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

JAN - 7 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

**MEMORANDUM**

SUBJECT: Conclusions Drawn from Structure-Activity-Relationship (SAR) Analysis of s-Triazine Pesticides and Related Compounds from OTS

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TERUTRYN 080813
ATRAZINE 080803
SIMAZINE 080802
PROPAZINE 080808
CYANAZINE 100101

CONCLUSIONS:

1. The SAR analysis does not support inclusion of sulfonylurea compounds into the group of triazine compounds for which there is a hazard concern.

2. SAR analysis suggests that 2-chloro-4, 6-bis (alkylamino) -s- triazines represent a subgroup of s-triazines that pose a hazard of equal concern, both qualitatively and quantitatively, when compared with one another.

3. Although SAR analysis indicates that some metabolites of the s-triazines are likely to be less potent carcinogens than the parent compounds, insufficient data are available to estimate quantitatively the differences in potencies.

4. The presence of metabolites as plant residues that span a range of high to moderate or low concern with respect to carcinogenic potential dictates that the $Q_1$* for atrazine should be used to estimate the risk unless additional information becomes available on the carcinogenic potential of specific metabolites and information is made available on the specific quantities of individual metabolites present as plant residues.

Background

At the request of the OPP staff evaluating a large number of s-triazines and several related compounds for their carcinogenic potential, an analysis of triazine structure-activity-relationship (SAR) was carried out by the staff of the Health and Environmental Review Division of the Office of Toxic Substances (OTS).

In the OTS analysis, all triazine compounds which had carcinogenic assays completed were used to provide information on structure activity. Until this analysis was completed, the only obvious commonality among the positive carcinogens was the presence in each case of an intact triazine ring with various substituents at the 2,4, and 6 positions on the ring.

OPP staff, however, sought to further elucidate changes that these various substituents might impose on the triazine ring with respect to the toxicity and carcinogenicity of the various triazine compounds.

SAR

This analysis has provided a structuring of the s-triazine compounds examined on a qualitative activity scale. Chemicals included in the analysis are Atrazine, Simazine, Propazine, Terbutryn, Cyanazine, Prometryn, and Prometon. Several other chemicals which contain the s-triazine ring and were also examined for SAR included the sulfonylurea herbicides, Ally, Amber, Glean, Express, and Harmony. Express, the only sulfonylurea which exhibits carcinogenic activity, was also the only chemical in the group which gave rise to an alkylamino-s-triazine metabolite upon hydrolysis.

Four of the s-triazines, Atrazine, Propazine, Simazine, and Cyanazine are noted to be members of the 2-chloro-4, 6-bis-(alkylamino) s-triazine subgroup. One other, Terbutryn, belongs to the 2-alkylthio-4,6-bis-(alkylamino) s-triazine subgroup. Three of the four chemicals in the 2-chloro subgroup, Atrazine, Propazine, and Simazine, exhibited the same type tumors in carcinogenesis bioassays and their calculated $Q_1$* values were similar. Terbutryn, however, of the alkylthio subgroup, produced tumor responses in different target organs and the $Q_1$* for this chemical was calculated to be approximately an order of magnitude lower than those of the 2-chloro subgroup. These results, though limited in number, suggest that the substituent at the 2 position could significantly effect carcinogenic activity of individual triazines. In addition, there are several other triazines which are included in the overall analysis. These include Prometon, an 2-alkoxy-4,6-bis (alkylamino) s-triazine, a suspect negative for

carcinogenicity and Cyanazine, a 2-chloro-s-triazine, a suspect positive for carcinogenicity.

Several of the mutagenicity studies conducted on the triazines have been reported to have positive results. The chlorinated herbicides, Propazine and Anilizine, produced positive results without metabolic activation which suggests that direct-acting electrophilic activity may occur. However, nonchlorinated triazines have not provided evidence of genotoxicity.

N-dealkylation of the 2-alkoxy-s-triazines appears to make the compounds more easily excreted.

The OTS analysis provided some generalities which were presented along with a scheme for qualitatively classifying the chemicals and their metabolites with regard to a level of carcinogenic concern.

SAR and Identification of Structural Features that may contribute to Carcinogenicity.

Analyzing the available carcinogenicity and genotoxicity data and taking metabolism data and physicochemical properties into consideration, the following structure-activity-relationships are evident:

1. The carcinogenic activity of any given s-triazine compound is greatly dependent on the nature of the substituent at the 2-,4-, and 6-positions. Even among closely related compounds, a significant difference in carcinogenic activity may occur as a result of minor structural changes.

2. Presence of N-alkyl group(s) appears to be crucial for carcinogenic activity of s-triazine herbicides and related compounds. It appears that s-triazine compounds containing two or more unalkylated amino groups may lack chemical carcinogenic activity (e.g., Cyromazine, Melamine).

3. The nature of the substituent at the 2-position plays an important modifying role on the carcinogenic potency of 4,6-bis-alkylamino-s-triazines. The relative activities follow the order: 2-chloro> 2-alkylthio> 2-alkoxy. Whereas information on 2-hydroxy derivatives is not available, it is speculated that the activity of 2-hydroxy derivatives should be less than or equal to the corresponding 2-alkoxy derivative because of easier excretion and because of the negative data on cyanuric acid (trihydroxy-s-triazine).

4. The enhancing effect of the 2-chloro group on carcinogenic activity may be/is supported by the metabolism data on 2-chloro-s-triazine herbicides as well as by the finding that glutathione (GSH) conjugation is the favored metabolic pathway of Cyanazine, probably

the most potent triazine herbicide. However, the presence of chlorine alone does not appear to be sufficient for carcinogenic activity, at least in feeding studies (e.g., Anilazine), possibly because of interaction of tissue nucleophiles before reaching target organs.

5. Insufficient information is available to evaluate the significance of sulfonylurea herbicides as a source of metabolic release of s-triazine metabolites.

Table 1

Ranking of Relative Carcinogenic Potential of s-Triazine Pesticides and Related Compounds Based on Carcinogenicity Data and SAR Consideration[1]

| Type of Substituents | | Concern Level |
|---|---|---|
| A | Halogen plus one of two alkylamino groups | High-Moderate |
| B | Alkylthio plus one or two alkylamino groups | Moderate |
| C | Alkoxy plus one or two alkylamino groups | Low-Moderate |
| D | Hydroxy plus one or two alkylamino groups | Marginal or low-Moderate |
| E | Halogen plus two (unsubstituted) amino groups | Low-Moderate |
| F | Combination of two or three (unsubstituted) amino or hydroxy groups | Marginal or Low |

[1]This ranking may also be applicable to certain sulfonylurea herbicides. However, there is uncertainty on the significance of sulfonylurea herbicides as a source of enzymatic release of free triazine compounds.

Metabolites of s-Triazines

The metabolites reported to be present as plant or animal residues of atrazine span a wide range of dechlorinated, dealkylated, hydroxylated, and glutathione conjugated residues (see appendix). Based on the rankings of carcinogenic concern expressed in Table 1, it is evident that concern levels per individual metabolites range from high to marginal or low and that many metabolites are expected to express at least moderate activity. However, the rankings presented in Table 1 are based on limited bioassay data on s-triazine derivatives and the rankings are based on assumptions made on the metabolic formation of reactive intermediates. Although the evaluation provides a preliminary basis for differentiating levels of hazard concern among s-triazine chemicals, there are insufficient data available to determine quantitative differences in carcinogenic activity among s-triazine metabolites. One should assume that the residues as a whole present risks comparable to that posed by atrazine.

Attachments

cc: Larry Dorsey
Penelope Fenner-Crisp

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# 003890

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|---|---|
| **Chemical:** | **Terbutryn (ANSI); Atrazine (ANSI); Simazine (ANSI); Propazine (ANSI); Cyanazine** |
| **PC Code:** | **080813; 080803; 080807; 080808; 100101** |
| **HED File Code** | **13000 Tox Reviews** |
| **Memo Date:** | **01/07/1990** |
| **File ID:** | **00000000** |
| **Accession Number:** | **412-01-0124** |

**HED Records Reference Center**
**03/04/2001**