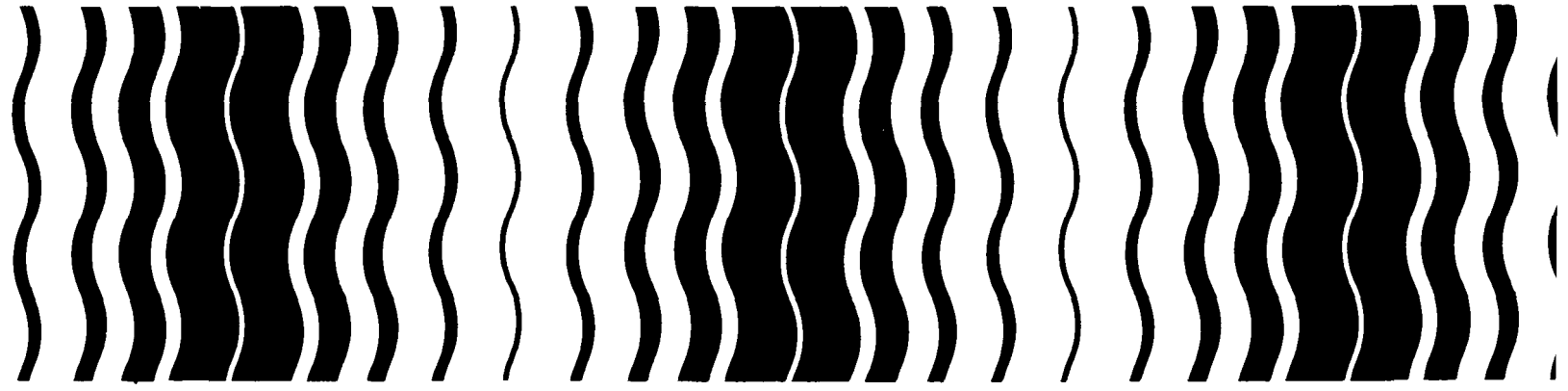
United States
Environmental Protection
Agency

Office of
Pesticides and Toxic Substances
Washington, DC 20460

April 1985

EPA

Cyanazine
Special Review Position Document 1



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ENVIRONMENTAL PROTECTION AGENCY

[OPP-30000/46]

CYANAZINE

SPECIAL REVIEW OF CERTAIN PESTICIDE PRODUCTS

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: [This Notice announces that EPA is initiating a Special Review of all pesticide products containing the active ingredient cyanazine.] EPA has determined that cyanazine, a registered herbicide, produces teratogenic effects in laboratory rats and that sufficient exposure to mixer/loaders and applicators exists so that cyanazine meets or exceeds a risk criterion described in 40 CFR 162.11. Accordingly, a Special Review of products containing cyanazine has been initiated to determine whether registration of these products should be permitted to continue and, if so, under what terms and conditions. During the Special Review process, EPA will carefully examine the risks and benefits of using cyanazine and will determine whether additional regulatory actions are required.

DATE: Comments, evidence to rebut the presumptions in this Notice, and other relevant information must be received no later than 45 days from the date this notice is received or until (insert date 45 days after date of publication in the FEDERAL REGISTER) (whichever is later).

85P-361

ADDRESS: Three copies of written comments identified as (OPP-30000/46) should be sent by mail to:

Information Services Section,
Program Management and Support Division (TS-757C),
Office of Pesticide Programs,
Environmental Protection Agency,
401 M St., SW.,
Washington, D.C. 20460.

In person, bring comments to:

Rm. 236, CM #2,
1921 Jefferson Davis Highway,
Arlington, VA.

Information submitted in any comment concerning this Notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information" (CBI). Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A copy of the comments that do not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice to the submitter. All non-CBI written comments will be available for public inspection in Rm. 236 at the Virginia address given above, from 8 a.m. to 4 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT:

Spencer L. Duffy,

Registration Division (TS-767C),

Office of Pesticide Programs,

Environmental Protection Agency,

401 M St., SW.,

Washington, D.C. 20460.

Office location and telephone number:

Rm. 728, CM #2,

1921 Jefferson Davis Highway,

Arlington, VA,

(703-557-7421).

SUPPLEMENTARY INFORMATION: The term "Special Review" is the name now being used by EPA for the process previously called the Rebuttable Presumption Against Registration (RPAR) process. Modifications to the process have recently been proposed in the Federal Register. The Special Review process provides a mechanism to permit public participation in EPA's deliberations prior to issuance of any final notice of intent to cancel pesticide registrations which may be issued under FIFRA Section 6(b). The Special Review process is described at 40 CFR 162.11 and is usually initiated because one or more of the risk criteria identified in that section have been exceeded, as revealed by testing of the pesticide's active ingredient.

EPA has determined that a Special Review will be conducted for all pesticide products containing cyanazine as an active

ingredient. EPA has also determined that data necessary to conduct the Agency's risk assessment must be developed on an accelerated basis, and that precautionary labeling is required to reduce risk during the Special Review process.

Issuance of this Notice means that potential hazards associated with the use of cyanazine have been identified. These hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of cyanazine, whether such risks cause unreasonable adverse effects on the environment.

A document entitled "Guidance for the Interim Registration of Pesticide Products Containing Cyanazine" (Guidance Document) has been issued. (The Guidance Document is also referred to as a Registration Standard). The Guidance Document is available to the public from the contact person named above. This Guidance Document explains the basis for EPA's decision to start a Special Review and also contains references, background information, data requirements, and other information pertinent to the continued registration of pesticides containing cyanazine.

I. INITIATION OF A SPECIAL REVIEW

A. GENERAL

A pesticide product may be sold or distributed in the United States only if it is registered or exempt from registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 et seq.). Before a product can be registered, it must be shown that it can be used without "un-

reasonable adverse effects on the environment" (FIFRA section 3(c)(5)), that is, without causing "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of the pesticide" (FIFRA section 2(bb)). The burden of proving that a pesticide meets this standard for registration is on the proponent of initial or continued registration. If at any time the Agency determines that a pesticide no longer meets this standard for registration, the Administrator may cancel the registration under section 6 of FIFRA.

The Agency has created an administrative process for fully evaluating whether a pesticide satisfies or continues to satisfy the statutory standard for registration. This Special Review process provides an informal procedure through which EPA may gather and evaluate information about the risks and benefits of a pesticide's uses. It also provides a means by which interested members of the public may comment on and participate in EPA's decision making process. The regulations governing this process are set forth in 40 CFR 162.11.

A Special Review is begun when EPA determines that a pesticide meets or exceeds one or more of the risk criteria set out in the regulations (40 CFR 162.11(a)(3)). The Agency generally announces the beginning of the Special Review by issuing a Position Document 1 (PD 1) which is published in the FEDERAL REGISTER. In addition, registrants of affected products will receive the PD 1 by certified mail. Registrants

and other interested persons are invited to scrutinize the basis for the Agency's decision to initiate the Special Review and to submit data and information which rebut or support the Agency's initial determination regarding risk. Commenters may also suggest methods to reduce risks of use of the pesticide. In addition to addressing risk issues, commenters are encouraged to submit evidence and discussions of the biological, economic, social, and environmental costs and benefits of use of the pesticide. The public participation stage is described in more detail in Unit IV. This Notice constitutes Position Document 1 for pesticide products containing cyanazine.

If risk issues are not satisfactorily resolved, EPA will proceed to evaluate the risks and benefits of cyanazine in order to determine whether to propose regulatory actions to reduce the risks. After providing an opportunity for comment by the Scientific Advisory Panel, the Secretary of Agriculture, registrants, and the public on those actions and the reasons for them, EPA will issue an appropriate final notice. If EPA determines that the risks of use exceed the benefits, EPA will issue a notice of intent to cancel the registration of products intended for such use. The notice may state the intention to cancel registrations outright or may require certain changes in the composition, packaging, application methods and/or labeling of the product. These changes would be intended to reduce the risks to levels that when considered against the benefits will not cause unreasonable adverse effects to man or the environment.

A notice initiating a Special Review is not a notice of intent to cancel the registration of a pesticide, and a Special Review may or may not lead to cancellation. This Notice initiating the Special Review for cyanazine products is an announcement of EPA's concern about the safety of the pesticide's use, and only after carefully considering the risks and benefits of cyanazine and determining that it appears to cause unreasonable adverse effects on the environment, would EPA issue a notice of intent to cancel.

B. PRESUMPTION

EPA has determined that the use of pesticide products containing cyanazine pose risks which meet or exceed one of the risk criteria in 40 CFR 162.11(a)(3)(ii)(B). This regulation provides that a Special Review shall be conducted if the use of a pesticide "produces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety." Studies submitted to the Agency have shown that cyanazine produces teratogenic and fetotoxic effects in laboratory animals. Based on these data and on an evaluation of potential exposure of mixer/loaders and applicators to cyanazine, the Agency concluded that cyanazine has exceeded the risk criteria for initiating a Special Review.

1. Toxicological concerns. The data base for the continued registration of cyanazine includes two studies submitted by

Shell Oil Company. The first study (MRID 0009102) designed to test for teratogenicity was conducted using Fischer 344 rats. In this study, rats were dosed daily by gastric intubation on gestational days 6-15. On the 20th day of gestation rats were sacrificed and necropsies were performed. Results from this test showed increased incidence of anophthalmia (no eyes) and microphthalmia (small eyes), in fetuses at a dose level of 25 mg/kg/day. A no observed effect level (NOEL) was established at 10 mg/kg/day. In addition, cyanazine caused increased incidence of diaphragmatic hernia in fetuses borne by treated rats. It was not clear, however, at the conclusion of the test whether the diaphragmatic hernia effect was a true teratogenic response. The registrant has been asked to submit by 12/31/85 additional data to clarify the diaphragmatic hernia issue.

In another study conducted by Shell Oil Company Laboratory, New Zealand rabbits 3-4 months old were mated at 7-11 months and dosed with cyanazine (orally via gelatin capsules) 6-18 days post coitum (p.c.). The rabbits were sacrified on the 29th day (p.c.). The results showed cyanazine produced fetotoxic effects at 2 mg/kg/day. A NOEL was established at 1 mg/kg/day. The primary fetotoxic response was low litter weights. No teratogenic effects were observed in this study.

2. Applicator (non-dietary) risk. The Agency has determined that the principal group of people exposed to cyanazine is mixer/loader and applicator personnel and that dermal absorption is the primary route of entry for cyanazine. Data from a

surrogate study with a pesticide which had similar use patterns were used because adequate exposure data on cyanazine were not available to the Agency. These estimates are based on a completely unprotected agricultural worker and assume 140 acres are treated per day (10 hours) by a 60 kg woman. The estimates of the amount of cyanazine absorbed by mixer/loaders and applicators are presented in the table below.

Table 1 Estimates of Cyanazine Absorbed by Workers

Operation	Exposure/Absorption
Mixing/loading (Open System)	1.95 mg/kg/day
Application	5.4 mg/kg/day

These exposure estimates suggest levels of exposure to cyanazine at or near the point where teratogenic and fetotoxic effects were observed in experimental laboratory animals.

A dermal absorption study requested during the development of the Registration Standard has been completed and was submitted to the Agency January 16, 1985. The Agency has determined that this study is unacceptable because of the excessive amounts of cyanazine which were not accounted for at the low (0.5 mg) and intermediate (5.0 mg) dose levels. Cyanazine losses ranged from 13.6-55.0 percent for the low dose level and from 15.3-23.4 percent for the intermediate dose level. These losses made it impossible to quantitate accurately absorption of cyanazine by the skin of the test animals. It

also prevented evaluation of the significance of the unusual absorption patterns which occurred during this test.

3. Dietary Risk. Dietary exposures to cyanazine result from use on corn and other crops which are used for human food and livestock feed. Ninety six percent of the cyanazine produced in the United States is applied to corn. A margin of safety (MOS) for dietary exposure to a teratogen is usually determined based on a single serving of a given food commodity. For cyanazine, the single serving for all raw agricultural commodities is very close to the food factor. (The food factor is the portion of the diet, usually expressed as a percentage, which is contributed by a given food based on the annual average consumption of that food.) Therefore the theoretical maximum residue contribution (TMRC) as a result of existing tolerances for each of these commodities can be used as an exposure estimate. Further, residues of cyanazine have not been found on crops and the tolerances were set at the limit of detection of the analytical method. On this basis, the margins of safety for the teratogenic and/or maternal and fetotoxic effects can be calculated according to the following formula:

$$\text{MOS} = \frac{\text{No observed effect level (NOEL) (mg/kg)}}{\text{Exposure (mg/kg)}}$$

Based on the above formula, the margins of safety (MOS) were acceptable for all crops. The Agency therefore determined that the dietary risk criterion set forth in 40 CFR 162.11 had not been exceeded.

C. ADDITIONAL DATA

Data considered pivotal to refine the Agency risk assessment have been required on an expedited basis via the Registration Standard. These data are needed to clarify the diaphragmatic hernia issue which may be an additional teratogenic response and to determine the amount of cyanazine absorbed upon contact with exposed skin. These data will be discussed at the time the Agency issues its proposed regulatory decision in the Position Document 2/3 (PD-2/3).

The following table shows the pivotal data requirements and the due dates for data on cyanazine.

Table 2

Pivotal Data

Pivotal Data Required	Submission Date
Teratogenicity study	December 31, 1985
Dermal absorption study	July 31, 1985 (study submitted 1/16/85 was found to be unacceptable)

D. ADDITIONAL CONCERNS

The Agency is concerned about ground and surface water contamination from agricultural uses of cyanazine. Cyanazine has the potential to move (leach) through the soil and contaminate ground water which may be used as drinking water. Cyanazine has been found in surface and ground water as a result of agricultural use. The Agency does not have the data necessary

to assess the health risks associated with consuming drinking water which has been contaminated with cyanazine. However, ground water data have been requested via the Registration Standard and are due in June 1986. In the interim, to address cyanazine's potential to contaminate drinking water, label changes have been imposed which advise users not to apply cyanazine to highly permeable soils or where the water table is close to the surface.

E. CURRENT REGULATORY ACTIONS

Because the Agency has determined that cyanazine produces teratogenic effects in laboratory animals at concentrations to which mixer/loaders and applicators may be exposed, the Guidance Document requires that an appropriate warning be added to the pesticide label regarding cyanazine's potential to cause birth defects in laboratory animals. The Guidance Document also requires the registrant to change the label to include the "Restricted Use" classification which limits the use of the pesticide to certified applicators or to persons directly under their supervision. The registrant, however, has not yet committed to implement these requirements. The Agency will take appropriate actions to ensure compliance with these requirements.

All currently registered cyanazine products will remain registered while the Special Review is in progress. In addition, the Agency is deferring final decisions on the reregistration of any products containing cyanazine as a sole active ingredient until the Special Review is concluded. The Agency is requiring data sufficient to recalculate existing tolerances which will include the combined residues of the parent compound and all metabolites that contain the triazine moiety.

F. COMMENTS ON THE INITIATION OF THE SPECIAL REVIEW

Prior to the initiation of a Special Review, the sole registrant of the active ingredient was given notification of the Agency's determination that one of the criteria to initiate a Special Review may have been met. This notification included information on the toxicity findings, route of exposure and related general information. The registrant was allowed 30 days following receipt of the notification to rebut the Agency's conclusions. The registrant responded to the notification requesting the Special Review be delayed until all teratogenicity data were submitted but failed to rebut the Agency's presumption of teratogenicity for cyanazine.

G. REBUTTAL CRITERIA

All registrants, applicants for registration, and other interested members of the public are invited to submit evidence either to support or to rebut the presumption that cyanazine causes teratogenic effects in rats and may cause such effects in humans. Under 40 CFR 162.11(a)(4)(iii) the presumption initiating a Special Review may be rebutted by proving, in the case of acute and chronic toxicity criteria, "that the determination by the Agency that the pesticide meets or exceeds any of the criteria for risk was in error."

H. BENEFITS INFORMATION

The Agency will conduct a comprehensive benefits review and analysis for cyanazine during the Special Review process and will consider that information in setting forth the Agency's

proposed regulatory decision in the Position Document 2/3. A preliminary analysis of the benefits of cyanazine has been performed and is presented here.

Ninety-six percent of the cyanazine produced in the U.S. is used as a herbicide on corn. About 3 percent is used on cotton and less than 1 percent is used on sorghum and wheat. About 14-16 percent of the total U.S. corn acreage was treated with cyanazine in 1982. Most of the cyanazine produced is applied in the corn belt states (IL, IN, IA, MO, OH) and a lesser amount applied in the Northern Plain States (KS, NE, and SD). About 3 percent is used on cotton mainly as a post-emergent, directed spray herbicide.

Growers selected cyanazine over other currently available corn herbicides for the following resasons:

(1) Cyanazine has a wide annual broadleaf and grassy type weed control spectrum.

(2) It can be tank-mixed with a number of herbicides (atrazine, butylate, alachlor and metolachlor) to broaden its weed control spectrum.

(3) Because of its relatively short persistence in the soil, cyanazine reduces the carryover effect of other more persistent triazine herbicides on subsequent crops.

(4) Cyanazine, unlike some of its alternatives, has no rotational crop restrictions.

There are several alternatives to cyanazine and data show no significant increase in production cost if they are used.

However, the alternative herbicides have a narrower weed control spectrum than cyanazine and may produce carryover effects when mixed with other more persistent herbicides such as atrazine.

In addition to submitting evidence to rebut the presumptions of risk in the Special Review, 40 CFR 162.11(a)(5)(iii) provides that a registrant or applicant "may submit evidence as to whether the economic, social and environmental benefits of the use of the pesticide subject to the presumption outweigh the risk of use." If the presumption of risk is not rebutted, the benefits evidence submitted by registrants, applicants, and other interested persons will be considered by the Agency when determining the appropriate regulatory action.

Registrants, applicants or other interested persons who desire to submit benefits information should consider submitting information on the following subjects along with any other relevant information they desire:

1. Identification of the biological and economic importance of cyanazine uses including market studies and estimated quantities applied for those uses.

2. Identification of alternative chemical and nonchemical methods of control for all registered uses and application techniques including any health effects and potential for water contamination associated with use of the alternatives.

3. Determination of any change in costs to cyanazine users for obtaining equivalent disease control with available substitute products or management techniques.

4. Assessment of the expected changes in the level of efficacy, crop yield, crop quality, crop injury, herbicide-resistant weed species, and environmental impacts associated with the use of alternative control measures.

5. Identification of increased or reduced risks associated with the mixing, loading, applying and disposing of alternative chemicals, and of other hazards associated with their potential increase in use if cyanazine were not available as well as descriptions of the application equipment types, protective clothing and mixing/loading and disposing procedures for the alternative chemicals.

6. Identification of cultural and spray application practices, and other factors that affect farmworker exposure to cyanazine.

7. Identification of any alternative cultural or integrated pest management practices which are enhanced or limited by use of cyanazine.

II. REBUTTAL SUBMISSION PROCEDURES

All registrants and applicants for registration are being notified by certified mail of the Special Review being initiated on their products containing cyanazine.

The registrants and applicants for registration will have 45 days from the date this notice is received or until (insert date 45 days after date of publication in the FEDERAL REGISTER) (whichever is later) to submit evidence in rebuttal to the Agency's presumption. Other interested parties may submit comments during the same period.

III. DUTY TO SUBMIT INFORMATION ON ADVERSE EFFECTS

Registrants are required by section 6(a)(2) of FIFRA to submit any additional information regarding unreasonable adverse effects on man or the environment which comes to their attention at any time. Registrants of cyanazine products must immediately submit any published or unpublished information, studies, reports, analyses, or reanalyses regarding any cyanazine effects in animal species or humans, and claimed or verified accidents to humans, domestic animals, or wildlife which have not been previously submitted to EPA. These data should be submitted with a cover letter specifically identifying the information as being submitted under section 6(a)(2) of FIFRA. Registrants should notify EPA of any studies on cyanazine currently in progress, their purpose, the protocol, the approximate completion date, a summary of all results observed to date, the name and address of the laboratory performing the studies, and a statement as to whether these studies are being conducted in accordance with the Good Laboratory Practices specified in 40 CFR Part 160, published in the FEDERAL REGISTER of November 29, 1983 (48 FR 53946).

IV. PUBLIC COMMENT OPPORTUNITY

During the time allowed for submission of rebuttal evidence, specific comments are solicited on the presumptions set forth in this Notice and in the Registration Standard. In particular, any documented episodes of adverse effects on humans or domestic animals should be submitted to the Agency

as soon as possible. Any information as to any laboratory studies in progress or completed should be submitted to the Agency as soon as possible with a statement as to whether those studies are in compliance with the Good Laboratory Practices specified in 40 CFR Part 160. Specifically, information on any adverse toxicological effects of cyanazine, its impurities, metabolites, and degradation products is solicited. Similarly, submission of any studies or comments on the benefits from the use of cyanazine is requested. All comments and information and analyses, which come to the attention of EPA, may serve as a basis for final determination of regulatory action following the Special Review.

All comments and information should be sent to the address given above, preferably in triplicate, to facilitate the work of EPA and others interested in inspecting them. The comments and information should bear the identifying notation [OPP-30000/46].

During the comment period, interested members of the public or registrants may request a meeting to discuss the risk issues and methods of reducing risks. Any records pertaining to such meetings, including minutes, agendas, and comments received will be filed under docket number [OPP-30000/46]

Dated: _____

_____

Director,
Office of Pesticide Programs.