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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

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

FROM: Joseph A. Cotruvo, Director
Health and Environmental
Review Division (TS-796)

TO: Penelope Fenner-Crisp, Director
Health Effects Division (H7509C)

In response to the request from your staff, Dr. Marion Copley, I have asked my staff, Dr. Yin-tak Woo, to review carcinogenicity studies on s-triazine pesticides and related compounds, analyze their structure-activity relationships, and address the various scientific issues raised in the request. In sum, his analysis indicates that the carcinogenic activity of any given s-triazine compound is greatly dependent on the nature of the ring substituents. There is no sufficient evidence to support OPP's tentative proposal to treat all residues/ metabolites of s-triazine pesticides as being equipotent to their parent compounds in carcinogenic activity. His detailed report is enclosed.

I would be glad to discuss with you any questions that you might have on this report. If you need any further assistance on this project, please let me know.

Attachment

cc: Marion Copley
[redacted]
Yogendra Patel
Vanessa Vu
Yin-tak Woo

DRAFT

Position Document on

Structure-Activity Relationships of s-Triazine Pesticides

and Related Compounds

prepared by
Health and Environmental Review Division
Office of Toxic Substances

Introduction

Substituted symmetrical triazine (s-triazine) compounds constitute an important class of synthetic chemicals with a variety of pesticidal activities. A large number of s-triazine herbicides are used in enormous quantities worldwide for selective weed control (Plimmer, 1980; Reinhardt and Britteli, 1981). Several other s-triazine compounds have been used as fungicide (e.g., Anilazine) and insecticide (e.g., Cyromazine). A string of recent reports of carcinogenic activity of a series of s-triazine herbicides (e.g., Atrazine, Simazine) has led to the suggestion (OPP, 1990) that all pesticides and their residues/metabolites that contain an intact s-triazine ring as a structural moiety should be of carcinogenic concern. The objectives of this document are (a) to review information on carcinogenicity/genotoxicity/metabolism of s-triazine pesticides and related compounds, (b) to analyze structure-activity relationships (SAR) and identify structural features associated with carcinogenicity, and (c) to propose/recommend a scheme to classify s-triazine pesticides according to their carcinogenic potential based on data and/or SAR considerations.

Overview of Carcinogenicity Data on s-Triazine Pesticides and Related Compounds

(A) s-Triazine Herbicides

The available carcinogenicity data on s-triazine pesticides and related compounds have been summarized in Table I. As the data indicate, among the s-triazine herbicides that have been reviewed by OPP Carcinogenicity Peer Review Committee, all four (Atrazine, Simazine, Propazine, Terbutryn) are carcinogenic in Sprague-Dawley rats inducing adenomas/adenocarcinomas in mammary gland. A fifth s-triazine herbicide, Cyanazine, which is currently under review, has also been shown to induce mammary tumors in Sprague-Dawley rats. Among these five, Terbutryn is the only s-triazine herbicide which induces tumors at target sites (thyroid gland, liver) other than the mammary gland. Based on chemical structure, Atrazine, Simazine, Propazine and Cyanazine can all be classified as members of the 2-chloro-4,6-bis-(alkylamino)-s-triazine subgroup whereas Terbutryn belongs to the 2-alkylthio-4,6-bis-(alkylamino)-s-triazine subgroup. Besides the difference in the spectrum of carcinogenicity target organs, there also appears to be a significant difference in the carcinogenic potency between these two subgroups. The calculated q_1^* values for Atrazine (0.22 per mg/kg/day), Simazine (0.12 per mg/kg/day) and Propazine (0.17 per mg/kg/day) are all in the same order of magnitude and are more than ten times higher than that of Terbutryn (0.0094 per mg/kg/day).

These results suggest that the nature of substituent at the 2-position can have profound effect on the carcinogenic potency as well as target specificity of 4,6-bis-(alkylamino)-s-triazines. Replacement of 2-chloro substituent by 2-alkylthio substituent appears to reduce the carcinogenic potency but broaden the spectrum of target organs of s-triazine herbicides.

Available (but still under OPP internal reviewing process) data on Cyanazine show that this 2-chloro-s-triazine herbicide is also quite potent (significant carcinogenic effects observed at dietary level as low as 25 ppm; possibly more potent than Atrazine) and specific toward the mammary gland. Preliminary data on Prometryn indicates a shift of carcinogenicity target organ from the mammary gland (for Propazine) to the liver (for Prometryn) possibly as a result of the change in the substituent at the 2-position.

There is only one study available on Prometon, an 2-alkoxy-4,6-bis-(alkylamino)-s-triazine herbicide. Preliminary data indicate lack of carcinogenicity in Sprague-Dawley rats. These data, when fully confirmed, may provide further support to the view that the substituent at the 2-position may play a key role in determining the carcinogenicity of s-triazine herbicides.

(B) Sulfonylurea Herbicides Containing s-Triazine Moiety

Five s-triazine-ring-containing sulfonylurea herbicides (Ally, Amber, Glean, Express, Harmony) have been tested for carcinogenic activity (see Table I). Both Ally and Amber were noncarcinogenic in Sprague-Dawley rats and CD1 mice at dietary doses of up to 5000 to 10000 ppm. Harmony and Glean were also inactive in CR1:CD BR rats and in an unspecified strains of rats, respectively, up to 2500 ppm (it is not known whether the Maximum Tolerated Dose has been reached). However, Express appears to be the exception in this group of sulfonylurea herbicides. When tested in Sprague-Dawley rats given dietary doses of 25, 250 or 1250 ppm for 2 years, Express was carcinogenic at the highest dose inducing mammary adenomas and adenocarcinomas that are histopathologically similar to those induced by Atrazine-type s-triazine herbicides. It is interesting to note that among these five sulfonylurea herbicides, Express is the only compound which can give rise to an alkylamino-s-triazine metabolite [2-(methylamino)-4-methoxy-6-methyl-s-triazine] upon hydrolysis. Whether the carcinogenic activity of Express may be related to the possible release the alkylamino-s-triazine metabolite remains to be investigated. Although sulfonylurea herbicides are known to be resistant to hydrolysis, metabolic studies (see "Overview of Metabolism of s-Triazine Pesticides") indicate that at least some sulfonylurea herbicides may be hydrolyzed to a limited extent. IF it can be shown that the carcinogenic activity of Express is related to the release of the alkylamino-s-triazine metabolite and IF it can be shown that the

other noncarcinogenic sulfonylurea herbicides can also release comparable amounts of the unalkylated amino-s-triazine metabolite (2-amino-4-methoxy-6-methyl-s-triazine), then the results would suggest that the N-methyl group plays an important role in the carcinogenic activity of the alkylamino-s-triazine metabolite of Express.

(C) Other s-Triazine Pesticides and Related Compounds

In addition to the herbicides listed above, a number of nonherbicidal s-triazine pesticides and related compounds have been tested for carcinogenic activity. Of the three triamino-s-triazine compounds [see Table I, group (III)] that have been tested, Cyromazine (N-cyclopropyl-2,4,6-triamino-s-triazine), a larvicide for use in poultry, was reported to be noncarcinongenic in Sprague-Dawley rats fed diets containing up to 3000 ppm of the compound. Melamine (2,4,6-triamino-s-triazine), a closely related compound, was considered carcinogenic in an NTP bioassay inducing urinary bladder tumors in 8 of 50 F344 male rats fed the maximum tolerated dose (4500 ppm in diet). However, 7 of these 8 tumors-bearing rats also bore bladder stones suggesting that the carcinogenic effect may be secondary to bladder stone formation rather than actual chemical carcinogenic effect. Melamine was noncarcinogenic in female rats and B6C3F1 mice of either sex given up to 9000 ppm of the compound in the diet. In contrast to the apparent lack of chemical carcinogenic activity of melamine, there is some evidence that its N,N',N"-hexamethyl derivative is a mammary carcinogen. Cohen et al. (1973) found a significant increase in the incidence of mammary adenocarcinoma (6/24 treated vs. 0/25 control) in Sprague-Dawley rats fed hexamethylmelamine (2000 ppm in the diet for 1 week, then decreased to 1000 ppm for 1.5 weeks and 250 ppm for 42 weeks; observed for another 20 weeks). If the difference between melamine and hexamethylmelamine is not due to rat strain difference, then the results would suggest that N-alkyl group is a structural requirement for mammary carcinogenicity.

Another nonherbicidal s-triazine pesticide which has been tested for carcinogenic activity is the fungicide, Anilazine [2,4-dichloro-6-(o-chloroanilino)-s-triazine]. The compound was found to be noncarcinogenic in F344 rats and B6C3F1 mice maintained on diets containing 500 or 1000 ppm (MTD) of the compound (NCI, 1978). The study indicates that the presence of chloro groups alone is insufficient for carcinogenic activity in feeding study despite of the fact that the chloro group in s-triazine compound is a good leaving group and can generate an electrophilic arylating intermediate upon its departure.

Since many s-triazine herbicides are readily hydrolyzed to 2-hydroxy-4,6-bis-alkylamino-s-triazine metabolites in plants, information on the carcinogenic potential of hydroxy-s-triazine compounds is crucial for evaluating the carcinogenic potential of

herbicide residues in plants. Cyanuric acid (2,4,6-trihydroxy-s-triazine) appears to be the only hydroxy-s-triazine compound that has been tested for carcinogenic activity. Cyanuric acid was reported to have some carcinogenic activity in a Russian study but the results were considered questionable due to the lack of proper control group (Reinhardt and Britelli, 1981). In a more recent, more thorough study on the sodium salt of cyanuric acid, the compound was reported to be noncarcinogenic in both CD rats and B6C3F1 mice given drinking water containing up to 5375 ppm of the compound (Hammond et al., 1986).

In addition to the compounds discussed above, 1,3,5-tris-aziridinyl-s-triazine and 2-(5-nitro-2-furyl)-4,6-diamino-s-triazine have been shown to be carcinogenic. However, their activity is most likely due to the aziridine and 5-nitrofuryl moieties which are known to be associated with carcinogenic activity (see Arcos and Argus, 1974; Arcos et al., 1982).

Overview of Genotoxicity Data and Mechanistic Studies on s-Triazine Pesticides and Related Compounds

To gain some insight into the possible mechanism of carcinogenic action of s-triazine pesticides, the results of available OPP-acceptable or supplementary genotoxicity data are summarized in Table II along with published genotoxicity data on several related compounds. As the data in the Table indicate, overall, s-triazine pesticides and related compounds are mostly apparently nongenotoxic. There are, however, some sporadic positive data. It is interesting to note that the positive data are mostly associated with chlorinated s-triazine compounds (Propazine, Cyanazine, Anilazine). The positive results for Propazine and Anilazine were observed without metabolic activation indicating direct-acting electrophilic activity. Inclusion of metabolic activation system decreased the mutagenic activity of Propazine. Information on the experimental conditions of the positive mutagenicity assay of Cyanazine was not available. For nonchlorinated s-triazine compounds, there is no evidence for genotoxicity. However, it should be noted that s-triazine compounds containing amino substituents can be considered as heterocyclic aromatic amines. There is increasing evidence that some heterocyclic aromatic amines (see Woo et al., 1988) may be metabolically activated by enzymes (e.g., prostaglandin H synthase) not present in significant amount in liver S-9. Studies using extrahepatic tissues as a source of enzymes are needed before the nongenotoxicity of amino-s-triazine compounds can be affirmed.

The consistent induction of mammary gland tumors by s-triazine herbicides has led Ciba-Geigy to initiate a number of endocrine studies to investigate a possible nongenotoxic mechanism via hormonal imbalance. Thus far, Ciba-Geigy speculated that the induction of mammary tumors in Sprague-Dawley rats may be the

result of a hormonal effect specific to this strain of rats. No details of their studies are available (OPP, 1990).

Overview of Metabolism Studies on s-Triazine Pesticides

(A) Metabolism of s-Triazine Herbicides

The metabolism of s-triazine herbicides may involve each of the three substituents at the 2-, 4- and 6-positions giving rise to a variety of metabolites. In general, the metabolites (hydroxylated, N-dealkylated, sidechain-oxidized or conjugated) are more polar and tend to be more easily excreted. The following overview emphasizes on information that may shed light on possible reactive intermediates that may contribute to carcinogenic activity.

The principal metabolic pathways of 2-chloro-bis-alkylamino--s-triazine herbicides in mammals are the two competing pathways: N-dealkylation and dechlorination via GSH conjugation. Some 2-hydroxy metabolites of Atrazine and Propazine have also been detected. The formation of GSH (a typical nucleophile) conjugate indicates that 2-chloro-s-triazines can generate electrophilic arylating agent upon departure of the chlorine. The extent of GSH conjugate formation may be a good indication of the electrophilic reactivity of s-triazine herbicides. In this respect, it is interesting to note that GSH conjugation is the major metabolic pathway for Cyanazine (Hutson, 1969), probably the most carcinogenic 2-chloro-s-triazine herbicide. The presence of the cyano group in the sidechain apparently favors the GSH pathway (over N-deethylation) indirectly indicating that Cyanazine can generate more electrophilic arylating agent than other 2-chloro-s-triazine herbicides. For Atrazine, Simazine and Propazine, the N-dealkylation pathway predominates over GSH conjugation pathway. Nevertheless, GSH conjugates have been detected. Both Atrazine and Simazine have been shown to bind covalently to SH-containing erythrocyte hemoglobin in rats (Dementi, 1986; Hamboeck et al., 1981). There is no information available on possible covalent binding of 2-chloro-s-triazine to DNA.

The metabolism of 2-alkylthio-s-triazine herbicides mainly involves N-dealkyation. The sulfur can, however, be oxidized to sulfoxide and sulfone (see Plimmer, 1980; Hathway, 1977). There is some evidence that alkylsulfoxide may be a potential leaving group. Bedford et al. (1975) synthesized the S-oxide of [2-methylthio-4-ethylamino-6-(1-cyano-1-methylethylamino)-s-triazine] and found it reactive toward GSH and other thiols suggesting that the S-oxide may generate an electrophilic intermediate.

The metabolism of 2-alkoxy-s-triazine involves N-dealkylation and O-dealkylation and appears to be mainly detoxifying in nature.

Both O- and N-dealkylation lead to more polar metabolites that can be easily excreted (see Ciba-Geigy, 1971).

(B) Metabolism of Sulfonylurea Herbicides

There is no information available in the open literature on metabolism of sulfonylurea herbicides in mammals. Industry data submitted to EPA indicate that, in general, sulfonylurea herbicides are quite resistant to enzymatic hydrolysis. Metabolic study by DuPont on Harmony indicated that, in the rat, only 0.5% of a very high dose (2 g/kg) of orally administered triazine-ring-^{14}C-labeled Harmony could be recovered as 2-amino-4-methoxy-6-methyl-s-triazine in the urine. Studies on phenyl-ring-^{14}C-labeled Ally and Glean in the rat showed that 88-99% of administered dose were excreted in the urine. In each case, the major radioactive compound (over 85%) in the urine was the intact parent compound. The presence of saccharin or sulfonamide metabolites indicated that the sulfonylurea linkage can be hydrolyzed, to some extent, in mammals. The details of a metabolic study on Express were not available to the author of the present Position Document. 2-(Methylamino)-4-hydroxy-6-methyl-s-triazine was detected as a metabolite and was proposed to be a secondary metabolite of 2-(methylamino)-4-methoxy-6-methyl-s-triazine. No information on their relative amounts was available. A more detailed comparative study/review of the extent of enzymatic hydrolysis of the sulfonylurea linkage to release free amino-s-triazine metabolites at doses close to carcinogenesis bioassays is needed before the significance of sulfonylurea herbicides as a source of free amino-s-triazine can be evaluated.

Structure-Activity Relationships 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 potency 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-triazine. The relative activities follow the order: 2-chloro > 2-alkylthio > 2-alkoxy. Whereas information on 2-hydroxy derivative is not available. it is speculated that the activity of 2-hydroxy derivative 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 may be related to its ability to serve as a leaving group thus generating an electrophilic arylating intermediate. This is supported by the metabolism data on 2-chloro-s-triazine herbicides as well as by the finding that 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.

Proposed Scheme for Classifying s-Triazine Herbicides Based on Data and/or SAR consideration

The present report clearly demonstrates that the available data and SAR consideration do not support the view that pesticides and pesticide residues containing intact s-triazine moiety should be treated equally in terms of carcinogenic potential. A qualitative or semi-quantitative approach should be used to classify the s-triazine pesticides. Based on available data and SAR consideration, a scheme for ranking relative carcinogenic potential of s-triazine pesticides is described in Table III. It is recommended that the scheme be considered in classification/regulation of s-triazine pesticides and their residues.

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Table I

Summary of Carcinogenicity Data on s-Triazine Pesticides and Related Compunds

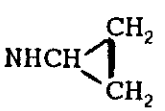
Compound	Chemical Structure R_1	R_2	R_3	Carcinogenicity	Ref.
(I) s-Triazine Herbicides					
(A) 2-chloro-4,6-bis-(alkylamino)-s-triazine herbicides					
✓ Atrazine	Cl	NHC_2H_5	$NHisoC_3H_7$	POSITIVE (OPP status: Group C) Rat, SD Mammary Gland (at 70, 500, 1000 ppm) [q_1*=0.22 $(mg/kg/day)^{-1}$] Mouse,CD1 Negative (up to 3000 ppm)	a
✓ Simazine	Cl	NHC_2H_5	NHC_2H_5	POSITIVE (OPP status: Group C) Rat, SD Mammary Gland (at 100, 1000 ppm) Liver (at 1000 ppm) [q_1*=0.12 $(mg/kg/day)^{-1}$] Mouse,CD1 Negative (up to 4000 ppm)	a
✓ Propazine	Cl	$NHisoC_3H_7$	$NHisoC_3H_7$	POSITIVE (OPP status: Group C) Rat, SD Mammary Gland (at 1000 ppm) [q_1*=0.17 $(mg/kg/day)^{-1}$] Mouse,CD1 Negative (up to 3000 ppm)	a
✓ Cyanazine	Cl	$NHisoC_3H_7$	$NHC(CH_3)_2CN$	POSITIVE (OPP status: under review) Rat, SD Mammary Gland (at 25, 50 ppm) Mouse.-- Negative (details not available)	b
Cyprazine	Cl	$NHisoC_3H_7$		NO DATA	

Table I -contined

Compound	Chemical Structure R_1	R_2	R_3	Carcinogenicity	Ref.
(I) s-Triazine Herbicides-cont'd					
(B) 2-alkylthio-4,6-bis-(alkylamino)-s-triazine herbicides					
✓ Ametryn	SCH_3	NHC_2H_5	$NHisoC_3H_7$	NO VALID DATA	a
✓ Prometryn	SCH_3	$NHisoC_3H_7$	$NHisoC_3H_7$	COMPLETE DATA DUE in 1991 Rat,-- Negative? (up to 1250 ppm) Rat,-- Liver? (details not available)	a b
Terbutryn	SCH_3	NHC_2H_5	$NHtertC_4H_9$	POSITIVE (OPP status: Group C) Rat, CR Mammary Gland, Thyroid Liver (at 3000 ppm) [q_1*=0.0094 $(mg/kg/day)^{-1}$] Mouse, CR Negative (up to 3000 ppm)	a
Dipropetryn	SC_2H_5	$NHisoC_3H_7$	$NHisoC_3H_7$	NO DATA	
(C) 2-alkoxy-4,6-bis-(alkylamino)-s-triazine herbicides					
Prometon	OCH_3	$NHisoC_3H_7$	$NHisoC_3H_7$	PRELIMINARY DATA Rat, SD Negative (details not available)	b

Table I -contined

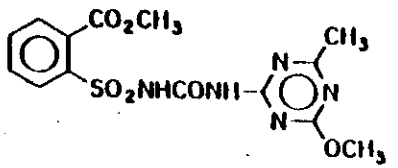
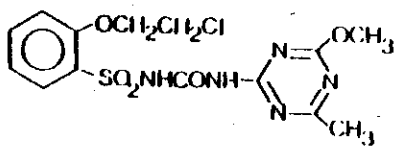
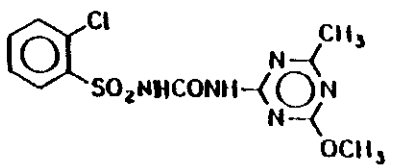
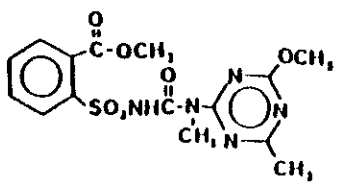
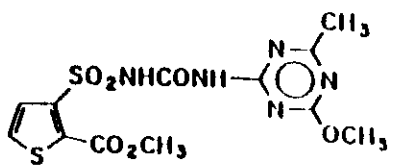
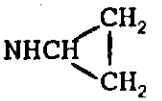
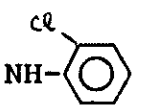
Compound	Chemical Structure	Carcinogenicity	Ref.
(II) Sulfonylurea Herbicides Containing s-Triazine Moiety			
Metsulfuron methyl (Ally)		NEGATIVE Rat,SD Negative (up to 5000 ppm) Mouse,CD1 Negative (up to 5000 ppm)	a
Trisulfuron (Amber)		NEGATIVE Rat,SD Negative (up to 6000 ppm) Mouse,CD1 Negative (up to 10000 ppm)	a
Chlorsulfuron (Glean)		NEGATIVE Rat,-- Negative (up to 2500 ppm) Mouse,-- Negative (up to 5000 ppm)	a
DPX-L5300 (Express)		POSITIVE (OPP status: Group C) Rat,SD Mammary Gland (at 1250 ppm) [q_1^*=0.045 (mg/kg/day)$^{-1}$] Mouse,-- Negative (up to 1500 ppm)	a,b
DPX-M6316 (Harmony)		NEGATIVE Rat,CD Negative (up to 2500 ppm) Mouse,CD1 Negative (up to 7500 ppm)	a

Table I -contined

Compound	Chemical Structure R_1	R_2	R_3	Carcinogenicity	Ref.
(III) Other s-Triazine Pesticides and Related Compounds					
Cyromazine	NH_2	NH_2		NEGATIVE Rat, SD Negative (up to 3000 ppm)	b
Melamine	NH_2	NH_2	NH_2	POSITIVE (solid state carcinogenesis?) Rat,F344 Urinary Bladder in males (at 4500 ppm) [q_1*=0.003 $(mg/kg/day)^{-1}$] Mouse,B6C3F1 Negative (up to 9000 ppm)	c,d
Hexamethyl-melamine	$N(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$	POSITIVE? Rat, SD Mammary Gland (initially 2000 ppm, then decreased to 250 ppm)	e
Anilazine	Cl	Cl		NEGATIVE Rat,F344 Negative (up to 1000 ppm) Mouse,B6C3F1 Negative (up to 1000 ppm)	f
Cyanuric acid sodium salt	OH (O^-Na^+)	OH	OH	NEGATIVE Rat,CD Negative (up to 5375 ppm) Mouse,B6C3F1 Negative (up to 5375 ppm)	

Sources of references: a, OPP TOX ONE-LINER; b, Dr. Henry Spencer, personal communication; c, NTP, 1983; d, q_1* for melamine calculated by OTS (should be used for comparative purpose only due to uncertainty on biological significance); e, Cohen et al., 1973; f, NCI, 1978; g, Hammond et al., 1986.

In addition to the compounds listed above, 1,3,5-tris-aziridinyl-s-triazine and 2-(5-nitro-2-furyl)-4,6-diamino-s-triazine have been shown to be carcinogenic. Their activity is most likely due to the aziridine and 5-nitrofuryl moiety, respectively. There is also an inconclusive study on cyanuric chloride and cyanuric acid.

Table II

Summary of Genotoxicity Data on s-Triazene Pesticides and Related Compounds[a]

Compound	Gene Mutation[b]				Chromosome Ab.		DNA Damage and Repair[c]
	Ames	B	C	D	in vitro	in vivo	
Atrazine	-					-	-
Simazine	-					-	
Propazine		-		+	-		-
Cyanazine	-?			+;-		-	+
Ametryn	-						
Prometryn	-						
Terbutryn	-	-				-	-
Metsulfuron methyl (Ally)	-			-	+?		-
Trisulfuron (Amber)	-			-	-		-
DPX-L5300 (Express)	-			-	-		-
DPX-M6316 (Harmony)	-					-	-
Melamine[d]	-			-	-	-	-
Anilazine	-		+		-		-
Cyanuric acid[e]	-			-		-	-

[a] Except where indicated, the data were summarized from data considered acceptable/supplementary in OPP Tox One-Liners.
[b] Designations for other tests: B, bacterial gene mutation assays other than Ames; C, yeast gene mutation assay; D, mammalian cell gene mutation assays.
[c] Data available in one or more of DNA repair, unschedule DNA synthesis (UDS) and sister chromatid exchanges (SCE) assays.
[d] Summarized from NTP, 1983.
[e] Summarized from Hammond et al., 1985.

Table III

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

Type of Substituents	Concern Level
(A) halogen plus one or 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

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

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Chemical:	**Atrazine (ANSI); Simazine (ANSI); Propazine (ANSI)**
PC Code:	***080803; 080807; 080808***
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