

US EPA ARCHIVE DOCUMENT



D-13920 / methazole

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

MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

**SUBJECT:** Methazole: Consideration of Registrant Suggestions for Modifying Margin-of-Exposure (MOE) Values.

**FROM:** John E. Whalan, D.A.B.T., Toxicologist  
Section 1, Toxicology Branch I  
Health Effects Division (H7509C)

*John E. Whalan*  
9-1-92

**TO:** Jack E. Housenger, Chief  
Special Review Branch  
Special Review and Reregistration Division (H7508W)

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

*Karl P. Baetcke*  
9/9/92

This memorandum is a follow-up to a meeting with representatives from Sandoz held on August 21, 1992, and responds to issues raised and information supplied at that time. The meeting centered on the following issues:

- ◆ The regulatory history of methazole.
- ◆ Possible mechanisms behind high cataract incidence in rat pups.
- ◆ The relevance of rat pup cataracts to adult humans.
- ◆ Resolution of the vast differences in worker exposure values and Margin-of-Exposure calculations performed by Sandoz and HED.
- ◆ Possible ways to adjust the MOE to obtain a value greater than 100.

Until June, 1992, HED had not received any toxicity studies of methazole for the past 14 years. Sandoz mentioned that several new studies with negative findings had been submitted to SRRD. Sandoz considered these studies to be important in showing that adult workers are not at risk from methazole exposure.

10 pages

Microfische copies of 5 toxicity studies performed during the 1980's were given cursory review (attached) to determine whether there was evidence of cataracts in any adult mammals. The dermal study was performed at Hazleton Laboratories, and the others were performed at American Biogenics Corporation. The following is a summary of the cursory findings. Sandoz considered the first three studies to be proof that cataracts were not found in adult animals:

**1-Year Feeding Toxicity Study in Beagle Dogs:** Ophthalmologic examination revealed no cataracts. The high-dose was reduced at week 17 to a level that was probably too low.

**90-Day Feeding Toxicity Study in Dogs:** Ophthalmologic examination revealed no cataracts. The high-dose should have been greater.

**93-Week Feeding Oncogenicity Study in Mice:** Although ophthalmologic examination is not required for this type of study, it would have been expedient to include examination of at least the control and high-dose mice. Eye opacities were seen in all groups, but did not seem to be a dose-related effect. An MTD may not have been reached.

**90-Day Feeding Study in Rats:** Ophthalmologic examination revealed no cataracts. The doses used appear appropriate.

**21-Day Dermal Toxicity Study in Rabbits:** Although ophthalmologic examination is not required for a 21-day dermal study, it would have been expedient to include examination of at least the control and high-dose rabbits.

Ophthalmologic examination in the 1-year and 90-day beagle studies revealed no cataracts. If, as Sandoz and HED surmise, methazole causes cataracts through a direct chemical effect over a period of several days or weeks, cataracts should have been observed in the dog. The maximum doses in both studies could have been higher.

It would have been helpful to have negative findings in a second mammalian species. Numerous opacities (probably cataracts) were observed clinically in the mice, but in the absence of ophthalmologic examination, little more can be determined about their significance. Sandoz is incorrect in claiming that there were no cataracts in this study. Clearly, ophthalmologic examination should have been included in the study protocol. The subchronic rat study had no cataracts.

The 21-day dermal toxicity study in rabbits would have been a good representation of human exposure, but unfortunately, the eyes were not examined. Sandoz told us about an *In Vitro* study in which cataracts were chemically induced with methazole and the azo- and azoxybenzene impurities. This strongly suggests that methazole can directly induce cataracts *In Vivo*. This study was not submitted to the Agency.

To summarize what is known to date, no cataracts were observed in adult dogs (90-days, 1-year) or rats (90-days) dosed in their feed at doses significantly greater than the maternal doses that induced cataracts in rat pups. Methazole may have induced cataracts in orally dosed mice and dermally dosed rabbits, but since their eyes were not examined, neither we nor Sandoz can make any claims about these studies. Cataracts were found in a high percentage of ducklings dosed with methazole in their feed at dosages sufficient to cause severe anorexia, failure to thrive, and death. If dogs, rats, and mice were dosed at severely toxic doses, they too may have developed cataracts, but this scenario would not in any way be representative of worker exposure.

The fetus appears to be far more susceptible than adults to developing cataracts following exposure to methazole. If the duckling study is representative of humans, then workers would only be at risk if they received a dose great enough to cause malnutrition and possibly death. Under real world conditions, the adult worker is probably at low risk of developing cataracts, but the fetus carried by a pregnant worker is conceivably at great risk. In this case, the MOE values (John E. Whalan memorandum, August 19, 1992) would be fully applicable. The following table compares the various new studies:

Study	Dose		Cataract Incidence
	PPM	mg/kg/day	
Reproduction Study in Rats (IBT)	50	2.5	2.4%
NOTE: Cataracts were observed in pups upon opening of eyes.	100	5	58%
	250	12.5	100%
Reproduction Study in Rats (IRDC)	15	0.75	5.5% - lowest dose
NOTE: Cataracts were observed in pups upon opening of eyes.	150	7.5	100%
	1000	50	100%
Reproduction Study in Rats (IRDC)	5	0.25	0%
	15	0.75	0%
	50	2.5	0%
Pilot Cataract Study in Ducklings (IBT)	0	0	0%
	10	~1.25	0%
	100	~12.5	0%
	300	~37.5	0%
	1000	~125†	0%
	3000	~375†	75%
	10,000	~1250†	75%
Cataract Study in Ducklings (IBT)	0	0	0%
	300	~37.5	0%
	1000	~125†	7%

Study	Dose		Cataract Incidence
	PPM	mg/kg/day	
1-Year Feeding Study in Dogs	0	0	0%
	15	0.375	0%
	75	1.875	0%
	300	7.500	0%
90-Day Feeding Study in Dogs	0	0	0%
	30	0.750	0%
	100	2.500	0%
	300	7.500	0%
93-Week Feeding Oncogenicity Study in Mice	0	0	N/A*
	30	4.5	N/A*
	100	15	N/A*
	300	45	N/A*
	1000	150	N/A*
90-Day Feeding Study in Rats	0	0	0%
	100	5	0%
	250	12.5	0%
	500	25	0%
21-Day Dermal Toxicity Study in Rabbits		0	N/A*
		10	N/A*
		100	N/A*
		1000	N/A*

† The true dose is significantly less than this value because of anorexia.

\* Ophthalmologic examinations were not performed.

Both Sandoz and HED assumed worst case scenarios in calculating their MOE 's. Because Sandoz annualized their exposure scenarios, their MOE values were significantly greater than 100. In contrast, HED 's MOE values were as low as 0.23. Sandoz suggested adjusting the scenarios in order to get away from the worst case scenario. The following text presents the assumptions used in calculating the MOE 's and discusses whether they can be adjusted.

1. **Application rate:** The maximum application rate used by OREB is 1.5 pounds active ingredient/acre/year in accordance with label instructions.

**MOE adjustment:** None

2. **Protective clothing:** The exposure values calculated by OREB take into account that a worker is wearing the protective clothing and impervious gloves specified on the product label.

**MOE adjustment:** The MOE can be increased if more uncomfortable protective measures are taken. Considering the climate in which this product is applied, this solution is probably unworkable.

3. **100% dermal and inhalation absorption:** This issue is potentially a good candidate for MOE adjustment, but Sandoz has not provided any dermal or inhalation absorption data that would allow the MOE to be adjusted upward. OREB's exposure calculations have shown that exposure is far greater by the dermal route than the inhalation route.

**MOE adjustment:** If dermal absorption were 0%, the mixer/loader/applicator MOE for inhalation exposure would still be 15.9. Dermal and inhalation absorption would have to be 0% and 16%, respectively, in order for the MOE to equal 100. This is unlikely.

4. **Direct eye contact:** All the toxicity studies involve lenticular exposure to methazole via systemic circulation following oral dosing. Workers, on the other hand, will also receive direct exposure to the eyeball. The risk to workers by this route is unknown.

**MOE adjustment:** If methazole is absorbed through the eye, the potential for inducing cataracts would be greatly increased, thus lowering the MOE even further.

5. **Annualization v 2-3 day exposure:** OREB assumed that a worker would be exposed to methazole in 2-3 day intervals separated by several weeks. This means that workers would receive a series of acute or subacute exposures. Sandoz annualized exposure by dividing exposure by 365 days. This dilutes exposure to an unrealistic level.

**MOE adjustment:** The MOE cannot be adjusted because annualization does not portray worker exposure.

6. **Comparison of Reproductive NOEL to a 2-3 day worker exposure scenario:** The length of time needed for the rat pups to develop cataracts is not known. Given that the lens placode appears on gestation day 11, birth is on gestation day 21, and the pups' eyes open on lactation day 7, the cataracts could have developed at any point during 12 days of gestation, 7 days of lactation, or both. Lenticular insult could have occurred in as little as 1 day, or as much as 19 days; the critical interval is probably 1 or 2 weeks. It is more reasonable to compare this interval to 2-3 days of worker exposure, than to 365 days as proposed by Sandoz, especially since workers are exposed acutely or subacutely.

**MOE adjustment:** If we knew that cataracts were induced following a single day of exposure, the MOE could be divided by 3 (3 days of worker exposure) for a mixer/loader/applicator MOE of 0.08. If we knew that cataracts were induced following 12 days of gestation and 7 days of lactation, the MOE could be multiplied by 19 for a mixer/loader/applicator MOE of 4.37. The true MOE is somewhere between these two MOE values.

- 7. Cataract risk to human adults vs fetuses:** Under real world conditions, the adult worker exposed to methazole is probably at low risk of developing cataracts, but the fetus carried by a pregnant worker is conceivably at great risk.

**MOE adjustment:** The MOE cannot be adjusted because the Agency must regulate for the pregnant female worker, even though men and nonpregnant women are probably at less risk.

- 8. Duration of lens susceptability - human vs rat:** Sandoz proposed adjusting the MOE to compensate for the longer duration of lens susceptability in humans (as a consequence of slower gestation) - approximately 60 days in humans vs 2 days in rats (30-fold difference). This argument might be justified if methazole-induced cataracts were a developmental effect, but neither Sandoz nor HED believe this to be the case. The time to expression is not known, except that it is <19 days in rat pups, and <17 days in ducklings.

In an August 27, 1992 letter, Charles G. Keefer of Sandoz recommended adjusting the MOE by the ratio of 210 gestation days (human) : 12 gestation days (rat) to account for the disparity in the "post-terato period." The justification for this was that cataracts generally form over an extended period of time, (and) the effect most likely is quantitative and cumulative. This was not the case in any of the positive studies, however, because cataracts appeared to form rapidly.

**MOE adjustment:** There is no justification for adjusting the MOE to account for human fetal development being slower than rat fetal development.

- 9. New NOEL for the IRDC Reproductive Toxicity study:** The low-dose in the Reproductive Toxicity study performed at IRDC was 7.36 ppm. In the Sec. 6 (a)(2) submission, Sandoz converted this dose to 0.736 mg/kg/day. This value was later changed to 0.614 mg/kg/day based on actual food consumption data. This is a 17% decrease in maternal dose.

**MOE Adjustment:** This information does not alter the MOE calculations. The NOEL is still not known. There is no reason to adjust the HED estimated NOEL on the basis on this small change.

Of these issues, the only two which may be negotiable are numbers 2 and 3 which deal with protective clothing and absorption factors. It is unlikely that even a "best case" scenario can produce MOE values greater than 100.

Attached to the August 27, 1992 letter from Charles G. Keefer was a letter from John P. Hopley, Toxicologist at Sandoz Agro, Inc. Dr. Hopley cited an interim report of the IRDC Reproductive Toxicity study in describing the ocular lesions being found in one F<sub>1b</sub> litter in the 15 ppm group at lactation day 21 as "Non-specific lenticular change and one that may be reversible." This information conflicts with the ophthalmology summary in the Sec. 6 (a)(2) report which described bilateral cataracts in pups upon opening their eyes. Dr. Hopley's letter did not mention the mid and high-dose pups.

**1-Year Feeding Toxicity Study in Beagle Dogs - MRID No. 40375201  
American Biogenics Corporation, Study No. 410-1828, June 27, 1987**

Groups of 6 male and 6 female dogs were dosed with technical methazole in their feed at 0, 15, 75, and 300 (reduced to 150 ppm at study week 17) ppm (0, 0.375, 1.875, and 7.500 mg/kg/day). A high-dose female was sacrificed on study day 95, and a low-dose male was sacrificed on study day 202. Both of these dogs had gastric mucosal atrophy with secondary changes of related tissues which could decrease the animal's ability to digest foods (these findings were not found in dogs which survived to termination). Food consumption was comparable for all groups. Body weights were significantly decreased at 300 ppm (especially in the females), with gradual recovery after the dose was reduced to 150 ppm. The high-dose dogs were emaciated and had a pale appearance, which reversed following dose reduction. The dogs were described as having signs of malnutrition.

No significant eye lesions were found pretest or at study termination by the Board-Certified Veterinary Ophthalmologist, Alan H. Brightman. Evaluation included pupillary light responses, indirect ophthalmoscope and slit lamp biomicroscope after dilation, and intraocular eye pressure. A detailed report by the ophthalmologist (Appendix H, fische 9 of 10) revealed a few minor eye lesions, but **no evidence of cataracts**.

This study received Quality Assurance review, and upon cursory review, appears to be a well conducted study. The doses were appropriate, although the high-dose was probably reduced more than it should have been.

**90-Day Feeding Toxicity Study in Dogs - MRID No. 155128  
American Biogenics Corporation, Study No. 410-1827, November 21, 1985**

Groups of 4 male and 4 female dogs were dosed with technical methazole in their feed at 0, 30, 100, and 300 ppm (0, 0.750, 2.500, and 7.500 mg/kg/day). There were no deaths or moribund sacrifices.

Food consumption was comparable for all groups. Body weights were significantly decreased at 300 ppm in the females.

No significant eye lesions were found pretest or at study termination by the Board-Certified Veterinary Ophthalmologist, Alan H. Brightman. Evaluation included pupillary light responses, and indirect ophthalmoscope and slit lamp biomicroscope after dilation. A detailed report by the ophthalmologist (Appendix F, fische 5 of 7) revealed a few minor eye lesions, but **no evidence of cataracts**.

This study received Quality Assurance review, and upon cursory review, appears to be a well conducted study. The high-dose could have been higher.

**93-Week Feeding Oncogenicity Study in Mice - MRID No. 40859701**  
**American Biogenics Corporation, Study No. 410-1825, June 10, 1988**

Groups of 50 male and 50 female CD-1 mice (with additional satellite groups of 10/sex) were dosed with technical methazole in their feed at 0, 30, 100, 300, and 1000 ppm (0, 4.5, 15, 45, and 150 mg/kg/day). Survival was reduced in the 300 and 1000 ppm males, and the 1000 ppm females (30%, 40%, and 27%, respectively).

Food consumption was comparable for all groups. Body weights were significantly decreased in the 1000 ppm males, and the 300 and 1000 ppm females.

The study design did not call for ophthalmologic examination, and there was no mention of a veterinary ophthalmologist in the list of key scientists. **Although ophthalmologic examination is not required for this type of study, it would have been expedient to include examination of at least the control and high-dose mice.** The only reference to eye lesions was on study page 27 which reports, "Antemortem clinical observations recorded during this study were typical of those normally seen in similar populations of CD-1 mice utilized in lifespan studies. The most commonly seen findings were changes of the eyes and body surface. These included opacities, abrasions, tissue masses, blue or yellow-brown discolorations, and thin hair coat or alopecia." A cursory examination of Appendix C reveals many eye opacities in all groups which begin as early as several months into the study. Only a lengthy evaluation could determine whether the incidence and time of onset of these opacities is dose-related, but this does not seem to be the case.

This study received Quality Assurance review, and upon cursory review, appears to be a well conducted study. It is likely that an MTD was not attained.

**90-Day Feeding Study in Rats - MRID No. 155131**  
**American Biogenics Corporation, Study No. 410-1822, November 20, 1985**

Groups of 10 male and 10 female Crl:CD(SD)BR-VAF+ rats were dosed with technical methazole in their feed at 0, 100, 250, and 500 ppm (0, 5, 12.5, and 25 mg/kg/day). Body weights were significantly decreased in the 500 ppm males, and the 100 and 500 ppm females (15%, 15%, and 27%, respectively). Food consumption paralleled body weights.

No significant eye lesions were found pretest or at study termination by the Board-Certified Veterinary Ophthalmologists, Alan H. Brightman and Lloyd C. Helper. Evaluation included indirect ophthalmoscope and slit lamp biomicroscope after dilation. A detailed report by the ophthalmologist (Appendix D, fiche 3 of 6) revealed a few minor eye lesions, but **no evidence of cataracts.**

This study received Quality Assurance review, and upon cursory review, appears to be a well conducted study. The doses appear to be appropriate.

**21-Day Dermal Toxicity Study in Rabbits - MRID No. 40972101  
Hazleton Laboratories America, Inc., Study No. 686-169, January 12, 1989**

Technical methazole was suspended in corn oil and applied to the skin of rabbits (10% body surface area) five days a week for 3 weeks. Each dosing interval was 6 hours. Groups of 5 males and 5 females were dosed at 0, 10, 100, and 1000 mg/kg/day. Epidural scaling at the dosing sites of 8 high-dose rabbits was confirmed histopathologically as hyperkeratosis. According to the study summary, there were no signs of systemic toxicity. **Although ophthalmologic examination is not required for a 21-day dermal study, it would have been expedient to include examination of at least the control and high-dose rabbits.**



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

OCT 19 1992

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

MEMORANDUM

SUBJECT: EVALUATION OF REGISTRANT EXPOSURE ASSESSMENT FOR  
METHAZOLE

FROM: David Jaquith  
Special Review and Registration Section I  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C)

*David Jaquith*

TO: Joe Bailey  
Special Review Branch  
Special Review and Reregistration Division (H7508W)

THRU: Steve Knott, Acting Head  
Special Review and Registration Section I  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C)

*Steven M. Knott*

Larry Dorsey, Acting Chief  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C)

*Larry Dorsey*

Please find below the OREB review of ....

DP Barcode:   N/A   Pesticide Chemical Code: \_\_\_\_\_

EPA Reg. No.: \_\_\_\_\_

Deferral to:

PHED: Yes

*memo: 11 pages  
attachment: 10 pages*

## I. INTRODUCTION

### A. Background

OREB has been requested to review an exposure assessment submitted by Sandoz Agro, Inc. for workers using the herbicide methazole on cotton. Methazole is marketed as a water dispersible granular formulation containing 75 percent active ingredient under the name Probe. The material is registered for use on cotton only and is applied using ground equipment. Both pre-emergent and post-emergent applications are allowed, using either broadcast or banded application techniques. The maximum total application rate of Probe is 2.0 pounds per acre (1.5 lb ai per year). Workers are required to wear protective clothing and protective gloves while handling this pesticide. Exposure is estimated to occur for 2-3 days per application to a typical 250 acre cotton farm, separated by an interval of several weeks. Sandoz Agro, Inc., the sole registrant for this material, has requested a voluntary cancellation of this material because of toxicological concerns. The company wishes to use the existing stocks of this compound.

### B. Purpose

OREB has previously calculated exposure estimates for methazole in a memorandum dated August 4, 1992 (1). These daily exposures were derived from data available in the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated May 13, 1992. The assumptions used in subsetting the database as well as the exposure scenarios are contained in OREBs previous review which is attached as Appendix A. The resulting dermal exposures from this assessment, normalized by pounds of active ingredient handled were 0.016 mg for applicators and 0.20 mg for mixer/loaders. The corresponding respiratory exposures were 0.00049 mg and 0.0027 mg, respectively. **Note that these are unit exposures only, not the daily exposures used for hazard assessment.**

## II. DETAILED CONSIDERATIONS

The registrant has submitted two separate assessments of handler exposure, one based on three surrogate studies found in the literature (2,3,4), and a second derived from PHED using different assumptions.

**A. Assessment derived from surrogate data from the scientific literature:**

**CITATION:** Atallah, Y.H., W.P. Cahill, and D.M. Whitacre (1982) Exposure of Pesticide Applicators and Support Personnel to O-Ethyl-O-(4-Nitrophenyl) Phenylphosphonothioate (EPN). Arch. Environm. Contam. Toxicol. Vol. 11, 219-225.

Dermal and respiratory exposures of workers during mixing/loading, application or flagging operations were monitored during application of O-Ethyl-O-(4-Nitrophenyl) Phenylphosphonothioate (EPN) to cotton. Applications were conducted using ground boom or aerial equipment. Dermal exposure of the body was monitored using denim patches attached outside the clothing at various locations. Hand exposure was measured by hand rinse. Respiratory exposure was estimated by drawing measured amounts of air through silica gel sampling tubes attached to the worker near the breathing zone.

The study consisted of four separate tests:

- Test I** Three pilots, one loader, and one flagger were monitored for EPN exposure. Open pour mixing/loading was used to transfer the insecticide into a nurse tank.
- Test II** Two ground boom applicators, spraying their own fields with their own equipment were monitored.
- Tests III/IV** A pilot, mixer/loader and flagger were monitored.

The exposures of individual body areas were not reported. The estimates of exposure, calculated by Sandoz for methazole using values from this study, are presented in Table 1. Sample calculations were not provided.

**Table 1. Estimates of Exposure to Methazole Provided by Sandoz Using Data From Atallah, Y.H., W.P. Cahill, and D.M. Whitacre (1982)**

Exposure of Pesticide Applicators and Support Personnel to O-Ethyl- O-(4-Nitrophenyl) Phenylphosphonothioate (EPN). Arch. Environm. Contam. Toxicol. Vol. 11, 219-225. Sample calculations were not provided.

	Minimum	$\mu\text{g}/8$ hrs Maximum	Mean	$\mu\text{g}/\text{kg}/\text{day}$ for an 8 hour day
<b>Ground Applicators</b>				
Respiratory	11.5	67.6	40	0.57
Dermal	2100	12900	7500	107.14
Total	2111.5	12967.6	7540	107.7
<b>Mixer/Loaders</b>				
Respiratory	10.5	18.3	15.2	0.027
Dermal	830	14700	6300	11.25
Total	840.5	14718.3	6315.2	11.3

**CITATION:** Putnam, A.R., M.D. Willis, L.K. Binning, and P.F. Boldt (1983) Exposure of Pesticide Applicators to Nitrofen: Influence of Formulation, Handling Systems, and Protective Garments. Jour. Agric. Food Chem. Vol. 31, 645-650.

Exposures of 10 cooperators were monitored during mixing/loading or application of the herbicide nitrofen. Either a wettable powder (50% active ingredient) or an emulsifiable concentrate (25% active ingredient) were used. Both open pour and closed loading systems were tested in the case of the emulsifiable concentrate. Workers wore protective coveralls (with a Teflon layer sandwiched between 2 rip stop nylon layers), rubber gloves, boots, and an air purifying helmet. One applicator used an air purifying closed cab tractor. Dermal exposure was monitored by attaching gauze pads, both inside and outside of the coverall or helmet, on the chest, lower leg, forearm, and head. Hand exposure was monitored using gauze

pads attached inside and outside the protective gloves with elastic bands. Inhalation exposure was estimated by drawing air through XAD-4 resin tubes. The estimates of exposure, calculated by Sandoz for methazole using values from this study, are presented in Table 2. Sample calculations were not provided.

**Table 2.** Estimates of Exposure to Methazole Provided by Sandoz Using Data From Putnam, A.R., M.D. Willis, L.K. Binning, and P.F. Boldt (1983) Exposure of Pesticide Applicators to Nitrofen: Influence of Formulation, Handling Systems, and Protective Garments. *Jour. Agric. Food Chem.* Vol. 31, 645-650. Exposures are based on a 5-hour work day (1 hour mixing/loading, 4 hours applying). Workers wore protective coveralls and helmets.

	Formulating and Handling		
	EC Closed	EC Open	Wettable Powder
Respiratory: Inside Helmet	11	20	208
Dermal: Inside Garment	215	228	327
Total	226	248	535
Exposure ( $\mu\text{g}/\text{kg}/\text{day}$ )	3.2	3.54	7.64

**CITATION:** Sutherland, J.A., W.J. King, H.M. Dobson, W.R. Ingram, M.R. Attique, and W. Sanjrani (1990) Effect of Application Volume and Method on Spray Operator Contamination by Insecticide, During Cotton Spraying. *Crop Protection*, Vol 9, 343-350.

Worker exposures to pesticides were estimated, using a fluorescent tracer technique, during treatment of cotton in Pakistan. The study addressed applicator exposure only. Applications were conducted using knapsack sprayers, a mistblower, spinning-disc apparatus, and an electrostatic sprayer. Several different spray volumes were used. Workers wore disposable polyolefin (Tyvek®) coveralls, cloths to protect the face, and shoes. Gloves were not worn. Fluorescent tracer was added to the spray mix at a nominal level of 1 percent. Suits were stored at 28 °C until analysis. Each suit was photographed under UV light prior to analysis. The suits were then cut into sections and analyzed for the dye. Hand exposure was not monitored. The exposure estimates, calculated by the

registrant using data from this study are presented in Table 3. Sample calculations were not provided.

**Table 3.** Estimates of Exposure to Methazole Provided by Sandoz Using Data From Sutherland, J.A., W.J. King, H.M. Dobson, W.R. Ingram, M.R. Attique, and W. Sanjrani (1990) Effect of Application Volume and Method on Spray Operator Contamination by Insecticide During Cotton Spraying. Crop Protection, Vol 9, 343-350.

	$\mu\text{g/hr}$	$\mu\text{g/8 hr day}$	$\mu\text{g/kg/day}$
	325	2600	37
	256	2048	29
	350	2800	40
	797	6376	91
Average Unprotected	432	3456	49
Average Protected (90% Protection)	43	346	5

#### B. Registrants Assessment Using PHED

The registrant conducted separate PHED exposure estimates for applicators and mixer/loaders.

Clothing: long pants, long sleeves, no gloves  
Respiration Rate = 29 liters per minute

##### Mixer/loader:

The mixer/loader subset, PROBE.MLOD, was created from the master PHED mixer/loader file MXLD.FILE. The dataset was subsetted by the parameter dry flowable formulation and open pouring, yielding 16 replicates. Protective coveralls over no clothing was selected to determine worker exposures. All data came from a single study. Total dermal exposure, using the best fit composite value, was 93  $\mu\text{g}$  per pound active handled. The geometric mean respiratory exposure was 0.78  $\mu\text{g}$  per pound active. Total exposure was 94  $\mu\text{g}$  per pound active ingredient handled. A copy of the summary statistics, generated by OREB to confirm the registrants unit exposure, is presented in Appendix B.

**Applicator:**

Applicator exposure was estimated using the subset PROBE.APPL created from the applicator file APPL.FILE. Tractor drawn ground boom was selected yielding a subset containing 83 records. Emulsifiable concentrates, aqueous suspensions, solutions and wettable powders were included. After comparing the results of this subset to others generated by the registrant it was judged that formulation type, quality grade (dermal or inhalation), application rate and spray rate had no appreciable effect on exposure. Dermal and respiratory exposures were 27  $\mu\text{g}$  and 0.67  $\mu\text{g}$  per pound of active ingredient handled, respectively. A copy of the summary statistics, generated by OREB to confirm the registrants unit exposure, is presented in Appendix C.

### III. CONCLUSIONS

OREB has examined the registrant's exposure assessments for the use of methazole on cotton, both an assessment derived from literature data and one using the Pesticide Handlers Exposure Database (PHED). The literature assessment was based on three studies of worker exposure. Each study has its own individual weaknesses. The registrant indicates that the mixer/loader exposures from these surrogate studies should be used because the PHED estimate is obtained from one study and that a typical container is completely emptied during mixing/loading, minimizing repeat contact. OREB notes that there are more replicates in this single study than in all three literature studies combined and that there is no indication that exposures are less when a container is completely emptied. Appreciable exposure could occur from contact with contaminated equipment rather than the container itself. It is OREBs opinion that none of these studies, either individually or in concert, provides as reliable an estimate of exposure to workers as that derived from PHED.

The registrant has also provided an exposure assessment obtained from PHED. While OREB was able to confirm the summary statistics provided by the registrant (see Appendices B and C), there were some differences between OREBs original assessments and those of the registrant. The differences between OREBs original assessment and those of the registrant are summarized in Table 4.

Preliminary information provided to OREB indicated that methazole (PROBE) was a wettable powder formulation. Recent information shows that it is a water dispersible granular formulation which is synonymous with a dry flowable. OREB accepts the registrants PHED assessment for the unit exposure for mixer/loaders handling a dry flowable formulation. This

assessment reduces the estimate of total mixer/loader exposure from 198  $\mu\text{g}$  to 94  $\mu\text{g}$  per pound of active ingredient handled.

The registrant provided PHED estimates of applicator exposure assuming that applicators wear long sleeve shirts, long pants, and no gloves. The label (5) requires individuals handling methazole to "wear impervious gloves and protective clothing when handling". OREB considers an applicator to be a pesticide handler as indicated in the Worker Protection Standards (6). Therefore, applicators as well as mixer/loaders must wear the required protective equipment. OREBs estimate of unit exposure for applicators (17  $\mu\text{g}$  per pound active applied) assumed the use of this equipment. The registrants estimate was based on the assumption of normal work clothing and yielded a value of 27  $\mu\text{g}$  per pound active applied. **OREB continues to use the values obtained using the label required clothing for purposes of exposure assessment and emphasizes that such clothing must be worn during application.**

**Table 4.** Comparison of OREB and Sandoz Estimates of Unit Exposure to Workers Applying Methazole.

Worker Category	Original OREB Estimate ( $\mu\text{g}/\text{lb ai}$ )	Registrant Estimate ( $\mu\text{g}/\text{lb ai}$ )	Revised OREB Estimate ( $\mu\text{g}/\text{lb ai}$ )	Reasons for difference/change
Mixer/loader	196	94	94	Difference in formulation category; wettable powders were originally selected by OREB, dry flowable judged to be more appropriate.
Applicator	16	27	16	No change in OREB estimate; registrant estimate did not include the label required protective clothing.
Total	212	121	110	See above.

The registrant has also proposed several label changes intended to reduce the potential exposures of these workers. These proposals and some toxicological considerations were submitted to the Agency in a letter dated September 23, 1992 (7). This review will only address those relating to exposure issues. Toxicological considerations are beyond the purview of OREB and need to be addressed by Toxicology Branch. The registrant also presented application parameters which should be evaluated by BEAD. Until changes are indicated OREB will continue to use the use parameters (areas treated, equipment, etc.) provided by BEAD and referenced in OREBs earlier assessment (1).

The registrant proposed a label change to reduce the maximum application rate to 0.25 pounds of active ingredient per acre, which they believe to be the maximum application rate in the major market area. The registrant further states that the classification as a wettable granular instead of a wettable powder, post-directed spray, respirators, and eye protection would further limit exposure. The changes produced by altering the classification of the Probe<sup>®</sup> formulation to water dispersible granular (dry flowable) have been discussed above. Since respiratory exposure was only a very small component of total exposure, the addition of respirators would have only minimal effect on the MOEs for this compound. Similarly, the use of eye protection (unspecified), while helping to protect the worker from spills and other incidences, has little effect (maximum of approximately 17 percent for mixer/loaders) on the total exposure, protecting only the area covered by goggles or face shield.

The registrant has proposed a label change of the maximum label application rate to 0.25 pounds of active ingredient per acre (0.33 lb product per acre) coupled with a post-emergent directed spray. The combination of these proposed parameters with the unit exposure values presented in Table 4, would yield the daily exposures presented in Table 5.

**Table 5. Revised Estimates of Dermal and Respiratory Exposures of Workers Applying Methazole to Cotton Using Ground Equipment. Exposures were derived from Pesticide Handlers Exposure Database (PHED), Version 1.01, dated May 13, 1992. Protective clothing and gloves are assumed. The formulation is considered to be a dry flowable. Values in **Boldface reflect proposed label changes.****

Application Type	Application Rate	Applicator Exposure		M/L Exposure		Combined		Total
		Dermal	Respiratory	Dermal	Respiratory	Dermal	Respiratory	
Broadcast-Preemergent	1.0	0.042	0.00130	0.25	0.0021	0.288	0.0030	0.29
	1.5	0.063	0.00194	0.37	0.0031	0.432	0.0050	0.44
Banded - Preemergent	0.33	0.017	0.00053	0.10	0.0008	0.118	0.0014	0.12
	0.50	0.026	0.00080	0.15	0.0013	0.178	0.0021	0.18
Broadcast-Postemergent	0.50	0.014	0.00043	0.08	0.0007	0.097	0.0011	0.10
	0.75	0.021	0.00065	0.12	0.0010	0.145	0.0017	0.15
	1.5	0.043	0.00130	0.25	0.0021	0.290	0.0034	0.29
Banded-Postemergent	0.17	0.003	0.00010	0.02	0.0002	0.023	0.0003	0.02
	0.25	0.005	0.00015	0.03	0.0002	0.034	0.0004	0.03
	0.50	0.010	0.00031	0.06	0.0005	0.069	0.0008	0.07

IV. REFERENCES

- 1) Memorandum from D. Jaquith (OREB) to K. Bouve (PMSD) titled "Exposure Assessment for Methazole on Cotton", dated August 4, 1992.
- 2) Atallah, Y.H., W.P. Cahill, and D.M. Whitacre (1982) Exposure of Pesticide Applicators and Support Personnel to O-Ethyl-O-(4-Nitrophenyl) Phenylphosphonothioate (EPN).
- 3) Putnam, A.R., M.D. Willis, L.K. Binning, and P.F. Boldt (1983) Exposure of Pesticide Applicators to Nitrofen: Influence of Formulation, Handling Systems, and Protective Garments. Jour. Agric. Food Chem. Vol. 31, 645-650.
- 4) Sutherland, J.A., W.J. King, H.M. Dobson, W.R. Ingram, M.R. Attique, and W. Sanjrani (1990) Effect of Application Volume and Method on Spray Operator Contamination by Insecticide During Cotton Spraying. Crop Protection, Vol 9, 343-350.
- 5) Label for PROBE<sup>®</sup> Herbicide, EPA Reg. No. 55947-23, accepted 23 April 1992.
- 6) Worker Protection Standard, Hazard Information, Hand Labor Tasks on Cut Flowers and Ferns Exception; Final Rule, and Proposed Rules. 40 CFR Parts 156 and 170, published August 21, 1992.
- 7) Letter from C. Keefer (Sandoz) to J. Housenger (SRB) dated September 23, 1992.

cc: D. Jaquith/OREB  
Correspondence File  
Chemical file/Methazole  
Circulation

APPENDIX A.



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

AUG 4 1992

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

MEMORANDUM

SUBJECT: EXPOSURE ASSESSMENT FOR METHAZOLE ON COTTON

TO: Kathryn S. Bouve  
Special Projects and Coordination Staff  
Program Management and Support Division (H7502C)

FROM: David Jaquith  
Special Review and Registration Section I  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C) *D. Jaquith*

THRU: Steve Knott, Acting Section Head  
Special Review and Registration Section I  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C) *Steve Knott*

THRU: Larry Dorsey, Acting Chief  
Occupational and Residential Exposure Branch  
Health Effects Division (H7509C) *Larry Dorsey*

Please find below the OREB review of ....

HED Project #: \_\_\_\_\_

RD or SRRD Record #: \_\_\_\_\_

Caswell #: \_\_\_\_\_

Date Received: 07/28/92 Review Time: 2 days

Date Returned: 7/31/92

Deferral to: \_\_\_\_\_ Biological Analysis Branch/BEAD

\_\_\_\_\_ Science Coordination Branch

\_\_\_\_\_ TB -I

\_\_\_\_\_ TB -II

## **1.0 INTRODUCTION**

OREB has been requested to estimate potential dermal and respiratory exposures of workers to methazole. Methazole is a wettable powder formulation containing 75 percent active ingredient and is marketed under the name PROBE. The formulation is registered for use on cotton only and is applied using ground equipment. The product is applied for both preemergent and post emergent weed control with a maximum total application of 1.5 lb active ingredient per year. The registrant for this material, Sandoz Agro Inc., has requested voluntary cancellation of this registration because of toxicological concerns and requests the ability to use existing stocks of material.

Workers using methazole are required to wear protective clothing and impervious gloves while handling the pesticide. OREB has estimated exposures using surrogate data contained in the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated May 13, 1992.

## **2.0 CONCLUSIONS**

OREB has estimated exposures for applicators, mixer/loaders, and mixer/loader/applicators to the herbicide methazole. The daily exposures were derived from data available in the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated 5/13/92. These estimated exposures are presented in Table 1. Exposure is likely to occur in 2-3 day intervals separated by several weeks.

## **3.0 CALCULATION OF EXPOSURES**

### **3.1 Use Parameters**

OREB has obtained use parameters for the use of methazole on cotton from BEAD and an earlier assessment for azodrin use on cotton. The following use information was used in these assessments:

- 1) An average cotton farm consists of 250 acres.
- 2) Preemergent application is either by broadcast or band application. Broadcast application is typically 1.0 to 1.5 lb ai per acre. Band application is at a rate approximately one third of the broadcast rate.
- 3) Postemergent application is at rates of 0.5, 0.75, or 1.5 lb ai per acre. Band application is again at a rate of about one third of the broadcast rate.

Table 1. Estimated Dermal and Respiratory Exposures of Workers Applying Methazole to Cotton Using Ground Equipment. Exposures were derived from Pesticide Handlers Exposure Database (PHED), Version 1.01, dated May 13, 1992. Protective clothing and gloves are assumed.

Application Type	lb ai/A	Applicator Exposure (mg/kg/day)		M/L Exposure (mg/kg/day)		Combined (mg/kg/day)				
		Dermal	Resp.	Total	Dermal	Resp.	Total	Dermal	Resp.	Total
Broadcast- Preemergent	1.0	0.042	0.00130	0.044	0.53	0.0071	0.536	0.571	0.0084	0.58
	1.5	0.063	0.00194	0.065	0.79	0.0107	0.804	0.856	0.0126	0.87
	0.33	0.017	0.00053	0.018	0.22	0.0029	0.219	0.233	0.0034	0.24
Banded - Preemergent	0.50	0.026	0.00080	0.027	0.33	0.0044	0.332	0.353	0.0052	0.36
	0.50	0.014	0.00043	0.015	0.18	0.0024	0.180	0.191	0.0028	0.19
	0.75	0.021	0.00065	0.022	0.27	0.0036	0.269	0.287	0.0042	0.29
Broadcast- Postemergent	1.5	0.043	0.00130	0.044	0.53	0.0072	0.539	0.574	0.0085	0.58
	0.17	0.003	0.00010	0.004	0.04	0.0006	0.043	0.046	0.0007	0.05
	0.25	0.005	0.00015	0.005	0.06	0.0008	0.064	0.068	0.0010	0.07
Banded- Postemergent	0.50	0.010	0.00031	0.010	0.13	0.0017	0.127	0.136	0.0020	0.14

- 4) While BEAD reports that 250 acres can be treated in one day if wide booms are used, the tables indicate that a 45 foot boom is more likely and this number was used for these assessments. Postemergent application must be conducted at a lower speed to prevent crop damage. Acres treated per day were obtained from a computerized database program written by BEAD personnel. The following parameters were used:

**a) Preemergent - Broadcast**

Tank Capacity = 250 gal.  
Swath width = 45 ft.  
Finished Spray = 30 gal/A  
Run length = 250 ft  
Water station = 200 yd  
Refill time = 2.5 min.  
Speed 5.0 mph  
The acreage treated per day under these conditions is 185.

**b) Preemergent - Banded**

Tank Capacity = 250 gal.  
Swath width = 45 ft.  
Finished Spray = 30 gal/A  
Run length = 250 ft  
Water station = 200 yd  
Refill time = 2.5 min.  
Speed 2.0 mph  
The acreage treated per day under these conditions is 229

**c) Postemergent - Broadcast**

Tank Capacity = 250 gal.  
Swath width = 45 ft.  
Finished Spray = 30 gal/A  
Run length = 250 ft  
Water station = 200 yd  
Refill time = 2.5 min.  
Speed 3.0 mph  
The acreage treated per day under these conditions is 124.

**d) Postemergent - Banded**

Tank Capacity = 250 gal.  
Swath width = 45 ft.  
Finished Spray = 30 gal/A  
Run length = 250 ft  
Water station = 200 yd  
Refill time = 2.5 min.  
Speed 2.0 mph  
The acreage treated per day under these conditions is 88.

These parameters indicate that a typical 250 acre farm will take about 2-3 days per treatment. The label allows only one preemergent application so these treatments would likely be several weeks apart. The total amounts of active ingredient applied per day are presented in Table 2. OREB notes that different combinations may be used under certain conditions and these should be considered typical amounts only.

Table 2. Amounts of Methazole Applied to Cotton Using Ground Equipment Under Different Application Rates and Application Types.

Application Type	Application Rate (lb ai/A)	Acres per day	Amount Handled per day (lbs ai)
Broadcast-Preemergent	1.0	185	185
	1.5	185	278
Banded - Preemergent	0.33	229	76
	0.50	229	115
Broadcast-Postemergent	0.50	124	62
	0.75	124	93
	1.5	124	186
Banded-Postemergent	0.17	88	15
	0.25	88	22
	0.50	88	44

### 3.2 Exposure Parameters

In order to estimate exposures of these workers a number of additional exposure parameters were necessary:

- 1) An average worker weighs 70 kg and has a respiratory volume of 25 liters per minute while mixing/loading or application.
- 2) The same worker performs both the mixing/loading and application tasks.
- 3) Growers apply methazole themselves. Commercial application is minimal.
- 4) Workers wear the label required protective clothing and impervious gloves.
- 5) The label does not specify a cab type so no attempt was made to isolate this factor.

Unit exposures were obtained from the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated 5/13/92. The following subsets and factors were used.

**Applicators:**

The APPL.FILE was subsetted for ground Boom tractor drawn or ground boom truck drawn, yielding 111 records. No cab type was selected. No attempt was made to adjust for quality assurance grade. Combined dermal and respiratory exposures were selected, normalized by pounds active ingredient handled. Respiratory volume was 25 liters per minute. Protective category was overalls over no additional clothing, with gloves. Actual and estimated head patches were used. A copy of the printout for this subset and the resulting exposures is presented in Appendix A.

**Mixer/loaders:**

Subset PROBEWP.MLOD was created from MIXLD.FILE and contained 41 records. Wettable powders were selected. No attempt was made to adjust for quality assurance grade. Combined dermal and respiratory exposures were selected, normalized by pounds active ingredient handled. Respiratory volume was 25 liters per minute. Protective category was overalls over no additional clothing, with gloves. Actual and estimated head patches were used. A copy of the printout for this subset and the resulting exposures is presented in Appendix B. The mixer/loader/applicator file (MLAP.FILE) contained insufficient data to use for this assessment.

The results provided by PHED for applicators and mixer/loaders are presented in Appendices A and B, respectively. It must be noted that the replicates used for these estimates were not selected on the bases of quality assurance score and that the number of available data points is minimal for certain body areas. The resulting unit dermal exposure values 16.1404  $\mu\text{g}/\text{lb ai}$  (0.016 mg/lb ai) for applicators and 195.7771  $\mu\text{g}/\text{lb ai}$  (0.20 mg/lb ai) for mixer/loaders. The corresponding respiratory exposures were 0.491  $\mu\text{g}/\text{lb ai}$  (0.00049 mg/lb ai) and 2.6977  $\mu\text{g}/\text{lb ai}$  (0.0027 mg/lb ai) for applicators and mixer/loaders, respectively. Total applicator exposure, as derived by PHED, was 16.6314  $\mu\text{g}$  per pound active ingredient applied (0.016 mg/lb ai). In the case of the mixer/loaders, the total exposure was 198.4748  $\mu\text{g}$  per pound active ingredient handled (0.20 mg/lb ai). **These numbers are composites derived by summing the best estimate of central tendency for each body area and inhalation exposure.** In the cases where the distribution of a body area was normal, the arithmetic mean was used. Where the distribution of an exposure source was lognormal or unknown (other) the geometric mean or median were used, respectively. It must be noted that, in cases where sample sizes are small the determination of the appropriate distribution cannot be reliably ascertained and the estimates must be used cautiously. The estimates of total daily exposure for mixer/loaders and applicators applying methazole are presented in Table 1.

Appendix A. Exposure Statistics for Applicators Applying Methazole to Cotton Using Ground Boom Equipment. Obtained from the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated 5/13/92.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Protective overall over no clothing, gloves		MICROGRAMS PER LB AI SPRAYED				Obs.
PATCH	DISTRIB.	Mean	Coef of Var	Geo. Mean	Mean	
LOCATION	TYPE	Median				
HEAD (ALL)	Lognormal	3.51	20.4558	220.9774	3.2635	105
NECK.FRONT	Lognormal	.36	2.5226	238.4405	.3608	103
NECK.BACK	Lognormal	.154	1.8342	233.486	.2303	102
UPPER ARMS	Other	.582	61.0918	228.8233	1.6244	16
CHEST	Lognormal	1.5975	4.4153	139.1049	1.6924	16
BACK	Lognormal	1.775	63.9	246.7903	2.8475	19
FOREARMS	Lognormal	.6655	4.5012	319.7481	.8009	20
THIGHS	Lognormal	.573	.573	47.1379	.5402	2
LOWER LEGS	Lognormal	1.666	2.6067	123.359	1.3326	21
FEET						0
HANDS	Lognormal	7.742	12.8573	114.1313	4.4902	18
TOTAL DERM:	16.1404	18.625	174.7579		17.1828	
INHALATION:	Other	.491	3.6831	227.1592	.5532	108
COMBINED:	16.6314	19.116	178.441		17.736	

95% C.I. on Mean: Dermal: [-2970.6567, 3320.1725]

95% C.I. on Geo. Mean: Inhalation: [.009, 33.8257]

Inhalation Rate : 25 Liters/Minute Number of Records: 111

Data File: APPLICATOR Subset Name: PROBE.APPL

Appendix B. Exposure Statistics for Mixer/loaders Handling a Wetable Powder Formulation of Methazole to Cotton Using Ground Boom Equipment. Obtained from the Pesticide Handlers Exposure Database (PHED), Version 1.01, dated 5/13/92.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Protective overall over no clothing, gloves

PATCH LOCATIONS

LOCATIONS	TYPE	Median	Mean	Coef of Var	Geo. Mean	Obs.
HEAD (ALL)	Lognormal	52.26	65.31	94.0289	22.9793	39
NECK.FRONT	Normal	9.165	10.6708	92.9537	3.8922	39
NECK.BACK	Normal	3.025	4.6056	118.8054	1.3032	39
UPPER ARMS	Lognormal	18.333	127.6035	140.0647	29.2713	8
CHEST	Lognormal	13.49	68.515	185.5086	20.6539	5
BACK	Lognormal	12.78	154.6025	157.03	33.4495	6
FOREARMS	Lognormal	13.189	19.0373	71.4508	14.7038	9
THIGHS	Lognormal	17.572	26.6636	52.9448	23.872	5
LOWER LEGS	Lognormal	4.76	8.7465	106.1659	6.1847	4
FEET						0
HANDS	Lognormal	29.4489	40.0501	77.5958	29.3862	8
TOTAL DERM:	195.7771	174.0229	525.8049		185.6961	
INHALATION:	Lognormal	3.1922	36.6771	276.4136	2.6977	41
COMBINED:	198.4748	177.2151	562.482		188.3938	

95% C.I. on Mean: Dermal: [-7638.1896, 8689.7994]

95% C.I. on Geo. Mean: Inhalation: [.0177, 411.1736]

Inhalation Rate : 25 Liters/Minute Number of Records: 41

Data File: MIXER/LOADER

Subset Name: PROBEWP.MLOD

Appendix B. Unit Exposure Summary Statistics for Mixer/loaders Using Dry Flowable Formulations, Calculated using the Pesticide Handlers Exposure Database (PHED) Version 1.01, dated 5/13/92. Statistics were generated by OREB to confirm results submitted by the registrant.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Protective overall over no clothing, gloves		MICROGRAMS PER LB AI MIXED				Obs.
PATCH	DISTRIB.	Mean	Coef of Var	Geo. Mean		
LOCATION	TYPE	Median				
HEAD (ALL)	Lognormal	16.575	109.9166	17.5482		16
NECK.FRONT	Lognormal	8.055	102.7059	5.8389		16
NECK.BACK	Lognormal	.5665	152.6005	1.1169		16
UPPER ARMS	Lognormal	5.82	122.0349	5.7753		16
CHEST	Lognormal	7.1	56.739	8.0221		16
BACK	Lognormal	5.325	29.4726	5.3841		16
FOREARMS	Lognormal	2.42	74.0267	2.8683		16
THIGHS	Lognormal	21.01	232.209	31.365		16
LOWER LEGS	Other	4.76	246.6433	8.3813		16
FEET						0
HANDS	Lognormal	10.6667	30.8631	10.5675		16
TOTAL DERM:	93.2463	82.2982	261.5814	96.8676		
INHALATION:	Lognormal	.7332	113.7862	.7752		16
COMBINED:	94.0215	83.0314	262.7768	97.6428		

95% C.I. on Mean: Dermal: [-5059.0451, 5582.2079]

95% C.I. on Geo. Mean: Inhalation: [.1209, 4.9721]

Inhalation Rate : 29 Liters/Minute      Number of Records: 16

Data File: MIXER/LOADER      Subset Name: PROBE.WDG.MLOD

Appendix C. Unit Exposure Summary Statistics for Applicators Using Ground Boom Equipment, Calculated using the Pesticide Handlers Exposure Database (PHED) Version 1.01, dated 5/13/92. Statistics were generated by OREB to confirm results submitted by the registrant.

SUMMARY STATISTICS FOR CALCULATED DERMAL EXPOSURES

SCENARIO: Long pants, long sleeves, no gloves		MICROGRAMS PER LB AI SPRAYED				Obs.
PATCH	DISTRIB.	Mean	Coef of Var	Geo. Mean		
LOCATION	TYPE	Median				
HEAD (ALL)	Lognormal	7.02	188.6086	5.4023		77
NECK.FRONT	Lognormal	.705	205.934	.5523		75
NECK.BACK	Lognormal	.3905	199.368	.3761		74
UPPER ARMS	Other	.291	0	.291		6
CHEST	Other	.71	205.7953	1.621		39
BACK	Other	2.13	181.4676	1.9108		24
FOREARMS	Lognormal	.726	151.5618	.8094		14
THIGHS	Other	.382	165.5202	.5749		14
LOWER LEGS	Other	.238	232.805	.4201		14
FEET						0
HANDS	Lognormal	20.8676	224.686	15.6989		60
TOTAL DERM:	26.59	33.4601	129.3517	27.6568		
INHALATION:	Other	.6664	196.7911	1.1602		80
COMBINED:	27.2564	34.1265	134.9299	28.817		
95% C.I. on Mean:	Dermal: [-1258.7391, 1517.4425]					
95% C.I. on Geo. Mean:	Inhalation: [.033, 40.8102]					
Inhalation Rate:	29 Liters/Minute					
Data File:	APPLICATOR					
	Number of Records: 83					
	Subset Name: PROBE.JSCF.APPL					



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  
Section 1, Toxicology Branch I  
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: 10 pages*

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 -  $\frac{1}{2}$  log of the low dose) are used:

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

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

DIET CONCENTRATION DOSAGE GROUP	GENDER	COUNTS	DESCRIPTION
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 <sup>a</sup> 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

CONFIDENTIAL

ATTACHMENT 2

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

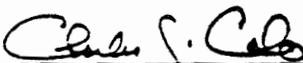
Copies to:

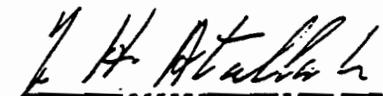
Date: May 7, 1992  
From: Y. H. Atallah 1300  
C. J. Calo 1305  
To: CRAC Members

\*\*\*\*\*  
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).

  
C. J. Calo

  
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 4

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

	<u>Exposure</u> <sup>1/</sup> ( $\mu\text{g}/\text{kg}/\text{day}$ )	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.



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

AUG 12 1992

OFFICE OF  
PESTICIDES AND TOXIC  
SUBSTANCES

Charles G. Keefer  
Director, Regulatory Affairs  
Sandoz Agro, Inc.  
1300 East Touhy Avenue  
Des Plaines, IL 60018

SUBJECT: Voluntary Cancellation of Methazole Products

Dear Mr. Keefer,

This letter is in response to your request, dated May 18, 1992, for voluntary cancellation of Sandoz registered pesticide products containing the active ingredient methazole. I am hereby notifying you that the Agency is accepting your request to cancel the two remaining methazole products. They are a 95% technical formulation (EPA Registration Number 55947-22) and a 75% wettable powder formulation (EPA Registration Number 55947-23).

The Agency is accepting your cancellation request and is waiving the 90-day comment period usually associated with voluntary cancellations. The decision not to allow the 90-day comment period is based on results of the Agency's review of recent 6(a)(2) data submitted by you. Review of that data indicates that the use of products containing methazole may pose unreasonable adverse effects to the environment. The Agency has conducted a risk assessment and calculated margin of exposure values which suggest that unreasonable risks may be posed to workers exposed to methazole. In addition, there are efficacious, cost-effective alternatives available in the marketplace.

Because your products are now cancelled, continued sale or distribution of these products is a violation of FIFRA section 12(a)(1)(A). We will soon issue a cancellation order which will establish provisions controlling the disposition

- 2 -

of existing stocks of these products. To establish acceptable provisions for dealing with existing stocks of methazole, my staff will be contacting you shortly to arrange a meeting.

If you have any questions, please contact Jack Housenger of my staff at (703) 308-8163.

Sincerely,



Douglas D. Campt, Director  
Office of Pesticide Programs