



8-19-92

D-13922<sup>SD</sup>/methazole

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

MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

**SUBJECT:** Calculation of Margin-Of-Exposure for Workers Exposed to Methazole. Based on Adverse Findings of Cataracts in Rat Pups.

**FROM:** John E. Whalan, D.A.B.T., Toxicologist  
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Health Effects Division (H7509C)

*John Whalan*  
8-18-92

**TO:** Kathryn S. Bouve, 6 (a)(2) Officer  
Special Projects & Coordination Staff  
Program Management & Support Division (H7502)

**THRU:** Karl P. Baetcke, Chief  
Toxicology Branch I  
Health Effects Division (H7509C)

*Karl P. Baetcke*  
8/19/92

In a series of recent letters to Jay Ellenberger, Charles G. Keefer, Director, Regulatory Affairs, has informed the Agency that Sandoz Agro, Inc. intends to voluntarily cancel methazole because of adverse findings of cataracts in pups in a Two-Generation Reproduction study, and leiomyosarcoma of the hindlimb in an ongoing Chronic Rat Feeding study. Although very little can be ascertained from the preliminary tumor data, the discovery of cataracts in pups is of immediate concern. Study reports have not been submitted for either study.

Ophthalmic examination revealed 100% cataract incidence in pups born to dams receiving the two highest dosages of 150 and 1000 ppm of methazole in their diet (Table 1, study IRDC II, attached). There was a 5.5% incidence at the low dose of 15 ppm. The untreated control pups had no cataracts. The letter describing these findings did not mention how old the pups were when the cataracts were observed. It also did not mention why cataracts were not observed in fetuses in the developmental toxicity studies, or in any adults.

Cataracts were observed in an earlier Industrial BIO-TEST (IBT) Reproduction study performed in 1977 (2.4% at 50 ppm, 58% at 100 ppm, 100% at 250 ppm). They were not observed in a 1980 IRDC Reproduction study at dosages up to 50 ppm. The fact that high incidences of dose-related cataracts were observed in both the IBT study and the new IRDC study demonstrates that cataracts are a genuine toxicologic effect. Methazole production ceased in 1976 over concerns about cataracts and chloracne. HED did not review the IBT

memo: 10 pages  
attachment: 6 pages



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study because methazole had no prospect for reentry into the market (Ed Budd memorandum, March 31, 1983). Production resumed sometime in the 1980's without HED's knowledge, and without resolution of the cataract and chloracne issues. The Material Safety Data Sheet for technical Probe® Herbicide (dated May 1, 1987) has a Health/Safety Alert that reads, "Warning Skin Contact might result in acneform reaction." The current product label has the same language. Neither document mentions cataracts.

The latest decision to cancel was made because of market pressures, and recent Section 6 (a)(2) issues that would require significant additional studies to clarify the findings. The majority of product is in the channels-of-trade. No additional product will be produced. The registrant has requested an allowance to sell the remaining 25,000 pounds currently in stock before May 18, 1993. Sandoz calculated Margins-Of-Exposure (MOE or MOS) that suggest a low risk from the continued use of the remaining stock (MOE's of 84-10,514).

The IRDC study lacks a NOEL because cataracts were found at the lowest dose tested (15 ppm). Sandoz performed a regression analysis in order to estimate a NOEL, but a reliable analysis is not possible with only a single data point (5.5% incidence at 15 ppm) with which to draw a dose-response curve. The true point of total incidence is not known, but it is less than 150 ppm. As the dose of total incidence decreases, the dose-response curve becomes steeper, and the estimated NOEL becomes greater.

Sandoz calculated a dietary NOEL of 7.36 ppm (Table 2, attached), which is 74% of the 15 ppm dose (log basis). The NOEL was converted to 0.736 mg/kg/day (1 ppm = 0.100 mg/kg/day, young rat), presumably on the basis of *post partum* cataract formation. Considering that a letter from IBT (August 16, 1976) describes bilateral cataracts in F<sub>1a</sub> pups upon opening their eyes, the cataracts probably developed *in utero*. Since the transplacental dose is not known, the conversion for mature rats must be used - 7.36 ppm = 0.37 mg/kg/day (1 ppm in the diet = 0.050 mg/kg/day), which is half the Sandoz value.

Sandoz calculated MOE (MOS) values for plant workers, applicators, and mixer/loaders (Tables 3 and 4, attached), but failed to document their methods. The exposure estimates were apparently reduced by prorating over a year. They assumed 100% dermal and inhalation exposure (acute data suggest this may be an overestimation, but no data were provided to prove otherwise). The most sensitive population is the applicators (35 years, 60 days/year) which have an MOE of 84. Correcting for the error in ppm → mg/kg/day conversion (for mature rats), the MOE should be 42, which is less than the generally accepted MOE value of 100. If a more conservative NOEL were used, such as 3.9 ppm (0.20 mg/kg/day) which is ½ log of the low dose, the MOE for applicators would be 22.

The Occupational and Residential Exposure Branch (OREB) has estimated exposure for applicators, mixer/loaders, and mixer/loader/applicators, assuming 100% dermal and inhalation exposure, and exposure in 2-3 day intervals separated by several weeks (David Jaquith memorandum, July 31, 1992). The data used in these estimates are from the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated May 13, 1992.

There are several good reasons for not prorating worker exposure over the course of a year. The rat gestation period is 21 days. The rat eye is most susceptible to teratogenic insult between gestation days 8 and 12. Considering that the lens placode (the thickened area of ectoderm overlying the optic vesicle) does not appear until gestation day 11, this only leaves one or two optimal days for terata to develop. Chemically induced cataracts, on the other hand, can develop at any point after appearance of the lens (gestation days 11-21). OREB's 2-3 day worker exposure interval is reasonably close to the 1-2 day window for lens terata, or the <12 gestation days needed for chemically induced cataracts. Thus, it is appropriate to use an estimated NOEL from the reproduction study in calculating the MOE. It is not appropriate to prorate exposure over the course of a year, as it appears Sandoz did.

The MOE formula is presented below. Calculations for dermal, inhalation, and total exposure scenarios for workers are presented at the end of this memorandum. It is assumed, as a worst case, that 1.5 pounds a.i./acre are applied as a preemergent broadcast spray. For each scenario, the Sandoz estimated NOEL of 7.36 ppm (0.37 mg/kg/day) and the HED estimated NOEL of 3.9 ppm (0.20 mg/kg/day - ½ log of the low dose) are used:

$$MOE = \frac{\text{animal NOAEL}}{\text{human exposure}}$$

Accounting for dermal and inhalation exposure, all MOE values are well below 100. The Mixer/Loader/Applicator MOE is 0.23. Even if dermal absorption were assumed to be only 10%, this MOE would only be 2.0. This suggests a genuine cataractogenic risk for workers. The Sandoz MOE values are as much as 4 orders of magnitude greater than those calculated by HED. This disparity cannot be explained because Sandoz did not describe how they estimated exposure. There are several other issues that deserve mention:

- ◆ Although the maternal doses are known for the reproduction study, there is no way of knowing whether the transplacental dose was more or less than the maternal dose.
- ◆ Cataracts are rare in young animals. This suggests a direct chemical effect (as opposed to a developmental effect) on the lens. Thus, the same effect should be seen in adult humans. There were 3 pups at 15 ppm with luxated (dislocated) lenses (Attachment 1) - probably a developmental effect.
- ◆ Adult humans are at greater risk of developing cataracts than rat pups because cataract formation is an age-related event. Methazole may shorten the time of onset.
- ◆ Because cataracts generally form over an extended time, a worker would not think to attribute them to methazole.
- ◆ The lenses of workers can be exposed to methazole in two ways - systemic exposure (as with the rats and ducks) and ocular exposure by deposition on the eye.

- ◆ Methazole or its metabolites may, like many other chemicals, directly induce cataracts. Another possible mechanism for cataractogenesis is impaired galactose metabolism, as in galactosemia, which can result in high blood galactose in the dams. This leads to cataracts and galactose accumulation in the tissues of fetuses. Impaired galactose metabolism could result from direct chemical effect, or from malnutrition due to feed unpalatability.

In 1976, HED requested a special cataract study in ducks, and reviewed a protocol (Ed Budd memorandum, January 27, 1977). A study was performed and submitted to the Agency, but it was not forwarded to HED for review. A copy of the report was found (Project No. 8580-10529, MRID No. 2401458-11, undated). The study was performed at IBT. Following a pilot study for dose selection, three groups of 15 Pekin ducklings were dosed with technical methazole in their feed at doses of 0 (untreated control), 300, and 1000 ppm. A fourth group dosed with 2,4-dinitrophenol served as a positive control. According to the study report summary,

"Grossly visible changes in the lens indicative of possible cataracts were observed at time of death or sacrifice in 11 of the 15 ducklings fed 2,4-dinitrophenol. No such changes were observed in any of the birds receiving Methazole Technical. Histologic studies were subsequently conducted to confirm the nature of the grossly visible ocular lesions and any lesions that were undetected by gross examination. These studies confirmed the presence of cataracts among the positive control birds and possibly one Test bird in Group T-II [high-dose group]."

Although this study summary describes a generally negative result, the body of the study presents a very different picture:

1. In the pilot study, ducklings dosed at  $\geq 1000$  ppm had anorexia, emaciation, lethargy, conjunctivitis, and piloerection; their mean weight at week 2 was half that of the controls. This suggests that the ducklings encountered the same feed unpalatability problem seen in mammalian studies, and thus consumed a lower than expected dose of methazole. Three of four ducklings dosed at 3000 ppm died (days, 6, 7, and 11), probably due to starvation. They were found to have bilateral lens opacities. Ducklings dosed at 0, 10, 100, and 300 ppm had no gross evidence of lens opacity.
2. In the main study, ducklings dosed at 300 ppm had reduced growth, and those dosed at 1000 ppm had reduced growth, anorexia, and generalized weakness. Eight of 15 ducklings dosed at 1000 ppm died between days 9 and 17, and were emaciated due to anorexia. One of the high-dose ducklings had a cataract with a severity of 2 on a scale of 1 to 5 (the positive controls had severities of 1 and 2). This is a definitive finding - not an equivocal one as implied in the study summary. There is no way of correlating this finding with other toxic indicators for a particular duckling since all left eyes and all right eyes were pooled.

3. Three eyes in the high-dose group could not be evaluated because the lens was absent in the plane of section. This should not happen for a structure that is so easy to identify during embedding.
4. Because of severe decreases in food consumption, the true cataract-inducing doses are a fraction of nominal. Adjusting for anorexia, cataractogenesis occurred at approximately 90 mg/kg/day in the pilot study, and 60 mg/kg/day in the main study.

Thus, cataracts have been found in the rat and the duck. While the rat pup cataracts may have developed *in utero*, the duck cataracts obviously did not since they developed in juveniles. Duck cataracts were clearly not a developmental effect. This suggests that workers, as well as the unborn, are at risk. Cataracts should have been observed in numerous mammalian studies, but they were not. Cataracts were observed in rats at doses low enough for unpalatability and anorexia to not be a problem (15 and 150 ppm) so malnutrition could not have been the primary cause of cataracts.

There are only a few acceptable toxicity studies in the methazole data base, and many studies were performed at IBT. The studies and HED reviews that are available are old. In order to avoid repeating old studies, the Registrant has proposed using "simulated dosing" as a way of getting around the lack of dosing information.

An inquiry from the State of Georgia (dated February 7, 1992) revealed that Sandoz is claiming the data base is virtually new, that new studies which replace the IBT studies have been submitted to the Agency, and that HED lacks the resources to review all this new data. None of these claims is true. The first toxicity studies to be submitted in 14 years arrived two months ago (June, 1992). These include a Rat Metabolism study, a Rabbit Developmental Toxicity Study, and a Micronucleus Cytogenetic Assay in Mice. None of these studies is a replacement for an IBT study.

Over the past four years, Sandoz has repeatedly delayed the initiation of new studies. After extensive protocol discussions, a chronic feeding study was initiated with full knowledge that HED was unwilling to accept it due to feed unpalatability problems. Interim reports were required because of the Registrant's repeated delays. These reports contained too little information for HED to ascertain what was happening. The Registrant was unwilling to discuss any aspect of this study. It was aborted with only a few months remaining because of the Sec. 6 (a)(2) findings. Interesting preliminary findings in this study include leiomyosarcoma of the hindlimb and "a possible increase in the incidence of slight corneal opacities" at week 50. This study highlights the failure of past studies to find cataracts in adult animals. This, combined with the findings in ducks and the MOE calculations, shows that workers exposed to methazole are at risk of developing cataracts.

## Conclusions:

There is very little reliable toxicity data for methazole, and the recent disclosures by Sandoz only provide preliminary information. The following are key points and areas of concerns:

1. Cataracts were observed in an IBT Reproduction study (2.4% at 50 ppm, 58% at 100 ppm, 100% at 250 ppm). Because of this study and findings of chloracne in factory workers, methazole production was discontinued in 1976. HED did not pursue the matter further because methazole was a "dead" chemical. Production resumed sometime in the 1980's without HED's knowledge, and without resolution of the cataract and chloracne issues. The Material Safety Data Sheet for technical Probe® Herbicide (dated May 1, 1987) has a Health/Safety Alert that reads, "Warning Skin contact might result in acneform reaction." The current product label has the same language. Neither document mentions cataracts.
2. The cataract findings in the IBT study were verified in another reproduction study performed this year at IRDC. Preliminary results, submitted as Sec. 6 (a)(2) data, revealed pups with cataracts born to dams dosed with methazole in their feed. The incidences were 5.5% at 15 ppm, and 100% at 150 and 1000 ppm.
3. Preliminary findings of leiomyosarcoma of the hindlimb and "a possible increase in the incidence of slight corneal opacities" were reported as Sec. 6 (a)(2) adverse findings in an ongoing Chronic Rat Feeding study.
4. Cataracts were not detected in past studies, most particularly in developmental toxicity studies.
5. A special cataract study was performed in juvenile Pekin ducks at IBT. The major findings were cataracts, severe anorexia, and decreased body weight gain. Adjusting for the effects of anorexia on dosing (in the feed), cataractogenesis occurred at approximately 700 ppm in the pilot study and 500 ppm in the main cataract study (approximately 88 mg/kg/day and 63 mg/kg/day, respectively).
6. Although methazole may promote cataracts as a developmental effect, it is more likely to have a direct chemical effect on the lens, both *in utero* and *post partum*. This suggests that workers, as well as the unborn, are at risk.
7. Using an estimated NOEL of 3.9 ppm (0.20 mg/kg/day) for cataracts, the Margin-of-Exposure (MOE) for a mixer/loader/applicator wearing protective clothing is 0.23. This value is well below the generally accepted MOE value of 100.
8. MOE values calculated by Sandoz are as much as 4 orders of magnitude greater than HED's values. This disparity cannot be explained because Sandoz did not describe how they estimated exposure, although it appears exposure was prorated over a year.

9. Because cataracts generally form over an extended time, a worker would not think to attribute them to methazole.
10. The lenses of workers can be exposed to methazole in two ways - systemic exposure (as with the rats and ducks) and ocular exposure by deposition on the eye.
11. Methazole or its metabolites may, like many other chemicals, directly induce cataracts. Another possible mechanism is impaired galactose metabolism, as in galactosemia, which can result in high blood galactose. This could result from direct chemical effect, or from malnutrition due to feed unpalatability.
12. Recent events, including the Registrant's decision to stop methazole production based on preliminary findings of cataracts, bear a striking resemblance to what happened in 1976. Efforts should be taken to prevent history from repeating itself a third time.

**Applicator [Dermal Exposure] = 0.063 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.063 \text{ mg/kg/day}} = 5.9$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.063 \text{ mg/kg/day}} = 3.2$$

**Mixer/Loader [Dermal Exposure] = 0.79 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.79 \text{ mg/kg/day}} = 0.47$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.79 \text{ mg/kg/day}} = 0.25$$

**Mixer/Loader/Applicator [Dermal Exposure] = 0.856 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.856 \text{ mg/kg/day}} = 0.43$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.856 \text{ mg/kg/day}} = 0.23$$



**Applicator [Inhalation Exposure] = 0.00194 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.00194 \text{ mg/kg/day}} = 191$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.00194 \text{ mg/kg/day}} = 103$$

**Mixer/Loader [Inhalation Exposure] = 0.0107 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.0107 \text{ mg/kg/day}} = 34.6$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.0107 \text{ mg/kg/day}} = 18.7$$

**Mixer/Loader/Applicator [Inhalation Exposure] = 0.0126 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.0126 \text{ mg/kg/day}} = 29.4$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.0126 \text{ mg/kg/day}} = 15.9$$

**Applicator [Total Exposure] = 0.065 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.065 \text{ mg/kg/day}} = 5.7$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.065 \text{ mg/kg/day}} = 3.1$$

**Mixer/Loader [Total Exposure] = 0.804 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.804 \text{ mg/kg/day}} = 0.46$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.804 \text{ mg/kg/day}} = 0.25$$

**Mixer/Loader/Applicator [Total Exposure] = 0.870 mg/kg/day**

Sandoz NOEL = 7.36 ppm = 0.37 mg/kg/day

$$MOE = \frac{0.37 \text{ mg/kg/day}}{0.870 \text{ mg/kg/day}} = 0.43$$

HED NOEL = 3.9 ppm = 0.20 mg/kg/day

$$MOE = \frac{0.20 \text{ mg/kg/day}}{0.870 \text{ mg/kg/day}} = 0.23$$

ATTACHMENT 1

**METHAZOLE RAT REPRODUCTION STUDY  
F<sub>1b</sub> OPHTHALMOLOGY SUMMARY**

<b>DIET CONCENTRATION DOSAGE GROUP</b>	<b>GENDER</b>	<b>COUNTS</b>	<b>DESCRIPTION</b>
Control (0)	Male	81/81	Normal
Control (0)	Female	78/78	Normal
15 ppm	Male	80/85	Normal
15 ppm	Male	3/85	Cataracts, both eyes
15 ppm	Male	1/85	Cataracts, luxated lens, both eyes
15 ppm	Male	1/85	Retained hyloid, left eye
15 ppm	Female	79/83	Normal
15 ppm	Female	2/83	Cataracts, both eyes
15 ppm	Female	2/83	Cataracts, luxated lens, both eyes
150 ppm	Male	62/62	Cataracts, both eyes
150 ppm	Female	55/55	Cataracts, both eyes
1000 ppm	Male	39/39	Cataracts, both eyes
1000 ppm	Female	51/51	Cataracts, both eyes

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ATTACHMENT 2

**SANDOZ AGRO, INC.**  
**Inter-Office Correspondence**

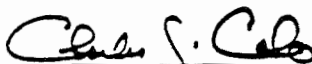
Copies to:

Date: May 7, 1992  
From: Y. H. Atallah 1300  
C. J. Calo 1305  
To: CRAC Members

\*\*\*\*\*  
Subject: Methazole/Cataract Incidence  
\*\*\*\*\*

Attached are four tables to assist in estimation of risk to the eyes (cataract) of workers during occupational exposure. The attached four tables are:

- Table 1 Methazole F<sub>10</sub> Cataract Incidence at 21 Days
- Table 2 Scenarios for NOEL
- Table 3 Occupational Exposure
- Table 4 Estimated Risk (NOEL 736 µg/kg/day).

  
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C. J. Calo

  
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Y. H. Atallah

YHA:CJC/eld  
Attachment

TABLE 1

METHAZOLE F<sub>1b</sub> CATARACT INCIDENCE AT 21 DAYS

Dose	IBT	IRDC I	IRDC II
5	-	0/160	--
15	-	0/194	9/168
50	2/84	0/187	--
100	38/66	--	--
150	-	--	117/117
250	71/71	--	--
1000	-	--	90/90
Neg. Control	1/76	0/162	0/159
Historical Cont.	3/4385	3/4385	3/4385

TABLE 2

SCENARIOS FOR NOEL

Examination of all available data (3 studies) indicate a dose-response relationship. All data were subjected to statistical analysis using both linear and Sigmoid relationships. The subject study (IRDC II) yielded NOEL's of 7.36 ppm (linear regression) and 12.3 ppm (Sigmoid relationships). These values fall within the range of values obtained from other studies separately or collectively.

$$\begin{aligned} 7.36 \text{ ppm in the diet} &= 0.736 \text{ mg/kg/day} \\ &= 736 \text{ } \mu\text{g/kg/day} \end{aligned}$$

$$\leq 0.37 \text{ mg/kg}$$

TABLE 3

OCCUPATIONAL EXPOSURE

- Plant Workers (86 min/day)

157  
4000

Hand  
mg/lit/day  
day of work

Based on three air monitoring studies; 60 days of production/year  
Estimated Lifetime Exposure (35 years) = 0.38  $\mu\text{g}/\text{kg}/\text{day}$   
Estimated Lifetime Exposure (10 years) = 0.11  $\mu\text{g}/\text{kg}/\text{day}$

- Field Workers <sup>1/</sup>

Based on three surrogate studies

• Mixer/Loader (1 hr/day)

Estimated Lifetime Exposure (35 years, 60 days/year) = 0.93  $\mu\text{g}/\text{kg}/\text{day}$

Estimated Lifetime Exposure (10 years, 60 days/year) = 0.31  $\mu\text{g}/\text{kg}/\text{day}$

Estimated Lifetime Exposure (10 years, 14 days/year) = 0.07  $\mu\text{g}/\text{kg}/\text{day}$

• Applicators

Estimated Lifetime Exposure (35 years, 60 days/year) = 8.8  $\mu\text{g}/\text{kg}/\text{day}$

Estimated Lifetime Exposure (10 years, 60 days/year) = 2.95  $\mu\text{g}/\text{kg}/\text{day}$

Estimated Lifetime Exposure (10 years, 14 days/year) = 0.69  $\mu\text{g}/\text{kg}/\text{day}$

<sup>1/</sup> Assumes use of gloves, long-sleeve shirts and long trousers as required for plant workers or stated on the product label.

TABLE 4

ESTIMATED RISK (NOEL 736  $\mu\text{G}/\text{KG}/\text{DAY}$ )

	<u>Exposure</u> <sup>1/</sup> <u>(<math>\mu\text{g}/\text{kg}/\text{day}</math>)</u>	MOS
Plant Workers (10 years, 60 days/year)	0.11	6690
Plant Workers (35 years, 60 days/year) <sup>2/</sup>	0.38	1937
Applicators (10 years, 60 days/year)	2.95	249
Applicators (35 years, 60 days/year) <sup>2/</sup>	8.8	84
Applicators (10 years, 14 days/year)	0.69	1067
Mixer/Loader (10 years, 60 days/year)	0.31	2374
Mixer/Loader (35 years, 60 days/year) <sup>2/</sup>	0.93	791
Mixer/Loader (10 years, 14 days/year)	0.07	10514

<sup>1/</sup> Assuming 100% inhalation and dermal absorption.

<sup>2/</sup> Common lifetime exposure assumptions. However, methazole has been in use for less than 10 years.