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

NOV 22 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Third Peer Review of Atrazine - Reevaluation Following the September 7, 1988 Scientific Advisory Panel Review

From: Marion P. Copley, D.V.M.
Acting Section Head, Section 2
Toxicology Branch I (IRS), HED (TS-769C)

To: Robert Taylor (PM 25)
Registration Division (TS-767C)

and

Jude Andreasen (TS-767C)
Special Review
Special Review and Reregistration Division

The Peer Review Committee met on September 29, 1988 to examine the issues raised by the Scientific Advisory Panel (SAP) with respect to the classification of the carcinogenicity of Atrazine.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated).

Theodore Farber	Theodore M. Farber
William Burnam	Wm J Burnam
Reto Engler	Reto Engler
Judith Hauswirth	Judith W. Hauswirth
Marsha van Gemert	Marsha van Gemert
Marion Copley	Marion Copley 10/7/88
Kerry Dearfield	Kerry Dearfield
Esther Rinde	Esther Rinde
John Quest	John A. Quest

(3)

Lynnard Slaughter

Robert Beliles

2. Reviewers: (Non-committee members responsible for data presentation, signatures indicate technical accuracy of panel report).

Marion Copley (Reviewer)

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion: signatures indicate concurrence with the overall conclusions of the Committee.)

Richard Hill

Richard Levy

Diane Beal

B. Material Reviewed:

The SAP response memorandum from the September 7, 1988 meeting was reviewed by the Committee (see attachment 1).

C. Considerations:

The Panel agreed with the Committee's overall assessment of the weight of the evidence of Atrazine, classifying it as a category C oncogen. Although "the Panel believes that mammary tumors in Sprague-Dawley rats should be considered as a biologically significant endpoint", they did not agree that a quantification of risk should be performed, since 1) the tumor site of concern was the mammary gland in Sprague-Dawley rats and 2) "the issue was further complicated by the influence of secondary factors such as endocrine imbalance at high, but not low doses".

Issues discussed:

Quantification of Risk:

The Committee originally felt (Peer Review Memorandum dated August 1, 1988) that a quantitative estimation of the oncogenic potential should be performed because of the occurrence of primarily malignant mammary tumors at doses that had few signs of toxicity.

Upon reevaluation of the data and considering the comments of the SAP, the Peer Review Committee determined that the data for Atrazine are not appropriate for quantitative risk assessment

(using the Weibull model). This was because the tumors occurred only in one sex (female), species (rat) and strain (Sprague-Dawley). Mammary tumors occur at a variable rate, with a high background incidence in this strain of rat. Additional mutagenicity data have lessened the concern for this endpoint, therefore genotoxicity could not be used to support quantification. There appears to be, although not yet substantiated by data, a hormonal mechanism.

According to preliminary data submitted by the registrant, there appears to be a hormonal mechanism involved in the induction of mammary tumors by Atrazine. Information contained in HED files on other s-triazines, structurally similar to Atrazine, indicates that they induce tumors only in hormonally sensitive tissues. Additional information discussed at the SAP meeting, but not yet substantiated by actual data, indicates that female rats produced in the first or second generation of an Atrazine reproduction study, and continued on diets containing Atrazine for two years, did not have mammary gland tumors at a higher rate than the corresponding controls. This would also raise the question of hormonal influence in the production of mammary gland tumors by Atrazine.

In addition, there are sketchy data, generated by the registrant, indicating that the Sprague-Dawley rat may metabolize Atrazine differently than the Fischer rat and humans.

Interim Alternative to the Above Quantification of Risk:

The Committee members felt that since the mammary tumors were considered a toxicologic concern, the RfD, as used by Office of Pesticide Program (OPP) was not adequate, therefore they discussed alternative methods to account for the oncogenic potential. Until further information is evaluated, see below, the following was agreed upon by the Committee: Use the LHA (lifetime health advisory) level set by the Office of Drinking Water (ODW) in their Health Advisory for Atrazine (dated August 1988, attachment 2) rather than either the Q_1* or the RfD. The ODW method differs from the current OPP policy for determining allowable dietary residues by including an additional uncertainty factor of 10 when calculating the lifetime drinking water health advisories (LHA), which are otherwise based on the Reference Dose (RfD), to account for possible carcinogenicity. The current RfD of 0.005 mg/kg/day, is based on a chronic dog NOEL of 0.48 mg/kg/day (cardiac effects). The value, after accounting for the additional uncertainty factor, would be 0.0005 mg/kg/day.

It should be noted that, although the Committee did not endorse a threshold mechanism, rat mammary tumors were significantly increased at 3.5 mg/kg/day (70 ppm) and above, not

at 0.5 mg/kg/day (10 ppm). In addition, in a Sprague-Dawley rat reproductive study, the NOEL for reproductive effects was also 0.5 mg/kg/day (10 ppm). Decreased pup weight was observed primarily at weaning with the next higher dose (50 ppm or 2.5 mg/kg/day). However, it could not be determined whether this effect was due to a maternal effect such as decreased milk production or direct pup toxicity from Atrazine.

New Data Needed to Reevaluate the Appropriate Risk Characterization Model

The listed studies are currently ongoing, or are in the planning stages at Ciba-Geigy. Preliminary results were pivotal in the above deliberations of the Peer Review Committee. Data provided by the completed studies are necessary for the Committee to determine the most appropriate method, if any, for quantifying the risk due to atrazine:

1) Hormone/receptor effects of Atrazine, including serum estrogen and other endocrine levels (including prolactin if possible);

2) Comparison of oncogenic potential between Fischer and Sprague-Dawley female rats;

3) Comparative metabolism between Fischer and Sprague-Dawley female rats, and between other mammalian species (rat hepatocytes).

D. Conclusions:

The Committee concluded that:

1) Atrazine should be classified as a category C oncogen.

2) The data were not convincing enough for quantitative risk characterization using the Weibull model.

3) The tumor response was of sufficient concern that the RfD should not become the default position for expressing long term risk levels for Atrazine.

Therefore, it was concluded that, until additional data (see above) are submitted to elucidate the most appropriate method of risk characterization, there should be an additional uncertainty factor of 10 added to the RfD to account for the oncogenic potential when determining allowable exposures to this compound.

The Committee strongly recommends that the registrant continue to generate data supporting a hormonal mechanism and

submit it to the Agency in a timely manner. The Committee also looks favorably upon the Registrant's decision to conduct an oncogenicity study in the Fischer rat. This information is required for the Committee to determine the most appropriate alternate method of risk determination.

COPLEY\PC6\ATRAZINE\PR3.RSP, 10/7/88

Attachment 1

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Peer Review Classification of Atrazine as a Class C Oncogen

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The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of a set of scientific issues being considered by the Environmental Protection Agency's peer review classification of atrazine as a Class C oncogen. The review was conducted in an open meeting held in Arlington, Virginia, on September 7, 1988. All Panel members, except Dr. Thomas W. Clarkson, were present for the review.

Public notice of the meeting was published in the Federal Register on Monday, July 25, 1988.

Oral statements were received from staff of the Environmental Protection Agency and from Dr. James Stephens of Ciba-Geigy and Dr. Robert Squire of Johns Hopkins University representing Ciba-Geigy.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF PANEL RECOMMENDATIONS

Atrazine

The Agency requested the Panel to focus its attention upon a scientific issue relating to the Peer Review of atrazine. There follows the issues and the Panel's response to the issues:

Issue:

Atrazine was classified by the Toxicology Branch Peer Review Committee as C (Possible Human Carcinogen), based on: 1) increased incidence of tumors in one sex (primarily malignant tumors in females); 2) a possible mutagenicity concern and 3) a structure activity relationship with agents demonstrated to produce mammary tumors. The tumors associated with atrazine included mammary fibroadenoma/adenocarcinomas and adenocarcinoma in female rats.

1. The Agency requests any comments the Panel may wish to make regarding the biological significance of the mammary tumors in Sprague-Dawley rat.

Panel Response:

The Panel believes that mammary tumors in Sprague-Dawley rats should be considered as a biologically significant endpoint. As such, one relies not only on statistics to determine whether or not an effect is compound related, but also biological plausibility. The variability of this endpoint and its potential for secondary hormonal influence make this an important issue.

ISSUE:

2. Does the Panel have any specific comments regarding our overall assessment of the weight of evidence and classification of this chemical in accordance with the Agency's Guidelines for Carcinogen Risk Assessment.

Panel Response:

The Panel agrees with the Agency's classification of atrazine as a category C oncogen. We are, however, concerned about performing quantitative risk assessment (QRA) on the mammary tumor data. The Sprague-Dawley rat is clearly different from humans in sensitivity, contrary to an inherent assumption in QRA. The issue is further complicated by the influence of secondary factors such as endocrine imbalance at high, but not low doses. Therefore, the Panel recommends that QRA not be done on atrazine.

FOR THE CHAIRMAN:

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 9-14-88

8/88

August, 1988.

Attachment 2

ATRAZINE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

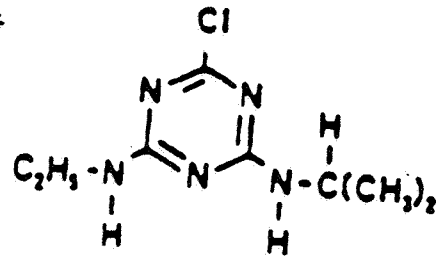
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the one-hit, Weibull, logit or probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1912-24-9

Structural Formula



2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine

Synonyms

- AAtrex; Atranex; Crisatrina; Crisazine; Farmco Atrazine; Griffex; Shell Atrazine Herbicide; Vectal SC; Gesaprim; Primatol (Meister, 1987).

Uses

- Atrazine over the past 30 years has been the most heavily used herbicide in the U.S. It is used for nonselective weed control on industrial or noncropped land and selective weed control in corn, sorghum, sugar cane, pineapple and certain other plants (Meister, 1987).

Properties (Meister, 1987; Windholz, 1976)

Chemical Formula	$C_8H_{14}ClN_5$
Molecular Weight	215.72
Physical State	White, ordorless, crystalline solid
Boiling Point (25 mm Hg)	--
Melting Point	175 to 177°C
Density (20°)	1.187
Vapor Pressure (20°C)	3.0×10^{-7} mm Hg
Water Solubility (22°C)	70 mg/L
Log Octanol/Water Partition Coefficient	2.33 to 2.71
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- In a monitoring study of Mississippi River water, atrazine residues were found at a maximum level of 17 ppb; residues were detected throughout the year, with the highest concentrations found in June or July (Newby and Tweedy, 1976).

- Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 343 of 3,208 ground water samples (STORET, 1988).

Samples were collected at 1,659 surface water locations and 2,510 ground water locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 1.9 ug/L in ground water sources. The maximum concentration found in surface water was 2,300 ug/L and in ground water it was 700 ug/L. Atrazine was foound in surface water of 31 States and in ground water in 13 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Atrazine has been found also in ground water in Pennsylvania, Iowa, Nebraska, Wisconsin and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986).

Environmental Fate

- An aerobic soil metabolism study in Lakeland sandy loam, Hagerstown silty clay loam, and Wehadkee silt loam soils showed conversion of atrazine to hydroxyatrazine, after 8 weeks, to be 38, 40 and 47% of the amount applied, respectively, (Harris, 1967). Two additional degradates, deisopropylated atrazine and deethylated atrazine, were identified in a sandy loam study (Beynon et al., 1972).

- Hurle and Kibler (1976) studied the effect of water-holding capacity on the rate of degradation and found a half-life for atrazine of more than 125 days, 37 days and 36 days in sandy soil held at 4%, 35% and 70% water-holding capacity, respectively.

- In Oakley sandy loam and Nicollet clay loam, atrazine had a half-life of 101 and 167 days (Warnock and Leary, 1978).

- Carbon dioxide production was generally slow in several anaerobic soils: sandy loam, clay loam, loamy sand and silt loam (Wolf and Martin, 1975; Goswami and Green, 1971; Lavy et al., 1973).

- ^{14}C-Atrazine was stable in aerobic ground water samples incubated for 15 months at 10 or 25°C in the dark (Weidner, 1974).

- Atrazine is moderately to highly mobile in soils ranging in texture from clay to gravelly sand as determined by soil thin layer chromatography (TLC), column leaching, and adsorption/desorption batch equilibrium studies. Atrazine on soil TLC plates was intermediately mobile in loam, sandy clay loam, clay loam, silt loam, silty clay loam, and silty clay soils, and was mobile in sandy loam soils. Hydroxyatrazine showed a low mobility in sandy loam and silty clay loam soils (Helling, 1971).

- Soil adsorption coefficients for atrazine in a variety of soils were: sandy loam (0.6), gravelly sand (1.8), silty clay (5.6), clay loam (7.9), sandy loam (8.7), silty clay loam (11.6), and peat (more than 21) (Weidner, 1974; Lavy 1974; Talbert and Fletchall, 1965).

- Soil column studies indicated atrazine was mobile in sand, fine sandy loam, silt loan and loam; intermediately mobile in sand, silty clay loam and sandy loam; low to intermediately mobile in clay loam (Weidner, 1974; Lavy, 1974; Ivey and Andrews, 1964; Ivey and Andrews, 1965).

- In a Mississippi field study, atrazine in silt loam soil had a half-life of less than 30 days (Portnoy, 1978). In a loam to silt loam soil in Minnesota, atrazine phytotoxic residues persisted for more than 1 year and were detected in the maximum-depth samples (30 to 42 inches) (Darwent and Behrens, 1968). In Nebraska, phytotoxic residues persisted in silty clay loam and loam soils 16 months after application of atrazine; they were found at depths of 12 to 24 inches. But atrazine phytotoxic residues had a half-life of about 20 days in Alabama fine sandy loam soil, although leaching may partially account for this value (Buchanan and Hiltbold, 1973).

- Under aquatic field conditions, dissipation of atrazine was due to leaching and to dilution by irrigation water, with residues persisting for 3 years in soil on the sides and bottoms of irrigation ditches, to the maximum depth sampled, 67.5 to 90 cm (Smith et al., 1975).

- Ciba-Geigy (1988) recently submitted comments on the atrazine Health Advisory. These comments included a summary of the results of its studies on the environmental fate of atrazine. This summary indicated that laboratory degradation studies showed that atrazine is relatively stable in the aquatic medium under environmental pH conditions and indicated that atrazine degraded in soil by photolysis and microbial processes. The products of degradation are dealkylated metabolites, hydroxyatrazine and nonextractable (bound) residues. Atrazine and the dealkylated metabolites are relatively mobile whereas hydroxyatrazine is immobile.

- Ciba-Geigy (1988) also indicated that field dissipation studies conducted in California, Minnesota and Tennessee show no leaching of atrazine and metabolites below 6 to 12 inches of soil. The half-lives of atrazine in soil ranged between 20 to 101 days, except in Minnesota where degradation was slow. A forestry degradation study conducted in Oregon showed no adverse effects on either terrestial or aquatic environments. Also, Bioconcentration studies have shown low potential for bioaccummulation with a range of 15 to 77X.

III. PHARMACOKINETICS

Absorption

- Atrazine appears to be readily absorbed from the gastrointestinal tract of animals. Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Total fecal

excretion after 72 hours was 20.3% of the administered dose; the remainder was excreted in urine (65.5%) or retained in tissues (15.8%). This indicates that at least 80% of the dose was absorbed.

Distribution

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Liver, kidney and lung contained the largest amounts of radioactivity, while fat and muscle had lower residues than the other tissues examined.

- In a metabolism study by Ciba-Geigy (1983a), the radioactivity of ^{14}C-atrazine dermally applied to Harlan Sprague-Dawley rats at 0.25 mg/kg was distributed to a minor extent to body tissues. The highest levels were measured in liver and muscle at all time points examined; 2.1% of the applied dose was in muscle and 0.5% in liver at 8 hours.

- Khan and Foster (1976) observed that in chickens the hydroxy metabolites of atrazine accumulate in the liver, kidney, heart and lung. Residues of both 2-chloro and 2-hydroxy moieties were found in chicken gizzard, intestine, leg muscle, breast muscle and abdominal fat.

Metabolism

- The principal reactions involved in the metabolism of atrazine are dealkylation at the C-4 and C-6 positions of the molecule. There is also some evidence of dechlorination at the C-2 position. These data were reported by several researchers as demonstrated below.

- Bakke et al. (1972) administered single 0.53-mg doses of ^{14}C-ring-labeled atrazine to rats by gavage. Less than 0.1% of the label appeared in carbon dioxide in expired air. Most of the radioactivity was recovered in the urine (65.5% in 72 hours), including at least 19 radioactive compounds. More than 80% of the urinary radioactivity was identified as 2-hydroxyatrazine and its two mono-N-dealkylated metabolites. None of the metabolites identified contained the 2-chloro moiety (which may have been removed via hydrolysis during the isolation technique or by a dechlorinating enzyme as suggested by the *in vitro* studies of Foster et al. (1979), who found evidence for a dechlorinase in chicken liver homogenates incubated with atrazine).

- Bohme and Bar (1967) identified five urinary metabolites of atrazine in rats: the two monodealkylated metabolites of atrazine, their carboxy acid derivatives and the fully dealkylated derivative. All of these metabolites contained the 2-chloro group. The *in vitro* studies of Dauterman and Muecke (1974) also found no evidence for dechlorination of atrazine in the presence of rat liver homogenates.

- Similarly, Bradway and Moseman (1982) administered atrazine (50, 5, 0.5 or 0.005 mg/day) for 3 days to male Charles River rats and observed that the fully dealkylated derivative (2-chloro-4,6-diamino-s-triazine) was the major urinary metabolite, with lesser amounts of the two mono-N-dealkylated derivatives.

- Erickson et al. (1979) dosed Pittman-Moore miniature pigs by gavage with 0.1 g of atrazine (80W). The major compounds identified in the urine were the parent compound (atrazine) and deethylated atrazine (which contains the 2-chloro substituent).

- Hauswirth (1988) indicated that the rat metabolism studies taken together are sufficient to show that in the female rat dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways. Oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. The total body half-life is approximately one and one-half days. Atrazine and/or its metabolites appear to bind to red blood cells. Other tissue accumulation does not appear to occur.

Excretion

- Urine appears to be the principal route of atrazine excretion in animals. Following the administration of 0.5 mg doses of 14C-ring-labeled atrazine by gavage to rats, Bakke et al. (1972) reported that in 72 hours most of the radioactivity (65.5%) was excreted in the urine, 20.3% was excreted in the feces, and less than 0.1% appeared as carbon dioxide in expired air. About 85 to 95% of the urinary radioactivity appeared within the first 24 hours after dosing, indicating rapid clearance.

- Dauterman and Muecke (1974) have reported that atrazine metabolites are conjugated with glutathione to yield a mercapturic acid in the urine. The studies of Foster et al. (1979) in chicken liver homogenates also indicate that atrazine metabolism involves glutathione.

- Ciba-Geigy (1983b) studied the excretion rate of ^{14}C-atrazine from Harlan Sprague-Dawley rats dermally dosed with atrazine dissolved in tetrahydrofuran at levels of 0.025, 0.25, 2.5 or 5 mg/kg. Urine and feces were collected from all animals at 24-hour intervals for 144 hours. Results indicated that atrazine was readily absorbed, and within 48 hours most of the absorbed dose was excreted, mainly in the urine and to a lesser extent in the feces. Cumulative excretion in urine and feces appeared to be directly proportional to the administered dose, ranging from 52% at the lowest dose to 80% at the highest dose.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- A case of severe contact dermatitis was reported by Schlicher and Beat (1972) in a 40-year-old farm worker exposed to atrazine formulation. The clinical signs were red, swollen and blistered hands with hemorrhagic bullae between the fingers. Although it is noted that the exposure of this patient may have been inclusive to exposure to other chemicals in addition to atrazine, it is also noted that atrazine is a skin irritant in animal studies.

Long-term Exposure

- Yoder et al. (1973) examined chromosomes in lymphocyte cultures taken from agricultural workers exposed to herbicides including atrazine. There were more chromosomal aberrations in the workers during mid-season exposure to herbicides than during the off-season (no spraying). These aberrations included a four-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks. During the off-season, the mean number of gaps and breaks was lower in this group than in controls who were in occupations unlikely to involve herbicide exposure. This observation led the authors to speculate that there is enhanced chromosomal repair during this period of time resulting in compensatory protection. However, these data may not be representative of the effect of atrazine since the exposed workers were also exposed to other herbicides.

Animals

Short-term Exposure

- Acute oral LD_{50} values of 3,000 mg/kg in rats and 1,750 mg/kg in mice have been reported for technical atrazine by Bashmurin (1974); the purity of the test compound was not specified.

- Acute oral studies conducted by Ciba-Geigy (1988) with atrazine (97% a.i.) reflected the following LD_{50}s: 1,869 mg/kg in rats and >3,000 mg/kg in mice.

- Molnar (1971) reported that when atrazine was administered by gavage to rats at 3,000 mg/kg, 6% of the rats died within 6 hours, and 25% of those remaining died within 24 hours. The rats that died during the first day exhibited pulmonary edema with extensive hemorrhagic foci, cardiac dilation and microscopic hemorrhages in the liver and spleen. Rats that died during the second day had hemorrhagic broncho-pneumonia and dystrophic changes of the renal tubular mucosa. Rats sacrificed after 24 hours had cerebral edema and histochemical alterations in the lungs, liver and brain. It is noted that the dose used in this study was almost 2 x the LD_{50} (Ciba-Geigy, 1988).

- Gaines and Linder (1986) determined the oral LD_{50} for adult male and female rats to be 737 and 672 mg/kg respectively and 2,310 mg/kg for pups. It is, therefore, noted that young animals are more sensitive to atrazine than adults. This study also reflected that the dermal LD_{50} for adult rats was higher than 2,500 mg/kg.

- Palmer and Radeleff (1964) administered atrazine as a fluid dilution or in gelatin capsules to Delaine sheep and dairy cattle (one animal per dosage group). Two doses of 250 mg/kg atrazine caused death in both sheep and cattle. Sixteen doses of 100 mg/kg were lethal to the one sheep tested. At necropsy, degeneration and discoloration of the adrenal glands and congestion in lungs, liver and kidneys were observed.

- Palmer and Radeleff (1969) orally administered atrazine 80W (analysis of test material not provided) by capsule or by drench to sheep at 5, 10, 25, 50, 100, 250 or 400 mg/kg/day and to cows at 10, 25, 50, 100 or 250 mg/kg/day. The number of animals in each dosage group was not stated, and the use of controls was not indicated. Observed effects included muscular spasms, stilted gait and stance and anorexia at all dose levels in sheep and at 25 mg/kg in cattle. Necropsy revealed epicardial petechiae (small hemorrhagic spots on the lining of the heart) and congestion of the kidneys, liver and lungs. Effects appeared to be dose related. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 5 mg/kg/day in sheep and a No-Observed-Adverse-Effect Level (NOAEL) of 10 mg/kg/day in cows can be identified from this study.

- Bashmurin (1974) reported that oral administration of 100 mg/kg of atrazine to cats had a hypotensive effect, and that a similar dose in dogs was antidiuretic and decreased serum cholinesterase (ChE) activity. No other details of this study were reported. Atrazine is not an organophosphate (OP), therefore, its effect on ChE may not be similar to the mechanism of ChE inhibition by OPs.

Dermal/Ocular Effects

- In a primary dermal irritation test in rats, atrazine at 2,800 mg/kg produced erythema but no systemic effects (Gzheyotskiy et al., 1977).

- Ciba-Geigy (1988) indicated that the studies it performed reflected dermal sensitization in rats but not irritation in rabbits' eyes.

Long-term Exposure

- Hazelton Laboratories (1961) fed atrazine to male and female rats for 2 years at dietary levels of 0, 1, 10 or 100 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of approximately 0, 0.05, 0.50 or 5.0 mg/kg/day. After 65 weeks, the 1.0-ppm dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. No treatment-related pathology was found at 26 weeks, at 52 weeks, at 2 years, or in animals that died and were necropsied during the study. Results of blood and urine analyses were unremarkable. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection were observed in some animals after 20 weeks of treatment at the 10- and 100-ppm levels but not at 52 weeks. Body weight gains, food consumption and survival were similar in all groups for 18 months, but from 18 to 24 months there was high mortality due to infections (not attributed to atrazine) in all groups, including controls, which limits the usefulness of this study in determining a NOAEL for the chronic toxicity of atrazine.

- In a 2-year study by Woodard Research Corporation (1964), atrazine (80W formulation) was fed to male and female beagle dogs for 105 weeks at dietary levels of 0, 15, 150 or 1,500 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of 0, 0.35, 3.5 or 35 mg/kg/day. Survival rates, body weight

gain, food intake, behavior, appearance, hematologic findings, urinalyses, organ weights and histologic changes were noted. The 15-ppm dosage (0.35 mg/kg/day) produced no toxicity, but the 150-ppm dosage (3.5 mg/kg/day) caused a decrease in food intake as well as increased heart and liver weight in females. In the group receiving 1,500 ppm (35 mg/kg/day) atrazine, there were decreases in food intake and body weight gain, an increase in adrenal weight, a decrease in hematocrit and occasional tremors or stiffness in the rear limbs. There were no differences among the different groups in the histology of the organs studied. Based on these results, a NOAEL of 0.35 mg/kg/day can be identified for atrazine.

- In a study by Ciba-Geigy (1987b) using technical atrazine (97% ai.), six-month-old beagle dogs were assigned randomly to four dosage groups: 0, 15, 150 and 1,000 ppm. These doses correspond to actual average intake of 0, 0.48, 4.97 and 33.65/33.8 (male/female) mg/kg/day. Six animals/sex/group were assigned to the control and high dose groups and four animals/sex/group were assigned to the low- and mid-dose groups. One mid-dose male, one high-dose male and one high-dose female had to be sacrificed moribund during the study period. Decreased body weight gains and food consumption were noted at the high-dose level. Statistically significant ($p < 0.05$) reductions in erythroid parameters (red cell count, hemoglobin and hematocrit) in high-dose males were noted throughout the study as well as mild increases in platelet counts in both sexes. Slight decreases in total protein and albumin ($p < 0.05$) were noted in high-dose males as well as decreased calcium and chloride in males and increased sodium and glucose in females. Decrease in absolute heart weight were noted in females and increased relative liver weight in males of the high-dose group. The mid-dose females reflected an increase in the absolute heart weight and heart/brain weight ratios. The most significant effect of atrazine in this study was reflected in the high-dose animals of both sexes as discrete mycardial degeneration. Clinical signs associated with cardiac pathology such as ascites, cachexia, labored/shallow breathing and abnormal EKG were observed in the group as early as 17 weeks into the study. Gross pathology reflected severe dilation of the right atrium and occasionally of the left atrium. These findings were also noted histopathologically as degenerative atrial myocardium (atrophy and myolysis). In the mid-dose group, two males and one female appeared to be affected with the cardiac syndrome but to a much lesser degree in the intensity of the noted responses. Therefore, the LOAEL in this study is 4.97 mg/kg/day and the NOAEL is 0.48 mg/kg/day.

- A two year chronic feeding/oncogenicity study (Ciba-Geigy, 1986) was recently evaluated by the Agency. In this study, technical atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). Twenty rats per sex per group were used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats per sex per goup were maintained on the treated and control diets for 24 months. An additional 10 rats per sex were placed on control and high dose (1,000 ppm) diets for a twelve month interim sacrifice and

another 10 per sex (control and high dose, 1,000 ppm) for a 13 month sacrifice (the 1,000 ppm group was placed on control diet for one month prior to sacrifice). The total number of animals/sex in the control and HDT groups was 90 and 70 for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. At the mid- and high-dose, there was a decrease in mean body weights of males and females. Survival was decreased in high-dose females but increased in high-dose males. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrolobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LOAEL for non-oncogenic activities in both sexes is 25 mg/kg/day and the NOAEL is 3.5 mg/kg/day. However, oncogenic activities were noted at 3.5 mg/kg/day (70 ppm) and above as reflected in the increased incidence of mammary gland tumors in females.

- A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 strain of mice, weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. This study shows that there are dose-related effects at 1,500 ppm or 3,000 ppm atrazine: an increase in cardiac thrombi, a decrease in the mean body weight gain at 12 and 91 weeks during the study, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. Cardiac thrombi contributed to the deaths of the group of mice that did not survive to terminal sacrifice. The LOAEL is set at 1,500 ppm based upon decreases of 23.5% and 11.0% in mean body weight gain found at 91 weeks in male and female mice, respectively. Also, an increase in the incidence of cardiac thrombi is found in female mice in the 1,500 ppm exposure group. None of the above effects are found at 300 ppm, thus the NOAEL is set at 300 ppm (corresponding to 38.4 mg/kg/day in males and 47.9 mg/kg/day for females).

Reproductive Effects

- A three-generation study on the effects of atrazine on reproduction in rats was conducted by Woodard Research Corporation (1966). Groups of 10 males and 20 females received atrazine (80W) at dietary levels of 0, 50 or 100 ppm. Based on the dietary assumptions that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of approximately 0, 2.5 or 5 mg/kg/day. Two litters were produced per generation but parental animals were chosen from the second litter after weaning for each generation. Young rats were maintained on the test diets for approximately ten

weeks in each generation. The third generation pups were sacrificed after weaning. It is noted that the parental animals of the first generation were fed only half of the dietary atrazine levels for the first 3 weeks of exposure. There were no adverse effects of atrazine on reproduction observed during the course of the three-generation study. A NOAEL of 100 ppm (5 mg/kg/day) was identified for this study. However, the usefulness of this study is limited due to the alteration of the atrazine content of the diet during important maturation periods of the neonates.

- A recent two-generations study in rats by Ciba-Geigy (1987a) was conducted using the 97% ai. technical atrazine. Young rats, 47 to 48 days old were maintained on the control and test diets for 10 weeks before mating. The concentrations used were 0, 10, 50 and 500 ppm (equivalent to 0, 0.5, 2.5 and 25 mg/kg/day using Lehman conversion factor, 1959). Thirty animals/sex/group were used in each generation; one litter was produced per generation. The level tested had no effect on mortality in either generation. Body weight and body weight gains were significantly depressed ($p < 0.05$) at the highest dose; however, food consumption was also decreased at this high-dose level in parental males and females during the premating period and for the first generation females (F_1) on days 0 to 7 of gestation. No histopathological effects were noted nor other effects were noted during gross necropsy in either parental generation with the exception of increased testes relative weight in both generations at the high dose. In pups of both generation, significant reduction ($p < 0.05$) in body weight was noted; however, this effect was only dose-related in the second generation (F_2) at both the mid- and high-dose levels on postnatal day 21. Therefore, maternal toxicity NOAEL is 2.5 mg/kg/day; the reproductive LOAEL is 2.5 mg/kg/day (reduced pup weight in F_2 generation on postnatal day 21) and the NOAEL is 0.5 mg/kg/day.

Developmental Effects

- In the three-generation reproduction study in rats conducted by Woodard Research Corporation (1966) (described above), atrazine at dietary levels of 50 or 100 ppm (2.5 or 5 mg/kg/day) resulted in no observed histologic changes in the weanlings and no effects on fetal resorption. No malformations were observed, and weanling organ weights were similar in controls and atrazine-treated animals. Therefore, a NOAEL of 100 ppm (5 mg/kg/day) was also identified for developmental effects in this study. However, the usefulness of this study is limited due to an alteration of the atrazine content of the diet during important maturation periods of the neonates.

- Atrazine was administered orally to pregnant rats on gestation days 6 to 15 at 0, 100, 500 or 1,000 mg/kg (Ciba-Geigy, 1971). The two higher doses increased the number of embryonic and fetal deaths, decreased the mean weights of the fetuses and retarded the skeletal development. No teratogenic effects were observed. The highest dose (1,000 mg/kg) resulted in 23% maternal mortality and various toxic symptoms. The 100 mg/kg dose had no effect on either dams or embryos and is therefore the maternal and fetotoxic NOAEL in this study.

- In a study by Ciba-Geigy (1984a), Charles River rats received atrazine (97%) by gavage on gestation days 6 to 15 at dose levels or 0, 10, 70, or 700 mg/kg/day. Excessive maternal mortality (21/27) was noted at 700 mg/kg/day, but no mortality was noted at the lower doses; also reduced weight gains and food consumption were noted at both 70 and 700 mg/kg/day. Developmental toxicity was also present at these dose levels. Fetal weights were severely reduced at 700 mg/kg/day; delays in skeletal development occurred at 70 mg/kg/ day, and a dose-related runting was noted at 10 mg/kg/day and above. The NOAEL for maternal toxicity appears to be 10 mg/kg/day, however, this is also the LOAEL for developmental effects.

- New Zealand white rabbits received atrazine (96%) by gavage on gestation days 7 through 19 at dose levels of 0, 1, 5 or 75 mg/kg/day (Ciba-Geigy, (1984b). Maternal toxicity, evidenced by decreased body weight gains and food consumption, was present in the mid- and high-dose groups. Developmental toxicity was demonstrated only at 75 mg/kg/day by an increased resorption rate, reduced fetal weights, and delays in ossification. No teratogenic effects were indicated. The NOAEL appears to be 1 mg/kg/day.

- Peters and Cook (1973) fed atrazine to pregnant rats (four/group) at levels of 0, 50, 100, 200, 300, 400, 500 or 1,000 ppm in the diet throughout gestation. Based on an assumed body weight of 300 g and a daily food consumption of 12 g (Arrington, 1972), these levels correspond to approximately 0, 2, 4, 8, 12, 16, 20 or 40 mg/kg/day. The number of pups per litter was similar in all groups, and there were no differences in weanling weights. This study identified a NOAEL of 40 mg/kg/day for developmental effects. In another phase of this study, the authors demonstrated that subcutaneous (sc) injections of 50, 100 or 200 mg/kg atrazine on gestation days 3, 6 and 9 had no effect on the litter size, while doses of ≥800 mg/kg were embryotoxic. Therefore, a NOAEL of 200 mg/kg by the sc route was identified for embryotoxicity.

Mutagenicity

- Loprieno et al. (1980) reported that single doses of atrazine (1,000 mg/kg or 2,000 mg/kg, route not specified) produced bone marrow chromosomal aberrations in the mouse. No other details of this study were provided.

- Murnik and Nash (1977) reported that feeding 0.01% atrazine to male *Drosophila melanogaster* larvae significantly increased the rate of both dominant and sex-linked recessive lethal mutations. They stated, however, that dominant lethal induction and genetic damage may not be directly related.

- Adler (1980) reviewed unpublished work on atrazine mutagenicity carried out by the Environmental Research Programme of the Commission of the European Communities. Mutagenic activity was not induced even when mammalian liver enzymes (S-9) were used; however, the use of plant microsomes produced positive results. Also, in *in vivo* studies

in mice, atrazine induced dominant lethal mutations and increased the frequency of chromatid breaks in bone marrow. Hence, the author suggested that activation of atrazine in mammals occurs independently of the liver, possibly in the acidic part of the stomach.

- As described previously, Yoder et al. (1973) studied chromosomal aberrations in the lymphocyte cultures of farm workers exposed to various pesticides including atrazine. During mid-season a 4-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks was observed. During the off-season (no spraying), the number of gaps and breaks was lower than in controls, suggesting to the authors that there is enhanced chromosomal repair during the unexposed period.

- Recently, Spencer (1987) and Dearfield (1988) evaluated several in vitro and in vivo mutagenicity studies on atrazine that were recently submitted to the U.S. EPA by Ciba-Geigy. They noted that most of these studies were inadequate with the exception of the following three tests: a Salmonella assay; an E. coli reversion assay; and a Host-Mediated assay. The first two assays were negative for mutagenic effects; the results of the third assay were equivocal.

- Ciba-Geigy (1988) indicated that Brusick (1987) evaluated atrazine mutagenicity and that the weight-of-evidence analysis he used placed the chemical in a non-mutagenic status. The Agency (Dearfield, 1988) evaluated Brusick's analysis. It is noted that the use of the weight-of-evidence approach is not appropriate at the present time. The in vivo studies by Adler (1980) suggest a positive response. These findings have not been diminished by other atrazine studies. In addition, Dearfield (1988) indicated that the scheme used by Brusick in this analysis is flawed by the lack of calibration of the chemical test scores to an external standard and by the use of some studies that are considered inadequate by design to determine the mutagenic potential of atrazine.

Carcinogenicity

- Innes et al. (1969) investigated the tumorigenicity of 120 test compounds including atrazine in mice. Two F_1 hybrid stocks (C57BL/6 x Anf) F_1 and (C57BL/6 x AKR) F_1 were used. A dose of 21.5 mg/kg/day was administered by gavage to mice of both sexes from age 7 to 28 days. After weaning at 4 weeks, this dose level was maintained by feeding 82 ppm atrazine ad libitum in the diet for 18 months. The incidence of hepatomas, pulmonary tumors, lymphomas and total tumors in atrazine-treated mice was not significantly different from that in the negative controls.

- A two-year feeding/oncogenicity study in rats by Ciba-Geigy (1986) has been evaluated recently by the Agency. Atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). The total number of animals/sex in the control and HDT groups was 90; and 70 animals/sex/group for the 10, 70 and 500 ppm groups. Histopathology

was performed on all animals. In females, atrazine was associated with a statistically significant increase in mammary gland fibroadenomas at 1,000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500 and 1,000 ppm, and in total mammary gland tumor bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical control range. In addition, U.S. EPA (1986a) indicated that there was evidence for decreased latency for mammary gland adenocarcinomas at the 12 month interim sacrifice that was already submitted by Ciba-Geigy in 1985. This study was also reported as positive in a briefing paper by Ciba-Geigy (1987).

- A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 mice weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/ group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. The following kinds of neoplasms were noted in this study: mammary adenocarcinomas, adrenal adenomas, pulmonary adenomas and malignant lymphomas. However, no dose-related or statistically significant increases were observed in the incidences of these neoplasms. Therefore, atrazine is not considered oncogenic in this strain of mice.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (___ \text{ L/day})} = ___ \text{ mg/L } (___ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100, 1,000 or 10,000) in accordance with EPA or NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No suitable information was found in the available literature for the determination of the One-day HA value for atrazine. It is, therefore, recommended that the Ten-day HA value calculated below for a 10-kg child of 0.1 mg/L (100 ug/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

Two teratology studies by Ciba-Geigy, one in the rat (1984a) and one in the rabbit (1984b), were considered for the calculation of the Ten-day HA value. The rat study reflected a NOAEL of 10 mg/kg/day for maternal toxicity but this value was also the LOAEL for developmental toxicity while the rabbit study reflected NOAELs of 5 mg/kg/day for developmental toxicity and 1 mg/kg/day for maternal toxicity. Thus, the rabbit appears to be a more sensitive species than the rat for maternal toxicity, hence, the rabbit study with a NOAEL of 1 mg/kg/day is used in the calculations below.

The Ten-day HA for a 10 kg child is calculated below as follows:

$$\frac{(1\ \text{mg/kg/d}) \times (10\text{kg})}{(100) \times (1\ \text{L/day})} = 0.1\ \text{mgL}\ (100\ \text{ug/L})$$

where:

1 mg/kg/day = NOAEL, based on maternal toxicity evidenced by decreased body weight gain and food consumption.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with EPA or ODW/NAS guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily consumption for a child.

Longer-term Health Advisory

No suitable information was found in the available literature for the determination of the longer-term HA value for atrazine. It is, therefore, recommended that the adjusted DWEL for a 10-kg child of 0.05 mg/L (50 ug/L) and the DWEL for a 70-kg adult of 0.2 mg/L (200 ug/L) be used at this time as conservative estimates of the Longer-term HA values.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an esti-

mate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Three studies were considered for the development of the Lifetime HA. A two-year dog feeding study (Woodard, 1964), a one-year dog feeding study Ciba-Geigy, 1987b) and a two-year rat oral feeding/oncogenicity study (Ciba-Geigy, 1986).

The first study in dogs (1964) reflected a NOAEL of 0.35 mg/kg/day and a LOAEL of 3.5 mg/kg/day that was associated with increased heart and liver weights in females. The new one-year dog study (1988) reflected a NOAEL of 0.48 mg/kg/day and a LOAEL of 4.97 mg/kg/day based on mild cardiac pathology intensified at the higher dose tested 33.65/33.8 (male/female) mg/kg/day. The two-year rat study (Ciba-Geigy, 1986) reflected a NOAEL at 3.5 mg/kg/day for systemic effect other than oncogenicity; however, this study indicated that atrazine caused mammary gland tumors at this dose level and above, no adverse effects were observed at the lowest dose tested, 0.5 mg/kg/day.

The 1964 dog study was initially used for the calculation of the RfD and the Lifetime HA. However, this study was partially flawed by the lack of information on the purity of the test material and by the inadequate documentation of the hematological data. Therefore, the recent one-year dog study (Ciba-Geigy, 1987b), using technical atrazine (97% ai.), is considered as a more adequate study for the calculation of the RfD and the Lifetime HA. The NOAEL in this study, 0.48 mg/kg/day, is also supported by the NOAEL of 0.5 mg/kg/day in the two-generation reproduction study (Ciba-Geigy, 1987a) and by the fact that no systemic effects or tumors were noted at this dose level in the two-year chronic feeding/oncogenicity study in rats (Ciba-Geigy, 1986). [Other studies: Woodard Research Corporation (1966) and Hazelton Laboratories (1961) identified long-term NOAEL values of 5 to 50 mg/kg/day and were not considered to be as protective as the dog studies for use in calculating the HA values for atrazine.]

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{0.48 \text{ mg/kg/day}}{(100)} = 0.005 \text{ mg/kg/day}$$

(rounded from 0.0048 mg/kg/day)

where:

0.48 mg/kg/day = NOAEL, based on the absence of cardiac pathology or any other/adverse clinical, hematological, biochemical and histopathological effects in dogs.

100 = uncertainty factor, chosen in accordance with EPA or ODW/NAS guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.0048\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.168\ \text{mg/L}\ (200\ \text{ug/L})$$

where:

0.0048 mg/kg/day = RfD (before rounding off to 0.005 mg/kg/day)

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(0.168\ \text{mg/L})\ (20\%)}{10} = 0.003\ \text{mg/L}\ (3\ \text{ug/L})$$

where:

0.168 mg/L = DWEL (before rounding off to 0.2 mg/L)

20% = assumed relative source contribution from water.

10 = additional uncertainty factor, according to ODW policy, to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- A study submitted by Ciba-Geigy Corporation (1986) in support of the pesticide registration of atrazine indicated that atrazine induced an increased incidence of mammary tumors in female Sprague-Dawley rats. These findings have been further confirmed in a briefing by Ciba-Geigy (1987) on this study.

- Atrazine was not oncogenic in mice (Ciba-Geigy, 1987c).

- Three closely related analogs: propazine, terbutryn and simazine are presently classified as Group C oncogens based on an increased incidence of tumors in the same target tissue (mammary gland) and animal species (rat) as was noted for atrazine.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of atrazine.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), atrazine may be classified in Group C: possible human carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Toxicity data on atrazine were reviewed by the National Academy of Sciences (NAS, 1977), and the study by Innes et al. (1969) was used to identify a chronic NOAEL of 21.5 mg/kg/day. Although at that time it was concluded that atrazine has low chronic toxicity, an uncertainty factor of 1,000 was employed in calculation of the ADI from that study, since only limited data were available. The resulting value (0.021 mg/kg/day) corresponds to an ADI of 0.73 mg/L in a 70-kg adult consuming 2 L of water per day.

- Tolerances for atrazine alone and the combined residues of atrazine and its metabolites in or on various raw agricultural commodities have been established (U.S. EPA, 1986c). These tolerances range from 0.02 ppm (negligible) in animal products (meat and meat by-products) to 15 ppm in various animal fodders.

VII. ANALYTICAL METHODS

- Analysis of atrazine is by a gas chromatographic (GC) method, Method No. 507, applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method has been validated in a single Laboratory. The estimated detection limit for the analytes in this method, including atrazine, is 0.13 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove atrazine from water include activated carbon adsorption, ion exchange, reverse osmosis, ozone oxidation and ultraviolet irradiation. Conventional treatment methods have been found to be ineffective for the removal of atrazine from drinking water (ESE, 1984; Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in atrazine removal (ESE, 1984; Miltner and Fronk, 1985a).

- Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed upon the rapid sand filters at the Fremont, Ohio

water treatment plant, reduced atrazine levels by 30 to 64% in the water from the Sandusky River. At Jefferson Parish, Louisiana, Lykins et al. (1984) reported that an adsorber containing 30 inches of Westvaco WV-G® 12 x 40 GAC removed atrazine to levels below detectable limits for over 190 days.

- At the Bowling Green, Ohio water treatment plant, PAC in combination with conventional treatment achieved an average reduction of 41% of the atrazine in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985a) reported that in jar tests using spiked Ohio River water with the addition of 16.7 and 33.3 mg/L of PAC and 15-20 mg/L of alum, PAC removed 64 and 84%, respectively, of the atrazine. Higher percent removals reflected higher PAC dosages. Miltner and Fronk (1985b) monitored atrazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 31 to 91% removal of atrazine, with higher percent removals again reflecting higher PAC dosages.

- Harris and Warren (1964) reported that Amberlite IR-120 cation exchange resin removed atrazine from aqueous solution to less than detectable levels. Turner and Adams (1968) studied the effect of varying pH on different cation and anion exchange resins. At a pH of 7.2, 45% removal of atrazine was achieved with Dowex® 2 anion exchange resin and with $H_2PO_4^-$ as the exchangeable ion species.

- Chian et al. (1975) reported that reverse osmosis, utilizing cellulose acetate membrane and a cross-linked polyethelenimine (NS-100) membrane, successfully processed 40% of the test solution, removing 84 and 98%, respectively, of the atrazine in the solution.

- Miltner and Fronk (1985a) studied the oxidation of atrazine with ozone in both spiked distilled and ground water. Varying doses of ozone achieved a 70% removal of atrazine in distilled water and 49 to 76% removal of atrazine in ground water.

- Kahn et al. (1978) studied the effect of fulvic acid upon the photochemical stability of atrazine to ultraviolet irradiation. A 50% removal of atrazine was achieved much faster at higher pH conditions than at lower pH conditions. In the presence of fulvic acids, the time needed for ultraviolet irradiation to achieve 50% removal was almost triple the time required to achieve similar removals without the presence of fulvic acids. Since fulvic acids will be present in surface waters, ultraviolet irradiation may not be a cost-effective treatment alternative.

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