

MEMORANDUM:

SUBJECT: REVIEW OF PARAQUAT WORKER M/L/A BIOMONITORING STUDY

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THRU: Mark I. Dow, Ph.D., Section Head
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Please find below, the OREB review of:

DP Barcode: D215885

Pesticide Chemical Code: 061601

EPA Reg. No.: 10182-280

EPA MRID No.: 436442-01, 436442-02

1. Introduction:

Zeneca conducted this worker biomonitoring study to support label revisions for paraquat dichloride products related to personal protective equipment (PPE) required for mixers, loaders, and applicators. Paraquat dichloride is currently undergoing reregistration. This study entitled "Paraquat: Worker Exposure During Mixing, Loading, and Application of GRAMOXONE® EXTRA to Pecans Using Vehicle-Mounted Ground Boom Equipment" (MRID 436442-02) was performed by Zeneca Ag Products and authored by Deborah Meier. Accompanying the study was a packet of MOE calculations and analytical method validations (MRID 436442-01).

A. Background:

Paraquat dichloride is the active ingredient in the product Gramoxone Extra herbicide. Gramoxone Extra is formulated as a soluble concentrate and is used as a weed, grass and harvest aid herbicide. It contains 37% paraquat dichloride and is a restricted use pesticide.

The toxicological end-point of concern for short- and intermediate-term worker exposure is a maternal and developmental NOEL of 1 mg/kg/day based on a 21 day rat study (Less Than Lifetime Meetings, 7/25/95 & 10/10/95). Paraquat (end-use product 34.4% paraquat cation) is a toxicity category I compound for acute dermal and primary eye irritation, category II compound for acute oral toxicity, category III compound for primary dermal irritation, and it is not a skin sensitizer. For inhalation toxicity paraquat (crystalline paraquat dichloride 99.9% pure) is a category I compound.

B. Purpose:

This review evaluates the study mentioned above to determine if it meets Subdivision U Guidelines for applicator exposure monitoring.

II. Detailed Considerations:

Project Summary

Gramaxone Extra herbicide was applied at a high label application rate by ground boom spray to pecan orchards in southwestern Georgia and southeastern Alabama in September, 1994 (See Table One).

Table One. Application Scenario	
No. replicates	17 workers, 15 different sites
Application rate	0.94 lb ai/acre
lb a.i. applied per replicate	9.5 to 69 lb a.i.
application method	ground boom, open cab
mixing/loading method	open
PPE ¹	varied, depending on worker preference

1. Only one worker wore all the PPE required on the Gramaxone label for mixing and loading. None wore all the applicator PPE.

Urinary excretion of paraquat was measured as the indicator of exposure to workers mixing, loading, and applying the herbicide. The following samples were taken for each subject: a complete 24 hour pre-exposure urine sample, a 24 hour exposure day (Day 1) urine sample, and 24 hour urine samples on days 2 through 6. Field fortified urine samples and controls were prepared and were stored with the experimental samples. Storage stability tests showed that paraquat was stable in urine over the storage period.

Air monitoring was conducted during mixing and loading and application of paraquat. Each subject wore two personal air sampling pumps, one for each activity. The raw data were never analyzed by the authors since the concentrations of paraquat in urine were so low.

Urinary paraquat was measured by a radioimmunoassay procedure described and validated in volume one of the study (MRID # 436442-01). It is not clear whether laboratory fortification and control samples were run concurrently with each set of field samples. The limit of quantification (LOQ) was 10 ng/ml for a 1 ml sample. The level of detection was 5 ng/ml. Urinary creatinine was measured by the Jaffe reaction and a Kone Specific Analyzer.

An overall compliance statement was signed on April 28, 1995 indicating that the study was in compliance with GLP standards, with two minor exceptions.

Toxicology branch has confirmed the pharmacokinetics data used in this study. As reported in the toxicology chapter for the paraquat dichloride red (9/95), a single dose of paraquat dichloride administered subcutaneously to rats was excreted mostly in urine (73-96%) as unchanged paraquat within 24 hours after dosing. Therefore adequate time was allowed in this experiment for urine collection.

Project Results

The study results showed that 6 of the urine samples contained detectable paraquat. All were in the Day 1 (application exposure day) samples. Because paraquat was not detected in day 2 and 3 samples, samples from days 4 to 6 were not analyzed. Results are presented in the following table (Table Two). Absorbed paraquat was estimated using a referenced excretion rate of 59% from a paraquat pharmacokinetics study in monkeys¹. Exposure was calculated by Hank Appleton (OREB contractor, see attachment) on the basis of the body weight of the replicate and amount of a.i. handled, calculating non-detects using 1/2 the detection limit (2.5 ng/ml) in lieu of 0, and the Day 1 urine volume.

Table Two. Study Results			
Replicate	Personal Protective Equipment	Pounds a.i. Handled	Exposure mg/kg B.W./lb. a.i.
4201	none	22.5	0.0000031
4202	none	37.5	n.d.
4203	none	17	0.00001
4204	none	37.5	n.d.
4205	Gloves while mixing	7.25	n.d.
4206	none	10.25	0.0000068
4207	none	9.5	n.d.
4208	none	69.0	0.0000047
4209	Gloves while mixing	18.75	n.d.
4210	none	64.75	0.0000067
4211	Respirator, face shield, goggles, apron, gloves; Tyvek for applying	18.75	n.d.
4212	Gloves for mixing	10.0	n.d.
4213	Gloves, face shield, apron	15	n.d.
4214	none	21.0	0.0000071
4215	Gloves while mixing	43.0	n.d.
4216	Face shield, goggles, apron, gloves; Tyvek for applying	18.75	n.d.
4217	Gloves, face shield, apron	43.75	n.d.
Arithmetic Mean			0.0000081

Geometric Mean			0.0000036
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Of the six workers with detectable paraquat exposure, none wore protective equipment while handling the formulation. In addition, however, there was no discernable trend between the amount of pesticide handled and the exposure incurred.

The authors also present an exposure assessment which contains a calculation of a Margin of Exposure (MOE), and proposed revisions in label requirements for PPE. Using a NOEL value of 0.6 mg/kg for a 90 day feeding study in dogs (this end-point has been changed to 1 mg/kg/day, Less Than Lifetime Meetings 7/25/95 & 10/10/95), and a maximum exposure rate (as reported from this study) of 0.00044 mg/kg/day, an MOE of 1,300 was derived. Based on this value, and the fact that this worker wore no PPE and handled 64.5 pounds of a.i., the authors suggest that appropriate handler PPE would be coveralls, or long-sleeved shirt and long pants, shoes plus socks, and protective eye wear. For mixers and loaders waterproof gloves would also be needed.

III. Conclusions:

OREB concludes that this paraquat mixer, loader, and applicator study is acceptable. The study meets most of the Subdivision U guidelines for mixers, loaders, and applicators. The following guidelines were not met: laboratory control and fortification samples were not run concurrently with each set of field samples, and there were 17 replicates but they were conducted at 15 different sites.

OREB feels that the authors should have more carefully discussed other routes of entry into the body, specifically inhalation. The amount of paraquat absorbed into the body was determined but it is not known what fraction of that entered through inhalation.

In the recently completed OREB chapter for the Paraquat Dichloride RED (12/7/95) this biomonitoring study was used to calculate worker exposure for groundboom and aerial mixers/loaders and applicators. Exposure to workers mixing/loading and applying paraquat under all other use scenarios was estimated using the Pesticide Handlers Exposure Database (PHED), Version 1.1. OREB recommends the following PPE based on the results: for mixers/loaders long-sleeve shirt and long pants, chemical-resistant gloves, shoes plus socks, chemical-resistant apron, and a face shield; for applicators long-sleeve shirt and long pants, chemical-resistant gloves, shoes plus socks, and a dust/mist respirator.

References

1. MRID # 00126096. Chevron Chemical Co. (1982) "Elimination of C-14 labeled paraquat in rhesus monkeys following a single parenteral dose."

Attachments

cc: T. Manville
Chemical File: **PARAQUAT (061601)**
Correspondence