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James M. Strock
Secretary for Environmental Protection

MEMORANDUM

TO: Anna M. Fan, Ph.D., Chief
Pesticides and Environmental Toxicology Section

VIA: Michael J. DiBartolomeis, Ph.D., Chief
Pesticide and Food Toxicology Unit MJD

FROM: Jolanta Bankowska, Ph.D.
Staff Toxicologist JB.

DATE: March 27, 1997

SUBJECT: Comments on the DPR's Draft Risk Characterization Document for Cyanazine

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Enclosed are staff's comments on the Department of Pesticide Regulation's (DPR's) draft risk characterization document for the active ingredient cyanazine. We focused primarily on several scientific issues which were identified following the review of DPR's draft document. Because of the short time frame specified by DPR for review and receipt of comments from the Office of Environmental Health Hazard Assessment, staff did not provide their usual details on the toxicological studies and the content of DPR's risk characterization. Our own independent search for information on cyanazine toxicology and health risks was also limited by the short time frame for review.

cc: Lubow Jowa, Ph.D.
David W. Rice, Ph.D.

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MEMORANDUM

TO: Gary Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street
Sacramento, CA 95814-5624

FROM: Anna M. Fan, Ph.D., Chief
Pesticides and Environmental Toxicology Section

DATE: March 31, 1997

SUBJECT: Comments on DPR's Draft Risk Characterization Document for Cyanazine

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Thank you for the opportunity to review the Department of Pesticide Regulation's (DPR's) draft risk characterization document for cyanazine. The draft document contains a large amount of information on the toxicity and health risks of cyanazine. In general, staff found the document to be well-written and complete.

The following are some of the scientific issues that we identified during our review of the draft risk characterization for you to consider when revising the document:

- Explanation for why interim sacrifice data were not used in estimating cancer potency and derivation of an alternative cancer potency.
- Additional information on the differences between DPR's and U.S. EPA's cancer risk assessment for cyanazine.
- Further discussion on the tolerance assessment for both non-oncogenic and carcinogenic toxicological endpoints.
- Multiple chemical exposures from triazine compounds.
- Specific suggestions for clarification and editing of text as noted.

We have provided more detailed comments and recommendations on these issues, as well as others, in the attached memorandum. If you have any questions

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please contact me or Dr. Michael DiBartolomeis at (510) 540-3063.

cc: Michael DiBartolomeis, Ph.D.
William Vance, Ph.D.

ATTACHMENT

Review of the California Department of Pesticide Regulation's Draft Risk Characterization for Cyanazine

The following describes the scientific issues and our recommendations for enhancing the draft risk characterization document.

Continued use of cyanazine

The Executive Summary states "... the current cyanazine registrants, DuPont and Griffin, have voluntarily agreed to phase out and eventually cancel the use of cyanazine, under certain conditions" (page i, paragraph one). However, cyanazine is currently the fifth most heavily used pesticide in the United States and its use in California on cotton has been increasing (see page five, paragraph four). If there are more details available on the schedule of phasing out cyanazine use, it would be useful to include them in the document.

Dietary exposure assessment

The risk characterization document states that tolerances for cyanazine residues were established based on the "... parent material alone without a toxicologically significant degradation product" (Appendix B, page one, paragraph one). Therefore, it appears that cyanazine residue measurements were obtained only for cyanazine parent compound. However, "toxicologically significant degradation products" might be responsible for adverse health effects from cyanazine use. It cannot be excluded that health risks estimated for dietary exposure to the parent compound account for only a fraction of the total estimated risks associated with cyanazine use. We recommend that this issue be addressed in the risk characterization document under a section devoted to uncertainties in risk assessment.

Tolerance assessment

Cyanazine tolerances were assessed only for potential risk resulting from non-oncogenic toxicological endpoints. DPR's tolerance assessment did not include an assessment of tolerances based on cyanazine potential for carcinogenicity. It can be reasonably assumed (based on the results for lifetime cancer

risks from dietary exposure to the anticipated cyanazine residues in food crops) that if carcinogenicity was incorporated into the tolerance assessment, the results would likely show excess individual cancer risks higher than *de minimus*. The document also does not include a determination as to the adequacy of tolerances for health protection. The document would be enhanced if these issues were addressed.

Cyanazine metabolism and biodegradation

A summary table on main cyanazine metabolites in mammals and plants as well as the predominant biodegradation products in soil and water would be useful. If available, information on the persistence of soil degradation products ($t_{1/2}$) containing the triazine ring should be included.

Subchronic toxicity

Several subchronic studies were performed in three species with the most consistent result being the loss of body weight. The risk characterization document summary expresses the concern that the available studies are unacceptable according to DPR's criteria. Nevertheless, NOELs were identified. The NOELs identified from these studies suggest that although there may be certain irregularities in the experimental protocols, data, or reports, DPR staff have a certain degree of confidence in the data. Only for one study description was there any elucidation of the study's deficiencies. It would be helpful if a brief statement of the major limitations, and their potential impact on the characterization of toxicological effects, was included for each subchronic toxicity study.

Chronic toxicity

Consistent with the results of the subchronic studies, the most prominent chronic toxic effect of cyanazine was weight loss. Furthermore, other effects noted such as chronic inanition, poor skin and fur condition and anemia, could be attributed to inadequate nutrition. The chronic studies exhibited fewer technical problems and had more reliable and consistent results than the subchronic studies. For the five studies that were

conducted in three different species, the identified LOELs do not vary by more than a factor of two (page 39).

Three additional effects reported in the chronic rat study of Bogdanffy (1990), and as noted by U.S. EPA (1994), were granulocyte hyperplasia of bone marrow in males, extramedullary hematopoiesis of the spleen in males, and demyelination of the sciatic nerve of female rats. The incidences of these effects were elevated over controls at the highest dose tested, but the draft risk characterization document states that effects were not statistically significant by Fisher's exact test. It would be useful to report the results of a determination of the statistical significance of these effects over historical controls. (NOTE: The U.S. EPA (1994) reference is not adequately identified in the text of the draft risk characterization document as there are two citations in the reference section, U.S. EPA 1994a and 1994b.)

Only one significant instance of compound-related tumors was reported. This was for combined adenocarcinomas and carcinosarcomas of the mammary gland of the female rat. An increased incidence rate (but not thought to be compound-related) of thyroid C cell adenomas was reported in an early study, but was not reproduced in a repeated study with the same strain. It would be useful to discuss whether any similarities exist among the other triazine active ingredients with respect to this thyroid tumor type.

Genotoxicity

The evidence for genotoxicity is equivocal; approximately 50% of the assays performed were positive. Therefore, we agree with DPR that cyanazine should not be ruled out as being a potential mutagen.

Risk characterization

In the risk characterization section of the draft document, it is mentioned that U.S. EPA derived two cancer risk factors for cyanazine; one that initially included interim sacrifice data and a second derivation in which the data were not used. DPR

apparently followed the latter method used by U.S. EPA, that of not including interim sacrifice data in deriving a cancer potency. The mammary tumor data were analyzed using the Linearized Multistage model.

The rationale for the use or non-use of interim sacrifice data is not adequately discussed in the draft risk characterization document. Because U.S. EPA had first used interim sacrifice data in its estimation of cancer potency from experimental data on cyanazine, it is not clear why a second method was chosen by U.S. EPA and DPR. It would be helpful to know whether there has been a change in U.S. EPA's general policy on the use of interim sacrifice data, or whether the data were omitted for the analysis of cyanazine only. Omitting interim sacrifice data may not be consistent with the U.S. EPA's current draft Cancer Risk Assessment Policy.

We recommend that DPR calculate a cancer risk potency using the interim sacrifice data and the Weibull Time-To-Tumor model. The results could then be included in the risk characterization document and compared to the cancer potency derived using the Linearized Multistage model.

DPR and U.S. EPA cyanazine risk assessment

Estimations of lifetime cancer risks from dietary exposure to cyanazine are higher in U.S. EPA's "PD-1; Special review of the Triazine Herbicides," than they are in the draft risk characterization document. U.S. EPA's upper-bound individual lifetime risk is 2.9×10^{-5} and DPR's upper-bound cancer risk is 7.7×10^{-6}. The difference appears to be due, in part, to the different slope factor used by U.S. EPA which is approximately twice that used by DPR. The major contributing factor to the different estimated risk values, however, appears to be the result of the dietary exposure estimates, specifically the anticipated residues. U.S. EPA considers all triazine-ring containing residues to be potentially carcinogenic. Accordingly, U.S. EPA factored in a contribution by triazine metabolites (with intact triazine rings) into the anticipated residues for a particular commodity. It appears that DPR only considered the parent compound. This difference is briefly noted on page 49 of

the draft risk characterization document. A more detailed explanation is warranted, however, given the importance of the endpoint and the magnitude of the cancer risks.

U. S. EPA's occupational cancer risks are also significantly different from those estimated by DPR. DPR reports upper-bound occupational risks of 10^{-5} to 10^{-6} whereas U.S. EPA reports estimates in the range of 10^{-2} to 10^{-6}. These differences should be explained in the risk characterization document.

Multiple chemical exposures

We suggest that the issue of additive exposure to triazine herbicides be addressed in the risk characterization document. This is especially important in relation to carcinogenic risk because the other currently used triazines (atrazine and simazine) display an identical carcinogenic endpoint in laboratory assays (i.e., mammary cancers in female SD rats).

Interpretation of the results

Staff suggest that more explicit statements relating to the description of the quantitative results of the cyanazine risk assessment be included in the document. In various sections of DPR's draft document are statements such as "The excess lifetime cancer risk for the general population was greater than 10^{-6} (1 in 1,000,000)" or "Excess lifetime cancer risk was greater than 10^{-5} (1 in 100,000) for both farmers and commercial applicators." Inclusion of the actual estimated values would provide more useful information.

In order to avoid any confusion with regard to the public health significance of these results, staff recommend that DPR provides interpretation of the results and conclusions regarding the magnitude of cancer risks and whether adequate margins of safety exist to protect public and worker health.

Specific Comments

Executive Summary and Introduction.

Pages iii and 3. It is unclear how statements such as "greater than 1 in 1,000,000" or "greater than 1 in 100,000" should be interpreted. Such statements can lead the reader to conclude that the cancer risks can be quite high because there is no upper end limit associated with these statements. The standard U.S. EPA interpretation of an estimated risk is that actual risk could be as high as the estimated risk, but it would more likely be less, and even possibly zero. Therefore, simplified expressions of risk are often expressed as (for this case) less than 1 in 100,000 or less than 1 in 10,000. It would even be more helpful if a range was given (e.g., more than 1 in 1,000,000 but less than 1 in 100,000).

Page 1, Summary, paragraph 4. A comma splits the superscript from the base number.

Page 1 Summary, paragraph 7. "Genotoxicity was evident in four types of assays using mammalian cells, although not in those assays which were potentially metabolically active." The way it is expressed here might be confusing as assays themselves are not actually "metabolically active." The chemical may become metabolically activated or there is a measurement under metabolic activation. Please clarify.

Page 3, Summary, paragraph 1. DPR states that "Dietary exposure to cyanazine in California is likely to be largely theoretical, as stated. In addition, because it is likely to be considerably less than occupational exposure, it was not considered necessary to calculate safety and risk from combined (dietary and occupational) exposure [*sic*]." It is true that dietary exposures are often less than occupational exposures, but this reasoning should not preclude the calculation of risks from the combined occupational and dietary exposures. DPR has calculated cancer risks resulting from combined occupational and dietary exposures in the past, and it would be appropriate scientifically to continue this practice with cyanazine.

Page 3, Summary, last sentence. This is a difficult sentence to follow; we suggest rewriting.

Pharmacokinetics.

Page 10, paragraph 2. We suggest changing the second sentence to read: "Assuming that the ^{14}C found in the feces was not from absorbed material, 82% of the dose was absorbed from the gut."

Page 10, paragraph 2. We suggest changing the fourth sentence to read: "An experiment in the dog showed 52 to 64% absorption by the oral route."

Page 10, paragraph 2. We suggest changing the last two sentences to read: "In male rats, dermal absorption of cyanazine from an aqueous solution of Bladex 4L averaged 0.9% at 10 hours and 2.0% at 24 hours (the maximum individual value was 4.6% absorbed at 24 hours)."

Page 10, paragraph 3. We suggest changing the fourth sentence to read: "Urine, feces and expired air were collected over a four day period and were assayed for ^{14}C. Radioactivity was also measured in the skin, gut and carcasses of the exposed animals."

Page 10, paragraph 3. We suggest changing the fifth sentence to read: "Over 50% of the radioactivity was eliminated in the first 24 hours (34% and 18% in the urine and feces, respectively). Trace amounts of radioactivity was observed in the feces for four days."

Page 10, paragraph 4. We suggest changing the first sentence to read: Since 18% of the label was eliminated in the feces within 24 hours of administration, it was assumed that...."

Page 11, paragraph 2. The third sentence, which states "The overall fate of cyanazine labeled with ^{14}C in either the ring, the isopropyl-, or the cyano-groups was reported as being similar," is unclear as to what is being compared.

Page 11, paragraph 3. We suggest changing the paragraph to: "A report found in the open literature (Crayford and Hutson, 1972)

suggests that the 2-hydroxy-6-carboxylic acid metabolite can be formed from either the hydroxylated metabolite or amide of cyanazine."

Page 11, paragraph 4. This paragraph discusses the mammalian metabolism of plant metabolites of cyanazine. Animals were dosed with radiolabelled metabolites and something excreted. It is unclear as to what was being excreted - the radiolabel or the "parent metabolite" or something else. Please explain.

Page 12, paragraph 1. We suggest changing the first word in the last sentence of this paragraph from "These ..." to "The solubility problems ...."

Page 12, paragraph 2. This paragraph is somewhat difficult to follow. We suggest rewriting the paragraph to improve its readability.

Page 12, paragraph 2, line one. It would be helpful if more information was provided on the number of time points that were investigated and the duration of the study.

Page 12, paragraph 2, line one. It is not clear what the fourth sentence, which starts "It increased ..." refers to. Perhaps this should say "Absorption increased ...."

Page 12, paragraph 3. We suggest changing the fourth sentence to read: "Peak blood levels of radioactivity following the dermal dose occurred at 10 hours and remained at this level until 96 hours." With regard to the fifth sentence it is not clear what is meant by "analogous plasma levels." It appears to be referring to a comparison of plasma levels of radioactivity following oral and dermal dosing measured at the same time after each dose. Please clarify.

Page 12, paragraph 3. We suggest changing the last sentence in this paragraph to read "It was found that 97 - >99% of the ^{14}C was removed from the skin by washing the application site, indicating that 1 to 3% of the test compound was absorbed during each dermal exposure period."

Page 13, figure 1. It would be helpful if the structures in this figure were labeled. It is difficult to relate the names in the legend to each structure in the text.

Acute Toxicity.

Page 14, paragraph 2. We suggest adding the word "symptoms" as the second word in the first sentence of this paragraph.

Page 14, paragraph 3. We suggest changing the second sentence to read: "Clinical signs and symptoms included those noted above for the technical mixture and diarrhea, tremors ...."

Page 14, paragraph 3. The third sentence is unclear. As written, the document implies that the performance of the necropsy caused the effect. We suggest rewording the sentence.

Page 14, paragraph 3. We suggest changing the second to the last line to read: "displayed similar signs as those dosed with 4L ...."

Page 24, paragraph 2. In the first sentence, the word "assay" in phrase: "... 4 types of assay using ..." should be "assays."

References

Bogdanffy, M.S. (1990). Combined chronic toxicity/ oncogenicity study with cyanazine (IN R1957): Two year feeding study in rats. E.I. DuPont de Nemours and Company, Haskell Laboratory, Report No. HLR 23-90. DPR 307-069 #91251.

U.S. EPA (1994a) or U.S. EPA (1994b).