

(OPTS-42032B, FRL-2975-7)

Decision Not To Test Formamide

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA is issuing a decision not to require further testing of formamide, CAS No. 75-12-7, for health effects. On August 24, 1984, U.S. District Court, Southern District of New York, ruling requires EPA to issue a proposed test rule for this chemical under section 4(a) of the Toxic Substances Control Act (TSCA) by March 1986 or state reasons for not issuing one. EPA has determined that data now available to the Agency, including data received pursuant to a negotiated testing agreement between the Agency and BASF Wyandotte Corporation (BASF), are adequate to characterize formamide for these effects and that no further testing is required at this time. However, EPA may develop proposed rulemaking under section 5(a)(2) or 8(a) of TSCA to monitor any significant change in exposure to this chemical.

FOR FURTHER INFORMATION CONTACT: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Room E-543, 401 M Street SW., Washington, DC 20460. Toll Free: (800-424-9065). In Washington, DC: (544-1404). Outside the USA: (Operator-202-554-1404).

SUPPLEMENTARY INFORMATION: The Agency is publishing a decision not to require additional testing of formamide for health effects.

I. Introduction

In its Tenth Report, published in the Federal Register of May 25, 1982 (47 FR 22582), the Interagency Testing Committee (ITC) designated formamide for priority testing consideration. The ITC recommended that formamide be tested for genotoxic effects, carcinogenicity, and other chronic health effects. EPA issued a notice, published in the Federal Register of May 23, 1983 (48 FR 23098), which announced the Agency's preliminary decision not to propose a rule under section 4(a) of the Toxic Substances Control Act (TSCA) (Pub. L. 94-469, 90 Stat. 2003, 15 U.S.C. 2601) to require health effects testing of

formamide. This decision was based on the Agency's evaluation of the existing data for formamide, the expected exposure profile for formamide, and the tentative acceptance of a testing program submitted by BASF. In the Federal Register of December 29, 1983 (48 FR 57365), EPA issued notice of a negotiated testing agreement (NTA) between EPA and BASF for formamide. Available data did not suggest that formamide is either genotoxic or carcinogenic. Therefore, to answer the concerns expressed by the ITC for other chronic effects, BASF proposed a range-finding study followed by a 90-day subchronic study which was designed to characterize the potential chronic effects of formamide. Because dermal exposure is the most common route of human exposure, the program was designed to clarify the doses at which formamide causes toxic effects after repeated exposure of intact skin over a prolonged period. The specific details of the NTA appear in the December 29, 1983 Federal Register notice. Both the range-finding and 90-day subchronic tests have been completed, and EPA has announced receipt of the test results in two Federal Register notices (49 FR 5190; February 10, 1984 and 50 FR 31919; August 7, 1985). These notices are included in the public docket (OPTS-42032B) for this notice.

On August 24, 1984, the U.S. District Court, Southern District of New York, ruled that negotiated testing agreements were not a legally adequate substitute for rulemaking under section 4 of TSCA in response to priority testing designations of the ITC (*VRDC v. EPA*, 595 F. Supp. 1255 (S.D.N.Y. 1984)). In its final order, the court required that EPA publish by March 1986 a notice of proposed rulemaking for formamide or its reasons for not initiating rulemaking. This notice is being published in response to the court's mandate and announces the Agency's decision not to require additional health effects testing for this chemical.

Under section 4(a) of TSCA, the Administrator shall by rule require testing of a chemical substance to develop appropriate test data if the Agency finds that:

(A)(i) the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or mixture, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment;

(ii) there are insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such

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activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data; or

(B)(i) a chemical substance or mixture is or will be produced in substantial quantities, and (I) it enters or may reasonably be anticipated to enter the environment in substantial quantities or (II) there is or may be significant or substantial human exposure to such substance or mixture.

(ii) there are insufficient data and experience upon which the effects of the manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted, and

(iii) testing of such substance or mixture with respect to such effects is necessary to develop such data.

EPA uses a weight-of-evidence approach in making a section 4(a)(1)(A)(i) finding; both exposure and toxicity information are considered in determining whether available data support a finding that the chemical may present an unreasonable risk. For the finding under section 4(a)(1)(B)(i), EPA considers only production, exposure, and release information to determine whether there is or may be substantial production and significant or substantial human exposure or substantial release to the environment. For the findings under section 4(a)(1)(A)(ii) and (B)(ii), EPA examines toxicity and fate studies to determine whether existing information is adequate to reasonably determine or predict the effects of human exposure to, or environmental release of, the chemical. In making the finding under section 4(a)(1)(A)(iii) or (B)(iii) that testing is necessary, EPA considers whether ongoing testing will satisfy the information needs for the chemical and whether testing which the Agency might require would be capable of developing the necessary information.

EPA's approach to determining when these findings are appropriately made is described in detail in EPA's first and second proposed test rules as published in the *Federal Register* of July 18, 1980 (45 FR 48528) and June 5, 1981 (46 FR 30300). The section 4(a)(1)(A) findings are discussed at 45 FR 48528 and 46 FR 30300, and the section 4(a)(1)(B) findings are discussed at 46 FR 30300.

II. Review of Available Data

A. Production, use, and Exposure

Detailed information on production, use, and exposure appears in the Agency's initial response to the ITC (48 FR 23098; May 23, 1983). The Agency is not aware of any new data that suggest that the production, use, and exposure

profile for formamide has changed since that time.

There is currently no United States production of this chemical; however, BASF imports between 1 and 11 million pounds per year. About 82 percent of the imported formamide is used by the pharmaceutical industry (Ref. 1). The major TSCA use of formamide (13 percent) is in petroleum production, where it acts as a carrier for the corrosion-inhibiting additives pumped into wells during drilling operations. In this capacity, formamide is expected to be quickly hydrolyzed. Furthermore, because formamide is readily biodegraded and does not bioaccumulate, it is not expected to persist in the environment. Other nonconsumptive TSCA uses include soil stabilization (1.0 percent), polymerization (0.5 percent), laboratory (1.0 percent), and ink solvent (1.5 percent) uses (Ref. 3). Consumer products containing formamide as a result of its use as an ink solvent include a number of fiber, plastic, and felt-tip pens and markers (Ref. 3).

There appears to be little opportunity for exposure to formamide based upon present uses. BASF Wyandotte, using data from a 1982 customer survey, estimated that about 400 workers are exposed to formamide under controlled use conditions (Ref. 4). Potential for exposure to formamide from its use as a solvent in water soluble inks occurs both in the formulation of the ink and in the loading of the ink into the writing instrument. The larger manufacturers of these instruments use automated equipment which approach enclosed systems. In less automated equipment, some inhalation of formamide could occur, although dermal exposure to the inks is expected to be minimal. Potential workplace exposure may also occur on an intermittent basis from loading, mixing, or drumming operations. In addition, the 1985 National Occupational Exposure Survey projected that about 1,800 chemists are potentially exposed to formamide (Ref. 22). Product labels advise workers and chemists to use protective equipment such as gloves, respirators, and goggles when handling formamide. Furthermore, because of formamide's known teratogenic potential, the label also warns pregnant workers to avoid contact with formamide unless adequate precautions are observed to minimize their exposure.

Worst-case estimates (assuming 100 percent absorption) suggest that if an adult female were to spill formamide on both hands, she could be exposed to 1.45 mg/kg/contact (Ref. 28). A male worker could also be exposed to 1.45 mg/kg/

contact (assuming 0.13 m² hand surface area and 70 kg body weight). EPA believes that the number of male or female workers so exposed to formamide is not substantial. Although no data on the levels of exposure in any of the industries using formamide were submitted, EPA has no evidence which might suggest that the levels of worker exposure coupled with the known toxicity potential of this chemical are significant or present an unreasonable risk, given the use of proper protective equipment recommended on existing labels and anticipated avoidance by pregnant workers.

Consumer exposure to formamide may result from its use in water-soluble ink formulations. Formamide is used in about 4.0 percent of the pens used in the United States, or 130 million pens (Ref. 5). Based upon conversations with several major U.S. pen manufacturers and their representatives and considering formamide's characteristic quick absorption by paper, resistance to smearing, and added expense, EPA believes that when it is used in consumer pens, it is generally used in finer point pens, not the marker pens often used by children (Ref. 4). Finer point pens usually contain about 5 percent formamide. Formamide is also used in high-performance industrial pens, such as high-speed computer plotter pens. These pens usually contain about 35 percent formamide; however, use of these pens should result in minimal opportunity for consumer exposure.

Several other factors tend to minimize the potential for exposure of persons writing with pens containing formamide. Formamide's low vapor pressure tends to reduce the probability of inhalation. Thus, the only significant potential route of exposure would be from skin contact with wet ink. Because of its low vapor pressure, complete miscibility with water, and lipid solubility, any direct skin contact with formamide would probably result in absorption through the skin. Therefore, worst-case dermal exposure estimates for a child were calculated by EPA using data submitted by BASF (Refs. 3 and 28). Calculations for the ink application exposures were based on a total formulation loading of 1.5 gm for a pen, 6.0 gm for a marker, and an average formamide concentration of 20 percent. If a child painted the central surface of both hands with ink from a broad-tip marker, assuming 100-percent absorption of formamide, the dermal exposure would be about 0.3 mg/kg. On the basis of the results of the 90-day subchronic toxicity testing conducted by BASF there is a

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risk quotient of 100 between the no-observed-effect-level (NOEL) and this exposure level. Since this NOEL is for daily dosing over a 90-day period and such misuse by a child is not expected to be repeated daily for 90 days, anticipated risk quotients should be much larger, suggesting lesser concern. Furthermore, considering the physicochemical properties of formamide and the construction of the porous-tip device, which acts to hold the ink in the pen, EPA believes the use of those products would not result in substantial exposure. On the basis of the above information, EPA has concluded that although a large number of consumers may use writing instruments containing formamide, the levels of individual exposure are likely to be well below those found to cause adverse effects.

Formamide has been used in the past or has been suggested for a multitude of other commercial uses, some of which could result in significant worker and/or consumer exposure. Such potential uses include: as an additive to lube oil and hydraulic fluid, as a component in deicing fluids for airport runways, as a curing agent for epoxy resins, as a plasticizer, as an affinity enhancer for dyes, and as a component of liquid fertilizers. The current import volume and predominantly pharmaceutical use of this imported formamide supports the conclusion that the amount of formamide used for these and other uses is small, if any. Furthermore, concern for formamide's recognized developmental toxicity has and undoubtedly continues to limit manufacture and TSCA-related use of this chemical.

B. Health Effects

A detailed review of the health effects information available to the Agency prior to the NTA was presented in the Agency's initial response to the ITC (48 FR 23098; May 23, 1983). A summary of these data and the new data on genetic toxicity developed by the National Toxicology Program (NTP) and on subchronic toxicity developed by BASF follows:

1. *Acute toxicity.* The acute toxicity of formamide to laboratory animals is in the slight-to-moderate range. Oral LD₅₀ values range from 3.2 g/kg in the mouse to 7.5 g/kg in the rat (Refs. 6 and 7). Dermal LD₅₀ values are reported to be as high as 17 g/kg in the rabbit; the lowest lethal dermal dose for this species is 6.0 g/kg (Refs. 8 and 9).

2. *Mutagenicity.* At the time of the Agency's initial response to the ITC, formamide had not demonstrated a mutagenic response in *in vitro* assays. No indication of mutagenicity was seen

using strains TA-98, TA-100, TA-1535, and TA-1537 (+S9) using the *Salmonella* assay (Ref. 10). It was also reported that formamide was nontoxic and nonmutagenic to *Salmonella* at concentrations up to 200 micrograms per plate but was toxic to the bacteria at 500 micrograms per plate (Ref. 11). In addition, no mutagenic effects were demonstrated in a dominant lethal assay after a single intraperitoneal application ($\frac{1}{2}$ LD₅₀) of formamide to NMRI mice (Refs. 12 and 13). Formamide was also without effect in a cell transformation test using rat embryo cells infected with Rauscher leukemia virus (Ref. 14) at concentrations from 0.001 to 100 mg/L.

The NTP recently completed the testing of formamide over five doses in four strains of *Salmonella* (TA 98, TA 100, TA 1535, and TA 1537) with and without activation. Testing was done in triplicate with an independent repeat. No indication of mutagenic activity was seen (Ref. 23). Formamide was also tested and found nonmutagenic in TA-98 with activation (Ref. 24). In addition, the NTP has selected formamide as a negative control in an on-going *Drosophila* sex-linked recessive lethal test (Ref. 25).

The Agency is aware that the data are limited on the potential for formamide to cause chromosomal aberrations. However, based upon the results of the dominant lethal assay (Refs. 12 and 13), the Agency has no grounds to require additional testing for these effects nor reason for concern.

3. *Developmental toxicity.* Three dermal studies were submitted by BASF: the teratogenic effects on rats after repeated percutaneous application (Ref. 15); the teratogenic effect in mice of commercial black ink containing 50-percent formamide following percutaneous application on the 8th day post coitum (Ref. 20); and the teratogenic effect in mice following percutaneous application of this ink on the 13th day post coitum (Ref. 21). In the multiple-dose study, formamide was applied 13 times. Dose-dependent embryotoxic and teratogenic effects were observed. The lowest observed reproductive/teratogenic effect level (LOEL) reported was 0.35 g/kg, the lowest dose tested. In the single-dose studies, significant embryo-lethal, embryotoxic, and teratogenic (fetal deformities) effects were reported at 2.8 gm/kg. When these effect levels are compared to the worst-case dermal exposure of 1.45 mg/kg for an adult female, a risk quotient of about 240 for repeated exposure for an adult female and her offspring was calculated. Similarly, a risk quotient of over 1,000 was calculated for single dermal

exposure to an adult female and her offspring (Ref. 28).

Three oral studies were submitted by BASF which reported dose-dependent embryotoxic and/or teratogenic effects in rats (Ref. 16), mice (Ref. 17), and rabbits (Ref. 18). Because these studies utilized lower dosages than the dermal studies both LOEL's and NOEL's were determined. Based upon the results of these studies:

(a) Rabbits appear to be the most sensitive species tested for embryotoxic effects (LOEL=0.11 g/kg; NOEL=0.037 g/kg) and least sensitive for teratogenic effects (no effect at the highest dose tested, 0.37 g/kg). Similar results were reported by Merkle and Zeller (Ref. 19). In addition, they reported that 0.2 g/kg formamide caused pronounced maternal toxicity and death.

(b) Mice appear to be more sensitive (LOEL=0.20 g/kg with 11 percent malformations; NOEL=0.13 g/kg) than rats (LOEL=32 g/kg with 4 percent malformations; NOEL=0.18 g/kg).

(c) The oral route of administration appears to cause a slightly greater response in Sprague-Dawley rat (LOEL=0.32 g/kg with 4 percent malformations) than the dermal route (LOEL=0.35 g/kg with 2 percent malformations).

(d) The types of dose-related malformations observed in these studies (cleavage of vertebrae, wavy or fused ribs, cleft palate, multilobular liver, and hydrocephalus internus) were the same in both rats and mice and in both dermal and oral tests.

Based upon these results, the Agency believes that the oral NOEL for rabbits (0.037 g/kg) is a conservative estimate of the dermal NOEL for the developmental effects of formamide. When this NOEL is compared to the worst-case dermal exposure of 1.45 mg/kg for an adult female, a risk quotient of 24 for repeated exposure to an adult female and her offspring was calculated. This risk quotient is an order of magnitude (10x) lower than the quotient calculated using the dermal LOEL. The Agency considers the developmental toxicity data submitted by BASF adequate under current limited use and exposure.

4. *Subchronic toxicity.* Prior to the NTA, the Agency received one study showing that repeated doses of formamide administered by gavage to rats 5 days per week for 4 weeks resulted in dose-dependent cumulative effects expressed as gastritis and erosion of the gastric mucosa (Ref. 2). The no-observed-effect level was 34 mg/kg. However, because of the short duration of exposure and the technical difficulties encountered with gavage

exposure, this study was judged inadequate for risk assessment.

Under the NTA, BASF successfully completed range-finding and 90-day subchronic studies specifically designed to assess the dermal toxicity of formamide, the most common route of human exposure. The studies were designed to clarify the doses at which formamide causes toxic effects after repeated exposure to intact skin over a prolonged period (Ref. 29). They were conducted according to the Organization for Economic Cooperation and Development Subchronic Dermal Toxicity Guideline No. 411 (Ref. 30) and have been reviewed and found acceptable (Refs. 28 and 27). Taking into account the limited current exposure to formamide, EPA believes that the 90-day subchronic test conducted by BASF provides an adequate screen for histopathological effects to the reproductive system and chronic toxicity (with the possible exception of ocular and oncogenic effects for which there is no suggestive evidence) because: extensive biochemical, hematological, and anatomical studies were included; both toxic and non-toxic doses were included; and toxic effects were observed at the high-dose which were not observed at the low-dose (Ref. 33).

The 90-day study conducted in male and female Wistar rats. Formamide was applied to intact, shaved skin, 6 hr/day, 5 days/week at dose levels of 0, 300, 1,000 and 3,000 mg/kg. Although dose levels were based on a 14-day range-finding study, a NOEL was not identified (Ref. 31). The predominant toxic effect observed was polycythemia. A second dermal study using doses of 0, 30, 100, and 3,000 mg/kg provided a NOEL of 30 mg/kg and confirmed the hematological response (Ref. 32). Compound-related effects occurring in a dose-related manner included changes in hematology, clinical chemistry, and weight, i.e., emaciation and decreased body weight (high dose only). Bilateral testicular tubular atrophy was also observed at the 3,000 mg/kg dose. In addition, male rats were clearly more sensitive than female rats to the hematological effects of formamide; significantly increased hemoglobin levels and red cell counts were observed at levels above 300 mg/kg. No abnormalities were detected in the 100 mg/kg or 30 mg/kg dose groups. However, because of the possibility of reduced platelet, lymphocyte, and leucocyte values (not dose-related) at 100 mg/kg, it appears prudent to consider 30 mg/kg the NOEL for the 90-day exposure. When this NOEL is compared to worst-case dermal

exposure estimate for a child (0.30 mg/kg) and adult male or female (1.45 mg/kg), risk quotients of about 100 for the child and 20 for the adult exist. Since the NOEL is for repeatedly daily dosing over 90 days and the worst-case exposure estimates are for events that would rarely be expected to occur, anticipated risk quotient should be much larger, suggesting lesser concern for formamide under current use.

5. *Oncogenicity.* EPA is unaware of any bioassay that has not been performed to assess the carcinogenic potential of formamide. However, there are no data which indicate any potential for oncogenic effects.

III. Decision Not to Initiate Rulemaking

EPA has reviewed all available data on formamide including structure-activity relationships, acute toxicity, mutagenicity, and teratogenicity data, and the subchronic toxicity data submitted to the Agency by BASF pursuant to the NTA. The data indicate that the chemical has a low but unique toxicity. Its acute toxicity to laboratory animals is in the slight-to-moderate range. Repeated-dose studies by gavage in rodents resulted in cumulative effects expressed as extensive gastritis and erosion of the gastric mucosa. *In vitro* tests used to predict mutagenic and carcinogenic potential indicate that formamide exhibits slight cellular toxicity, but no mutagenic response. Studies in rats, mice, and rabbits indicate that formamide is embryotoxic and teratogenic at widely varying doses, by several routes of administration. Subchronic dermal studies indicate that repeated exposure to formamide may result in polycythemia. No other significant pathology was observed. Since bilateral testicular tubular atrophy was observed in male rats only at a dose level 100 times the NOEL for hematological effects, the data from the BASF 90-day subchronic study do not suggest a potential unreasonable risk of chronic or abnormal reproductive effects from current exposure to formamide.

The Agency finds that these data are valid and, when coupled with earlier data, are sufficient to reasonably predict the identified health effects of formamide and do not suggest potential for unreasonable risk at current exposures. Furthermore, current and anticipated future release and exposure for formamide do not appear sufficient to warrant testing for any other effects on a section 4(a)(1)(B) basis.

EPA has therefore decided that testing of formamide under section 4(a)(1)(A) or (B) of TSCA is not warranted at this time. However, the Agency may develop proposed rulemaking pursuant to section

5(a)(2) and/or 8(a) of TSCA to require notification of the Agency prior to any change in manufacturing (importing), processing, handling, use, release, and disposal patterns that would significantly increase exposure to formamide. Other action (e.g., listing of formamide as a hazardous waste, restricting waste disposal practices) may also be taken by the Agency.

IV. Public Record

EPA has established a public record for this decision not to test under section 4 of TSCA (docket number OPTS-42032B). The record includes the following information:

A. Supporting Documentation

- (1) Federal Register notices pertaining to this decision consisting of:
 - (a) a Notice containing the ITC designation of formamide to the Priority List (47 FR 22582; May 25, 1982).
 - (b) Notice containing the preliminary response to the ITC for formamide (48 FR 23098; May 23, 1983).
 - (c) Notice containing the decision to adopt the Negotiated Testing Program for formamide (48 FR 57365; December 29, 1983).
 - (d) Receipt of data notices (49 FR 5190; February 10, 1984 and 50 FR 31918; August 7, 1985).
- (2) Communications consisting of:
 - (a) Written public and intra-agency or interagency memoranda and comments.
 - (b) Summaries of telephone conversations.
 - (c) Summaries of meetings.
- (3) Reports—published and unpublished factual materials, including contractor's reports.

B. References

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- (2) BASF Wyandotte Corp. "Internal Report: Results of the toxicity of formamide in a four-week investigation in the rat." Industrial Hygiene and Toxicology Laboratory, BASF Aktiengesellschaft, Ludwigshafen, West Germany. (1982).
- (3) BASF Wyandotte Corp. Letter from R. F. Flaherty, BASF Wyandotte Corp., 100 Cherry Hill Rd., P.O. Box 181, Parsippany, NJ 07054, to Steven D. Newburg-Rinn, U.S. Environmental Protection Agency, Test Rules Development Branch, Washington, DC 20460 (September 7, 1982).
- (4) BASF Wyandotte Corp. Product literature. Worker exposure survey presented at a meeting with the EPA Assessment Division. (August 19, 1982).
- (5) BASF Wyandotte Corp. Letter from R. F. Flaherty, BASF Wyandotte Corp., 100 Cherry Hill Rd., P.O. Box 181, Parsippany, NJ 07054, to S.D. Newburg-Rinn, U.S. Environmental Protection Agency, Test Rules Development Branch, Washington, DC 20460. (August 9, 1982).
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(17) BASF. Badische Anilin und Soda-Fabrik. "Internal Report: Report on the examination of formamide for teratogenic effects in mice after oral application." XIX/197. Ludwigshafen/Rhein, West Germany. (1974).

(18) BASF. Badische Anilin und Soda-Fabrik. "Internal Report: Examination of the influence of formamide upon pregnant rabbits and their fetuses after administration by gavage." XXIII/245. D-2104 Hamburg 92 (Hausbruch), West Germany. (1974).

(19) Merkle J. and Zeller H. "Tests of acetamides and formamides for embryotoxic and teratogenic effect in rabbits." *Arzneim Forschung*. (In German; English trans.) 30:1557-1582. (1980).

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examination of a commercially available ink (black) for teratogenic effects in mice by percutaneous application on the 13th day post coitum." XXII/341. Ludwigshafen/Rhein, West Germany. (1974).

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(32) BASF. "Report on the study of subchronic dermal toxicity of formamide in rats after 3 months exposure." Vols. 1 and 2. Project No. 38H0294/8255. Ludwigshafen/Rhein, West Germany. (1985).

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Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, along with other information considered by the Agency in development this notice is available for

inspection in the OPTS Reading Rm. E-107, 401 M Street SW., Washington, DC, from 8 a.m. to 4 p.m. Monday through Friday, except legal holidays.

Authority: 15 U.S.C. 2603.

Dated: February 21, 1986.

John A. Moore,

Assistant Administrator for Pesticides and Toxic Substances.

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