomach tube. Milk and urine samples were collected twice daily for six days before the start of dosing and continued for six days posttreatment. Total ^{14}C-residues (expressed as paraquat ion equivalents) were determined by liquid scintillation counting. Results of the radioactivity analysis of the milk are given in Table 6. Colorimetric analysis of the milk from an unspecified sample interval detected no paraquat at a sensitivity of 0.005 ppm, suggesting, therefore, that a large proportion of the radioactivity was due to metabolites. A similar result was obtained in the urine analysis; as little as 2% of the radioactivity in some samples was parent compound. No attempts were made to further characterize the residues in milk or urine.

02 to ^{14}C-galactose, since methyl-labeled paraquat was used.

Table 5. Percentage Composition of radioactive compounds in daily milk samples.

Compound	Day 1	Day 2(a.m.)	Day 3(a.m.)
% Paraquat	15	17.5	9
% Monopyridone of of paraquat	3	18	10
% Monoquat [a]	15	17.5	25
% Lactose [b]	27.5	27.5	28
% Total Daily Radioactivity Identified	60.5	80.5	72

[a] Since monoquat has lost one of the two original radioactive carbons, the residue in ppm will be double that for paraquat, when the two compounds are present at the same % of the total radioactivity.

[b] These results are based on milk containing 4% lactose. This is a normal lactose content and in agreement with 20 g crude lactose from 500 ml milk.

Table 6. Paraquat ion equivalents in milk (ppm) determined by radioactivity analysis.

	Day 1 Dose		Day 2 Dose		Day 3 Dose		Day 4		Day 5	
	am	pm	am	pm	am	pm	am	pm	am	pm
Cow 1	0	0	0.005	0.005	0.009	0.009	0.007	0.010	0	0
Cow 2	0	0	0	0.008	0.007	0.005	0.008	0.009	0	0

A third cow study, prepared by ICI, was submitted by Chevron Chemical Company (MRID 00089748). Each of three cows received a single oral dose of unlabeled paraquat dichloride (4 g) and ^{14}C-methyl-labeled paraquat dichloride (90 mg, 0.8 µCi) in one half pint water. Milk was collected once on the day of the dose and twice daily thereafter for seven days. Radioactivity in the milk was determined by liquid scintillation counting. Concentration of ^{14}C-residues expressed as ppm paraquat are given in Table 7. Total ^{14}C-residues were highest on the day after dosing in cows 913 and 1155, but were highest on the second day after dosing in cow 1132. No attempt was made to characterize the activity further. Cows 913 and 1132, used in the study just described, had been used two months earlier in a study of diquat metabolism. Cow 913 was used in a total of five experiments involving dosing with radiolabeled diquat and paraquat. In addition to the above study, the cow also was used in another ICI study submitted by Chevron (MRID 00117783) with ^{14}C-ring-labeled paraquat dichloride administered as a single dose of 4 g containing 0.7 µCi activity. Milk was collected and analyzed as described above. Total ^{14}C-residues were highest on the day following dosing (0.0173 ppm) and declined irregularly to nondetectable (<0.001 ppm) by day 7. No attempt was made to

characterize the residues.

The above studies (MRIDs 00114422, 00089748, and 00117783) demonstrate that a large percentage (>96%) of an administered dose of paraquat is excreted in the feces (>95%) and urine (<1%) within a few days after dosing ends. Much less than one percent of the dose is secreted in milk. Only about 84% of the administered dose is eliminated in the original form; the rest is either metabolized or remains unaccounted for. In milk, 20 to 40% of the radioactivity has not been characterized. Paraquat comprised about 14%, the monopyridone of paraquat about 8%, and monoquat about 19% of the the radioactivity found in milk; 28% of the activity is present in lactose. No data were submitted concerning the nature of the residues in tissues.

Hwc Goats: Chevron Chemical Co. (MRID 00028597) submitted a study prepared by ICI concerning metabolism of ring-labeled [^{14}C]paraquat dichloride in goats. One lactating goat was fed radiolabeled paraquat in its diet for seven days at a rate of 206.6 mg/day, an equivalent of 103 ppm paraquat in the diet. Feces and urine were collected daily, and milk twice daily from two days before the start of dosing to the end of the experiment. The treated goat and an untreated control were killed four hours after the last dose was administered and the liver, kidney, hindquarter and forequarter muscle, peritoneal and subcutaneous fat, heart, blood, lungs, brain, and the stomach, rumen, intestines and their contents were sampled. All samples were assayed for radioactivity by liquid scintillation counting. Subsamples of milk and tissues were analyzed for paraquat and metabolites by reverse isotope dilution. Slightly more than 50% of the administered radioactivity was excreted in the feces before the goat was killed; 2.4% was excreted in the urine; 33.2% was found in the digestive tract and its contents upon slaughter. Radioactivity in the milk increased daily to a high of 0.0092 ppm paraquat ion equivalent 4 hours before slaughter. Reverse isotope dilution of this sample indicated that 75.7% of the total ^{14}C-residue was paraquat, but the remaining 24.3% was uncharacterized. The radioactive residues in tissues and the percentage of total ^{14}C-residues

Table 7. Concentration of ^{14}C-residues (expressed as ppm paraquat) in the milk of dairy cows after dosing.

	Dose Paraquat (ppm)	Day 1 Dose p.m. ↓	Day 2 a.m. p.m. ↓	Day 3 a.m. p.m. ↓	Day 4 a.m. p.m. ↓	Day 5 a.m. p.m. ↓	Day 6 a.m. p.m. ↓	Day 7 a.m. p.m. ↓	Day 8 a.m. p.m. ↓
Cow 913	6.99	-0.0010[a]	0.0110 0.0374	0.0110 0.0116	0.0037 0.0022	0.0004 0.0023	0.0013 -0.0007[a]	0 -0.0006[a]	-0.0010[a] -0.0006[a]
Cow 1132	8.02	0.0019	0.0021 0.0064	0.0032 0.0090	0.0031 0.0014	0.0065 0.0016	0.0003 0.0021	0.0011 0.0014	0.0034
Cow 1155	8.26	-0.0013[a]	0.0091 0.0463	0.0232 0.0325	0.00130 0.0075	0.0073 0.0062	0.0047 0.0016	0.0041 0.0042	0.0011 0.0015

[a]In the published version of this report (MRID 00031838) negative values are explained as the result of a slight difference in color between a particular milk sample and a control milk sample.

identified as paraquat, compound IV, or compound VI are given in Table 8. High ^{14}C-residues in lung tissue was attributed to contamination by stomach contents when the goat vomited as it was killed. Compound IV was present in the liver (3.2%) and compound VI was present in the liver (3.4%) and peritoneal fat (6.5%). Forty-five percent of the radioactivity in the liver and 44.5% in the peritoneal fat was uncharacterized.

Pigs: Chevron Chemical Company submitted two studies prepared by ICI concerning metabolism of paraquat by pigs. One study (MRID 00028598) used ^{14}C-methyl-labeled paraquat, and the other (MRID 00028599) used ^{14}C-ring-labeled paraquat. In each study, there was one experimental and one control pig. The experimental pig received radiolabeled paraquat in its diet twice daily for seven days at a rate of approximately 48 ppm paraquat/day in the diet. The pig that received ^{14}C-methyl-labeled paraquat was sampled for blood at hourly intervals after first dose to determine how soon after dosing peak radioactivity occurs in the blood. Feces and urine of all pigs were collected daily starting the day before dosing and continuing to the day of death. All pigs were killed two hours after the last dose was administered on the morning of the seventh day. The pigs were bled, and samples taken of the liver, kidneys, forequarter and hindquarter muscle, subcutaneous and peritoneal fat, heart, lungs, and brain. Samples were stored at -20 C until analyzed. Liquid scintillation counting was used to determine total radioactivity of samples, and reverse isotope dilution was used to characterize the activity in the tissues as parent compound or metabolite.

In the experiment with ^{14}C-methyl-labeled paraquat, it was determined that peak radioactivity in the blood occurred two hours after dosing. Because of this, the pigs were killed two hours after the last dose in both studies. At slaughter, 69% of the total ^{14}C-methyl dose and 72.5% of the ^{14}C-ring dose had been excreted in the feces, and 3.4% and 2.8%, respectively, had been excreted in the urine. The distribution of radioactivity in the tissues is presented in Tables 9 and 10.

Table 8. Radioactive residues in the tissues of a goat dosed with ^{14}C-paraquat at a rate equivalent to 100 ppm in the diet. The percentage of the residues identified as paraquat, compound IV and compound VI are given.

Tissues	^{14}C-Residues Expressed as ppm Paraquat Ion Equivalents (ppm)	% of Residues Identified as:		
		Paraquat	Comp. IV	Comp. VI
Heart	0.16	118	-	-
Brain	0.13	106	-	-
Liver	0.56	48.1	3.2%	3.4%
Kidney	0.74	94.5	-	-
Muscle (Fore-quarter)	0.08	90	-	-
Muscle (Hind-quarter	0.12	99.7	-	-
Blood	0.06	81.7	-	-
Fat (Peri-toneal)	0.03	49	-	6.5%
Fat (Subcuta-neous)	0.02	120.5	-	-
Lung	0.99-1.92 [a]	101.5	-	-

[a] Range of five determinations.

The radioactivity in these tissues accounted for 6.9% and 5% of the administered ^{14}C-methyl- and ^{14}C-ring-labeled doses, respectively. Reverse isotope dilution revealed that in the ^{14}C-methyl study all or virtually all of the activity was present as parent compound in all tissues except liver; only 73% of the activity in the liver was parent, 7% was monoquat, and some was identified as the monopyridone of paraquat, but the error is

Table 9. Residues in the tissues of a pig dosed with ^{14}C-methyl labeled paraquat dichloride at 2.4 ppm/day for 7 days.

Tissues	^{14}C-Residues Expressed as Paraquat Ion Equivalents (ppm)	% of residues identified as		
		Paraquat	Monoquat (VI)	Monopyridone of Paraquat (IV)
Liver	0.20	73	7	0.6 ± 10
Kidney	0.46	109	-	-
Heart	0.12	104	-	-
Lung	0.12	105	-	-
Brain	0.02	108	-	-
Hindquarter Muscle	0.03	94	-	-
Forequarter Muscle	0.06	106	-	-
Peritoneal Fat	0.06	102	-	-
Sucutaneous Fat	0.02	115	-	-
Blood	0.07	104	-	-

so large as to make this result meaningless. In the ^{14}C-ring study, lower percentages of parent compound were identified in several tissues, notably the liver, heart, brain, and blood. Only liver was analyzed for metabolites, and was found to contain 3.6% monoquat. Twenty seven percent of the activity in the liver, 19% in the heart, 38% in the brain, and 29% in the blood remained uncharacterized.

Table 10. Residues in the tissues of a pig dosed with ^{14}C-ring labeled paraquat dichloride at 2.44 ppm/day for 7 days.

Tissues	^{14}C-Residues Expressed as Paraquat Ion Equivalents (ppm)	% of residues identified as Paraquat (I)	% of residues identified as Monoquat (VI)
Liver	0.20	69.6	3.6
Kidney	0.38	100.6	-
Heart	0.08	81.3	-
Lung	0.21	94.3	-
Brain	0.03	62.3	-
Hindquarter Muscle	0.05	92.6	-
Forequarter Muscle	0.05	94.9	-
Peritoneal Fat	0.01	105.7	-
Subcutaneous Fat	0.01	105.2	-
Blood	0.06	71.2	-

In both studies, approximately 20% of the administered radioactive dose was unaccounted for. It is possible that a large portion of this activity was present in the gastrointestinal tract and its contents, as suggested in one of the studies (MRID 00028599). In the goat metabolism study (MRID 00028597), 33% of the administered activity was found in the stomach, rumen, intestines and their contents. However, no data were presented in these studies to confirm this possibility.

Poultry and Eggs: Chevron Chemical Company (MRID 00028596) submitted a study prepared by ICI concerning the metabolism of paraquat in hens and eggs. Three hens received daily (10 a.m.) doses of 4.52 mg of ^{14}C-ring-labeled paraquat dichloride (0.247 Ci) administered in a gelatin capsule forced down the throat; this is equivalent to approximately 30 ppm paraquat/day in the diet. A fourth hen served as a control. Feces and eggs were collected daily. All hens were killed on the tenth day of the experiment, the dosed hens four hours after the final dose. Samples were taken of abdominal and subcutaneous fat, kidney, liver, heart, breast, and leg muscle, and gizzard. Samples were stored at -20 C until analysis. Total radioactivity of all samples was determined by liquid scintillation counting. Acid extraction and chromatographic partitioning were used to isolate fractions and identify parent and metabolites. Reverse isotope dilution was used to quantify the parent and metabolite content of tissues and eggs. By the end of the study, 99% of the administered radioactivity had been excreted in the feces. Paraquat accounted for 97% of the recovered radioactivity; the monopyridone of paraquat accounted for 0.25%, and monoquat accounted for 0.4%. Radioactive residues were found in all tissues examined. The largest proportions were found in the kidney, liver, gizzard, abdominal fat, and leg muscle, although the results for abdominal fat may be aberrant. One hen (#4) showed residues of 0.046 ppm paraquat ion equivalents, while the other two hens showed residues of 0.002 and 0.006 ppm.

The percentage of tissue residues identified as paraquat by reverse isotope dilution (Table 11) ranged from 80.1% to 98.1%. Monoquat was identified

in liver (3.6%) and kidney (4.1%). The proportions of residues not characterized in the tissues ranged from 1.9% to 17.4%.

Table 11. The percent of radioactive residues identified as paraquat and monoquat in hen tissues.

Please note on p. 27 that 99% of the administered activity was recovered in feces.

Tissue	% Paraquat	% Monoquat
Liver	80.1	3.6
Kidney	86.0	4.1
Leg Muscle	98.1	
Lung	86.0	
Heart	86.9	
Gizzard	97.9	
Abdominal Fat (hen #4)	82.6	

The radioactive residues in the yolks and albumen of the eggs of individual birds increased irregularly from nondetectable (<0.001 ppm paraquat ion equivalent) on the first two days of the study to a high of 0.1812 ppm in the yolk and 0.0014 ppm in the albumen on day 8, the last day for which eggs were available. The yolk represented 36.3% of the edible portion of the egg, giving an equivalent 0.067 ppm paraquat equivalents in the whole egg. Reverse isotope dilution identified 102.8% of the radioactive residue in the yolk as paraquat. No analysis of the albumen was reported.

Rats: Chevron Chemical Company submitted a published study prepared by ICI (MRID 00114414) concerning the metabolism of paraquat in rats. Laboratory rats received a single dose orally by intubation or subcutaneously by injection, of ^{14}C-methyl-labeled paraquat dichloride or ^{14}C-methyl-labeled paraquat dimethosulphate. Dosed rats were placed in individual metabolism cages fitted with urine and feces collectors, cooled with dry ice and protected from light. The report points out that these precautions

were necessary to prevent progressive loss of paraquat from the samples. Bile was sampled from anesthetized rats by direct removal from the bile duct. Total radioactivity was determined by liquid scintillation counting. Paraquat also was determined chemically by colorimetry. The excretion of radioactivity in the feces and urine is presented in Table 12. Most of the orally administered dose of the dichloride form was excreted within two days, and about 93% to 96% was in the feces. Excretion of orally administered dimethosulphate generally took longer, and no more that 86%, and as little as 68%, was excreted in feces; 3-4 times more dimethosulphate activity was excreted in the urine compared with dichloride activity. A similar difference in the excretion of the two forms of paraquat is seen in Table 13 (which also confirms the radioactive results with colorimetric analyses). The authors attribute these differences to different strains of rats used in the study (Table 12). Table 13, however, does not indicate that different strains were used, and the obvious experiments to confirm this view were not performed. It is equally likely that the differences are due to the chemical differences in the compounds, or to a combination of both factors.

The last three columns of Table 12 present the difference in percent paraquat residues determined by the two methods as the percent metabolized. However, the authors claim that the consistent difference obtained by the two techniques may not indicate metabolism after all. The urine of rats dosed subcutaneously with 12.5 ppm or 13.2 ppm ^{14}C-paraquat dichloride was analyzed 24 hours after dosing by both radioactivity and colorimetry methods. The two methods gave very similar results (radioactivity method, 80.5%-98% excreted in urine; colorimetry method, 79.5%-96% excreted in urine). (Paraquat dichloride administered subcutaneously is excreted very rapidly in the urine, which agrees with the result for paraquat dimethosulphate administered subcutaneously.) In one case, the colorimetric method gave higher recovery than the radioactivity method. The authors, therefore, suggest that the differences are due to uptake in the gut of degradation products of orally ingested paraquat, rather than metabolism. Comparison of radioactive and colorimetric determinations of paraquat in

Table 12. Excretion of radioactivity by rats dosed with ^{14}C-methyl labeled paraquat dichloride or ^{14}C-methyl labeled paraquat dimethosulphate.

Compound	Dose (Mg/Kg)	Route	Day	% of Radioactivity Recorded 1	2	3	4	Total %	
a) Paraquat Dichloride	4	oral	urine	5.0	1.0	0	-	6.0	102.0
			feces	75.0	20.0	1.0	0	96.0	
	6	oral	urine	5.0	0.6	0	-	5.6	99
			feces	38.0	51.0	4.0	0	93.0	
b) Paraquat Dimetho-sulphate	2.5	oral	urine	16.0	2.0	0.7	0.4	19.1	105
			feces	3.7	0	66.0	16.0	85.7	
	24	oral	urine	16.2	5.1	1.0	0.6	22.9	91
			feces	16.5	19.0	30.0	3.0	68.5	
	24*	oral	urine	12.6	3.3	0.5	0	16.4	97
			feces	17.0	63.6	0.4	0	81.0	
	24*	oral	urine	16.0	4.2	0.6	0	20.8	98
			feces	0	54.0	19.0	3.8	76.8	
	23*	subcu-	urine	93.0	2.0	1.1	0	96.1	12
		taneous	feces	8.5	6.5	0.7	0	15.7	
	21*	subcu-	urine	69.5	2.2	1.3	0	73.0	87
		taneous	feces	10.5	2.4	1.3	0	14.2	

A - Strain 1; B - Strain 2; * - Female rats

the feces of a rat dosed orally at 0.7 mg/kg showed a difference of 26.3% on the first day and 39.3% on the second. However, when paraquat was incubated for 21 or 69 hours in a homogenate of rat caecum that was either fresh or had been heated in boiling water bath for 3 minutes, much

Table 13. Analysis of urine from rats dosed orally with ^{14}C-methyl-labeled paraquat dichloride or ^{14}C-methyl-labeled paraquat dimethosulphate, using radioactivity and colorimetric analyses.

Compound	Dose (ppm)	% Dose Excreted Daily				% Dose Metabolized		
		Radioactivity		Colorimetry				
		Day 1	2	Day 1	2	Day 1	2	Total
Paraquat Dichloride	50	5.7	8.6	5.2	7.3	0.5	1.3	1.8
	50	5.2	3.4	4.5	2.9	0.7	0.5	1.2
	50	8.4	4.3	7.0	3.6	1.4	0.7	2.1
Paraquat Dimetho-sulphate	22	16.3	5.2	12.1	4.3	4.2	0.9	5.1
	22	16.2	5.1	11.8	5.2	4.4	0	4.4
	22	14.2	1.8	12.6	1.7	1.6	0.1	1.7

greater loss of paraquat occurred in the fresh homogenate (38 to 43%) than in the heat-treated homogenate (4 to 11%). The authors conclude that most of the degradation of paraquat was due to the activity of bacteria in the gut. No radioactivity was discovered in the bile of three treated rats, but the dose administered (0.5 mg/kg) was far less than was used in the excretion studies, and may not have been sufficient to permit detection. No attempt was made to characterize the metabolites, or degradation products of paraquat or their distribution in the tissues.

This study contributes little to an understanding of the metabolism of paraquat dichloride, and is reviewed primarily because of the possible significance of the different rates of excretion of paraquat dichloride and paraquat dimethosulphate.

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