D-13920 SD Methazole

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

9-9-92

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 pecentage 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	100	5	**58%**
in pups upon opening of eyes.	250	12.5	**100%**
Reproduction Study in Rats (IRDC)	15	0.75	**5.5%** ~lowest dose
NOTE: Cataracts were observed	150	7.5	**100%**
in pups upon opening of eyes.	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_{1b} 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, abrations, tissue massses, 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, fische 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.**