See pp. 7 & 8 This is a review of oncogenic initiation studies for the potato petition. (Section is referencing these data in The in Response to the Reg. Std.

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

MEMORANDUM

DATE: MAR 23 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Request for Tolerance for Pesticide Diquat in or on Potatoes and Other Products, Resulting From the Preharvest Use of Diquat 2 Spray on Potato Vines.

PP 9F2265 and FAP 9H5239 Accession Nos. 098972, 098973 and 098976
Reg. No. 239-2247, 239-1663.
Caswell No. 402

Proposed Tolerances:

1. Potatoes	0.1 ppm
2. Potatoes, processed (includes pototo chips)	0.2 ppm (FAT)*
3. Potato waste, processed, dried	1.0 ppm (FAT)
4. Milk, eggs, meat, fat and meat byproducts of poultry	0.01 ppm*
5. Meat, fat, and meat by-products of cattle, goats, hogs, horses and sheep	0.02 ppm

* RCB requested that the tolerances proposed under 2. and 4. be changed to 0.5 ppm and 0.02 ppm, respectively.

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THRU: William L. Burnam, Acting Branch Chief
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KKL 3/10/81
MLQ, 3/23/81
for C.C. C.J. Aluisio 3/23/81

Petitioner: Chevron Chemical Company
Ortho Division
Richmond, California

Recommendations:

Adequate toxicity data are available to support conditional registration of Diquat 2 Spray on potato vines. All of the tolerances (published, pending and currently proposed) will use up 30.26% of the ADI. The following studies will be required for permanent registration:

1. Both acute and subchronic (21 days) inhalation toxicity studies, with technical diquat dibromide as well as formulated product (Diquat 2 Spray) as test material.

2. Primary skin irritation study, using undiluted formulated product and abraded skin of the test animals.

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3. An acute dermal toxicity study, using abraded skin and technical product.

4. Primary eye irritation study, using both technical diquat dibromide and Diquat 2 Spray as test materials.

5. Teratology study with species other than rats because two teratology studies are required. The already submitted study with rats is acceptable.

6. Two-generation reproduction study in which both parents and offsprings are fed diquat.

7. Mutagenicity studies.

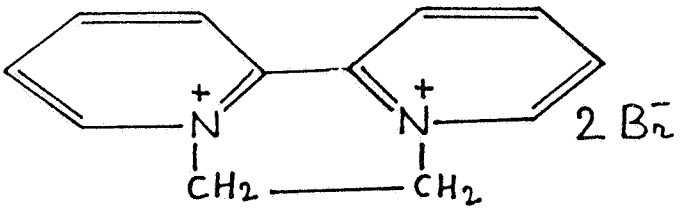
Substance Identification:

Chemical Name: 6,7-Dihydrodipyrido (1,2-a: 2', 1'-c)pyrazinediium dibromide.

Synomyms: Diquat, Reglone, FB/2

Purity of Technical Material: 95-100%

Structure:



Other physical/chemical properties: Pale-yellow powder, soluble in water (70% at 20° C), stable in acid or neutral media; a dipyridylium compound.

Referenced Petitions:

7F 0594; 4/3/67
3H 5022; 11/6/72
4G 1470; 2/15/74

Formulation: Diquat 2 Spray

Active ingredients: (% by weight)

Diquat dibromide	35.30% (minimum)

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Inert ingredients:

[redacted]

[redacted] which "are not likely to produce a residue problem" (Alfred Smith, RCB; 3/18/80).

Proposed Uses:

The formulation will be used for preharvest desiccation of potato vines as an aid in harvesting. An aerial or ground application is proposed at 0.25 lb. a.i./acre. A second application may be used if necessary, allowing a minimum of 5 days between applications. The application will be made at least 7 days before harvest (7-days PHI). The spray mix will contain 8 to 16 oz. of ORTHO X-77 Spreader (non-ionic) per 100 gals. of mix. The ingredients of X-77 are cleared for use under 180.1001.

Toxicity Studies:

Toxicity studies submitted by reference are summarized in Attachment I. Both detailed reviews and summaries of the currently submitted studies constitute Attachment II.

Pharmacology, Metabolism, and Fate or Residues:

These topics are discussed in detail in RCB review (Alfred Smith; 3/18/80). Diquat itself is a compound of toxicological concern.

Evaluation of ADI

Based on a NOEL of 0.5 mg/kg (10 ppm; 2-year rat feeding study; no cataracts observed at this level) and SF of 100, an ADI = 0.0050 mg/kg/day and a MPI = 0 3000 mg/day/60 kg person. Published, pending (TOX approved) and currently proposed tolerances use up 30.26% of the ADI, as is detailed below:

Tolerance	%ADI
Published	0.91
Pending	11.81
Current action	17.54
Total	30.26

(Printout attached)

INERT INGREDIENT INFORMATION IS NOT INCLUDED

RPAR Criteria:

Diquat appears to be very toxic by the inhalation route, but available studies do not permit conclusion whether or not RPAR criteria have been exceeded. New studies were, therefore, requested.

Summary:

Primary criterion of diquat toxicity is the production of cataracts in experimental animals. Low levels of diquat can also cause changes in the lung tissue, but properly conducted inhalation studies are lacking and are considered as toxicity data gap. Lacking also are the following studies:

1. Both acute dermal and skin irritation studies in which abraded skin of the test animals was exposed to diquat.

2. A multi-generation reproduction study in which not only parents but also offsprings were fed diquat.

3. A teratology study in species other than rats.

4. Mutagenicity studies.

The proposed regulation is supported by the following studies:

1. Acute (17)

   8 Oral feeding (rat, rabbit, mouse, dog, cow and hen).
   2 Intraperitoneal (rat, rabbit).
   2 Dermal (rabbit).
   1 Skin irritation (rat)
   2 Eye irritation (rabbit)
   1 Inhalation (rat).
   1 Subcutaneous injection (rat).

2. Subchronic (4)

   2 Dermal (rabbit).
   2 Inhalation (rat)

3. Long-Term (8)

   5 Chronic feeding (rat, dog).
   1 Reproduction (one-generation; rat).
   1 Teratology (rat).
   1 Oncogenic (mouse)

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All of these studies but five (acute oral and eye irritation, 2-year rat feeding, teratology and oncogenic studies) were conducted by Imperial Chemical Industries (ICI) during 1956-68. The remaining five studies were conducted by ICI during 1973-79. Only one study, a rat chronic feeding study dated 2/27/65 and as yet unvalidated, was conducted by IBT.

As far as the acute studies are concerned, 8 studies were classified as Core-Minimum Data and 9 as Core-Supplementary. Included in the latter category were the required dermal, skin irritation and inhalation studies. The two dermal studies, considered together, could be classified as Core-Minimum data, with a note that only intact skin was used. Dosage levels of only 10 and 20 mg were used in the skin irritation study, and the number of rats tested was not stated. The only acute inhalation study submitted, in which no toxic symptoms were observed, was conducted with only 2 rats, very low exposure level (23 ug diquat/L) and short exposures (15 or 30 min.).

As far as the subchronic studies are concerned, both inhalation studies were classified as Core-Supplementary. Data for one study were reported only as a short summary. However, noteworthy is a comment that 2.0 ug of diquat/L produced changes in rat lung tissue (details in Attachment II). According to another inhalation study, 1.06 ug of diquat/L, the only level tested, was a NOEL for rats, mice, guinea pigs and a dog. However, rabbits showed shallow breathing at that level. Visual observations for toxic signs were the only parameters evaluated in that study.

As far as the long-term studies are concerned, two 2-year rat feeding studies were classified as Core-Supplementary and Core-Invalid, respectively. In the first study, only 10 male and 10 female rats and one exposure level (500 ppm of diquat) were used. The second study contains many discrepancies and ambiguities which require clarification. This study was first submitted to EPA in 1977 and then resubmitted in 1979, and it was rejected on both occasions. However, another valid 2-year rat feeding study is available. The LD50/LC50 values and NOELs for Core-Minimum or Supplementary studies are summarized below:

Study	Animals	NOEL mg/kg	LD50/LC50 mg/kg	Test Material
Acute Oral	Rats	-	810	F
Acute Oral	Rats	-	421	T
Acute Dermal	Rabbits	-	> 500	T
Acute Inhalation	Rats	-	> 23 ug/L	T
Subchronic Dermal	Rabbits	20*	-	T
Subchronic Dermal	Rabbits	3.13*	-	T

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Subchronic Inhalation	Rats	> 1.0 ug/L but < 2 ug/L	T
Chronic Feeding Cataractogenic	Rats	0.5 (10 ppm)*	T
Chronic Feeding Cataractogenic	Dogs	1.7 (68 ppm)*	T
Reproduction	Rats	25 (500 ppm)**	T
Teratogenic	Rats	25 (500 ppm)**	T
Oncogenic	Mice	45 (300 ppm)**	T

T = Technical diquat dibromide.

F = Formulated product (19.3% diquat cation).

*.Lowest level tested

** Highest level tested.

OPP:HED:TOX: K.LOCKE:sb 1/6/81 X71511 TS-769 Rm. 824 CM 2 #2

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The Acute Oral Toxicity of Diquat Water Weed Killer

SOCAL 1396/37:67, 5/10/79

Accession No.
098073
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Experimental Procedures:

Sprague-Dawley rats, five male and five female per dose level, received Diquat Water Weed Killer (19.3% diquat cation) at the following levels: 0, 0.30, 0.45, 0.67, 1.0 and 1.8 g/kg of body weight. At the time of dosing, the males were 55-61 days old and weighed 208-269 g; the female were 73-79 days old and weighed 201-226 g. The dose levelof 0.30 g/kg was started six days after the other levels. Following the 14-day observation period, the rats were sacrificed and examined for gross pathological changes. The following organs and tissue were examined: heart, lungs, liver, stomach, small and large intestine, spleen, adrenals, kidneys, bladder, gonads, skin and fat. The LD50 and confidence limits were dtermined by the procedure of J. Berkson (Biometrika, 44:411-435, 1957).

Results

The mortality rate for male rats was 0, 0, 0, 20, 80 and 100% at dose levels of 0, 0.30, 0.45, 0.67, 1.0 and 1.8 g/kg, respectively. The corresponding values for female rats were 0, 0, 0, 100, 100 and 100%. Most of the deaths occurred within one or two days after dosing. Depression and decreased food intake were reported for all animals (male and female), but the controls. In the case of females, diarrhea, weakness and collapse were also observed in one or two animals at the highest two dosages. No gross pathological changes were observed that could be attributed to the test material.

LD50. (95% Limits)	Toxicity Category
Males 0.81 (0.44-1.5) g/kg	III
Females 0.60 (0.31-1.2) g/kg*	III

Core Category: Minimum

* With zero deaths at the two lowest levels and 100% deaths at the remaining three levels, it is impossible to determine a meaningful LD50 value according to B. Litt, Statistician, Toxicology Branch.

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S-960: The Eye Irritation Potential of CC 7019

SOCAL 901 A/22:36, 7/13/76

Accession No.
098973

Experimental Procedures:

One-tenth ml of CC 7019 (Diquat 2 Spray) was placed in the conjunctival sac of one eye in each of six male rabbits (New Zealand strain). The eyes were examined at one hour and at 1, 2, 3, 7, 10 and 14 days. (J. H. Draize et al., J. Pharmacol. Expt. Therap., 82:377-390, 1944).

Results:

There was no corneal opacity or iritis during the 14-day observation period. Moderate to severe conjunctival redness and discharge, and slight chemosis, were observed during the first seven days of the study. Slight conjunctival redness persisted through the 10th day of observation period and slight conjunctival discharge was still seen, in three rabbits, on the last day of the observation period. Except for this discharge, the eyes of the surviving rabbits appeared normal. One rabbit, which had severe diarrhea during most of the study, was found dead on the 14th day.

Toxicity Category: II.

Core Category: Minimum.

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Toxicity of Paraquat and Diquat Aerosols Generated by a Size-Selective Cyclone: Effect of Particle Size Distribution.

J. C. Gage. Brit. J. Industr. Med., 25:304-314, 1968. ICI

Accession No. 098973

Only about one page of this 10-page paper is concerned with diquat. Results are reported only as short summaries and data for individual animals are not presented.

Test Material:

Pure crystalline diquat dichloride was used in all of the studies.

Experimental Animals:

Rats, mice and guinea pigs were of the Alderley Park SPF strain. The body weight of rats in the single exposures was about 200 g, and in the repeated exposures 160-180 g. Mice weighed 25-30 g and guinea pigs, about 500 g. Rabbits (4 kg) were a cross between New Zealand White and California White. Beagle dogs (9-13 kg) were from the Alderley Park kennels.

I. Acute Study:

Two male rats were exposed to 23 ug/L of aerosolized diquat, one for 15 min. and the other for 30 min. The aerosol composition with regard to particle size was as follows: < 2.5 u, 12.9%; 2.5 u, 53%; 5 u, 31%; 10 u, 2.9%; and > 10 u, 0.2%.

There were no signs of toxic effects during or after the exposure.

Toxicity Category: Cannot be determined from this experiment.

Core Category: Supplementary, for the following reasons: too few animals, one low level and too short exposures were used.

II. Subchronic Study (A):

Rats, four males and four females, were exposed to 0.5 ug or 2.0 ug of diquat aerosol/L, for 15 daily 6-hour periods. The aerosol was composed of the following particles: < 2.5u, 48.5%; 2.5 u, 43%; 5 u, 6.3%; 10 u, 1.5%; and > 10 u, 0.9%.

Results:

Glucose, billirubin, hematology, urinalysis, weight gain, organ weight and histopathology were all normal at the 0.5 ug/L level. At the 2.0 ug/L level, the weight gain was "a little below normal" for both sexes. The lungs showed congestion, irritation, peribronchial lymphoid hyperplasia, slight perivascular edema and an excess of macrophages in the alveoli. All other tissues appeared normal.

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NOEL: 0.5 ug/L

Core Category: Supplementary, because too few rats were used, and data were reported only in the form of a short summary.

III. Subchronic Study (B)

The following species were exposed to an average concentration of 1.06 ug of diquat dichloride/L for 15 daily 6-hour periods: 4 male and 4 female rats, 5 male and 5 female mice, 4 male and 4 female guinea pigs, 2 female rabbits and one male beagle dog. The aerosol composition with regard to particle size was as follows: < 2.5 u, 68%; 2.5 u, 25.6%; 5 u, 2.2%; 10 u, 2%; and > 10 u, 1.5%.

All animals, except rabbits, remained in good condition during the exposure. There was also no deterioration in condition of any of the animals after the exposure. The rabbits had rapid, shallow breathing but recovered at the end of the experiment.

NOEL: Not determined in this study, but apparently > 1.06 ug/L, the only level used, for male and female rats, mice, guinea pigs and a male dog. For two female rabbits, NOEL = < 1.06 ug/L.

Core Category: Supplementary, for the following reasons:

1. It is not clear whether the animals were observed only visually for toxic symptoms or whether other parameters were also studied.

2. Only one exposure level and too few animals per level were used.

3. The results are reported only as a 2-sentence summary.