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

AUG 20 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Addendum to Toxicology Branch Memorandum regarding the toxicological significance of CGA 150829, a metabolite of Triasulfuron (Amber)

TOX CHEM # 861C

To: Robert Taylor, PM 25
Herbicide-Fungicide Branch
Registration Division (H7505C)

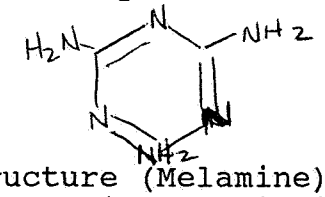
From: Joycelyn Stewart, Ph.D.
Melba Morrow, D.V.M.
Toxicology Branch I
Health Effects Division (H7509C)

Thru: Karl Baetcke, Ph.D., Chief,
Toxicology Branch I
Health Effects Division (H7509C)
and
William Burnam, Deputy Director,
Health Effects Division (H7509C)

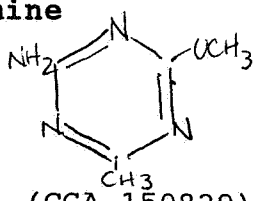
Toxicology Branch had requested information on the acute toxicity, mutagenicity and perhaps metabolism of CGA 150829, a metabolite of triasulfuron, because of concerns raised by EFGWB that the degradate might leach into and affect ground and/or surface water (see Toxicology Branch memo: Morrow to Taylor dated 6/13/91). CGA 150829 is structurally similar to melamine, which has been reported by NTP to be carcinogenic in bladders of male Fisher 344 rats.

Based on a meeting with the registrants on 7/30/91, and a letter from the registrants to Robert Taylor, PM 25, Toxicology Branch has decided to re-evaluate its decision based on the following issues.

1. Relationship of CGA 150829 to Melamine



Structure (Melamine)
2,4,6,amino-s-triazine



(CGA 150829)
2 amino, 4 methoxy, 6 methyl-
s- triazine

With respect to the toxicology of melamine, the chemical was tested for carcinogenicity by the NTP in Fisher 344 rats and in B6C3F1 mice. The chemical did not demonstrate any carcinogenic effects in mice or in female rats but there was an increased incidence of bladder tumors accompanied by bladder stones in high dose male rats. The high dose tested was 4500 ppm.

In subchronic studies, dietary administration of melamine to rats at levels of up to 1800 ppm was associated with hyperplasia of the transitional epithelium of the bladder in male rats at 3000 ppm and above. Bladder stones were found in all males dosed at levels of 750 ppm and above.

Melamine is rapidly absorbed and distributed in tissue body water and is rapidly eliminated in urine unchanged after oral dosing. Six hours after administration of a single oral dose of 250 mg of melamine to rats, 50% of the dose was excreted in the urine, and within 24 hours of administration of a single oral dose of 0.38 mg of ^{14}C melamine, 90% of the radioactivity was excreted in the urine of rats.

CGA 150829 differs from melamine by being substituted at N4 with a methoxy group and at N6 with a methyl group. It has been postulated that the carcinogenic activity of any given s-triazine depends upon the nature of the substituents at the 2, 4, and 6 positions (document on SAR Analysis of s-triazine compounds). The methoxy and methyl substitutions render this metabolite more water soluble than melamine, thus it is expected that these substituents will decrease its toxicity and/or its carcinogenic potential.

2. METABOLISM

Upon metabolism and the cleavage of the sulfonylurea bridge, Glean (Chlosulfuron), Ally (Metsulfuron methyl) and Amber (Triasulfuron) can be expected to produce the metabolite, 2-amine-4-methoxy-s-triazine. This metabolite has been identified in the tissue of goats and chickens after administration of Amber. Based on the results from several rat metabolism studies, seventy to ninety percent of the administered dose of Amber is excreted in the urine and feces as parent compound. Approximately 2% of the substituted phenyl ring structure, found on the left side of the parent compound, was found in the rat metabolism study conducted with Amber. This finding implies that the triazine portion of the parent molecule would also be present.

In a rat metabolism study conducted with Ally, this s-triazine molecule (CGA 150829) has been associated with metabolite III (1.4% of the total metabolites), and with metabolite I which constituted only 0.05% of the total metabolites. (See attachment I for the proposed metabolic pathway of Ally).

The metabolism of Glean in rats resulted in 86% intact parent compound, 5% 2-chlorobenzene sulfonamide and 4% minor metabolites. It is possible that CGA 150829 is included in the fraction characterized as "minor metabolites".

Table I shows the chemical name and structure of the parent compound and the metabolite, CGA 150829.

3. Carcinogenicity

Since the metabolite CGA 150829 has been identified in Ally, and possibly in Amber, it is expected to have been tested, although at low levels in the carcinogenicity bioassays. Glean, Amber and Ally all tested negative in carcinogenicity bioassays. Glean was tested in rats at levels up to 2500 ppm and in mice at up to 5000 ppm. Ally was tested in SD rats and CD 1 mice at up to 5000 ppm. Amber was tested in the same strains of rats and mice at levels of 6000 ppm and 10,000 ppm, respectively.

To date, the only sulfonylurea s-triazine herbicide that has been identified as a positive carcinogen is Express. This compound has been associated with mammary adenomas and adenocarcinomas at levels of 1250 ppm. Unlike the negative chemicals, the metabolism of Express results in the formation of a [2-(methylamino)-4-6 methyl]-s-triazine. It is postulated that the carcinogenicity of Express may be related to the substitution of the methylamino group at the number "2" position on the triazine ring. This suggests a relationship between the compound structure and carcinogenic activity. Based on this, it is not expected that CGA 150829, which is substituted at the 4 and 6 positions on the triazine ring, would be likely to have carcinogenic potential.

Additionally, based on negative results in bioassays for carcinogenic activity on the parents, it is not expected that the metabolite, CGA 150829, produced by Ally and (possibly) Glean and Amber will have carcinogenic activity.

4. Systemic Toxicity

Neither Glean, Ally or Amber are highly toxic compounds. In subchronic feeding studies in rats the following conclusions were made:

Ally - Systemic NOEL = 1000 ppm, LEL = 7500 ppm based on decreased body weight gain in females and decreased serum protein levels.

Glean - Systemic NOEL = 100 ppm, LEL = 500 ppm based on slight decrease in plasma creatinine levels and slightly increased hematocrit in male rats.

Amber - Systemic NOEL = 200 ppm, LEL = 10000 ppm based on decreased body weights, decreased food consumption, increased

incidence of kidney atrophy and epithelial hyperplasia.

Lower toxicity of CGA 150829 can be expected based on the fact that the methoxy and methyl substitutions increase the solubility of the metabolite in water (as discussed in SAR document) and decrease the bioavailability.

5. Additional Information on Related Chemicals

Ciba- Geigy has proposed that prometon is metabolized to 2,4-amine-6-methoxy-s-triazine, which is supposedly closer in structure to melamine than CGA 150829, with the only difference being the substitution of a methoxy group at the N6 position on the triazine ring and that prometon gave negative results in carcinogenicity bioassays. However, Toxicology Branch could not verify that this metabolite was formed and the registrant does not intend to provide any additional metabolism data because there are no proposals for the use of prometon on food or feed crops, (telephone conversation between J. Stewart and Eileen King-Watson on 8/14/91.

6. Tolerance Considerations

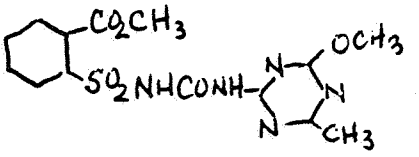
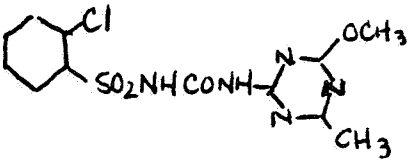
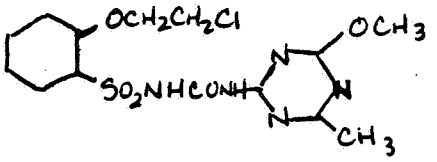
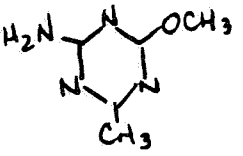
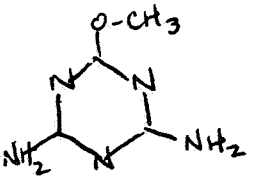
The RfD for Triasulfuron was 0.01 mg/kg/day, using a NOEL of 1.2 mg/kg/day for centrilobular hepatocytomegaly in males in the mouse carcinogenicity study. (An uncertainty factor of 100 was used to calculate the RfD).

A tolerance of 0.02 ppm is proposed for residues of parent triasulfuron in milk. A revised analysis by Chemistry Branch I indicates that total anticipated residues in milk are 0.012 ppm of which 0.005 ppm is from the parent compound and 0.007 ppm is from the metabolite CGA 150829. These levels are 4 and 3 times lower than the proposed tolerance of 0.02 ppm, respectively.

Based on our conclusion that the metabolite, CGA 150829,is no more toxic and probably less toxic than the parent, the attached DRES run using tolerance levels of 0.02 ppm in milk, indicate that even for non-nursing infants, only 15% of the RfD would be used. This would result in an MOE of approximately 780.

Based on this analysis, the toxicology data (acute toxicity and mutagenicity) requested in Toxicology Branch's memorandum (Morrow to Taylor, 6/12/91) are no longer required.

TABLE I

COMPOUND	CHEMICAL NAME	STRUCTURE
METSULFURON METHYL (ALLY)	Methyl 2[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino] carbonyl] amino] sulfonyl]-benzoate	
CHLORSULFURON (GLEAN)	2-Chloro-N-(((4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino) carbonyl) benzene-sulfonamide	
TRIASULFURON (AMBER)	2-(2-Chloroethoxy)-N-(((4-methoxy-6-methyl 1,3,5- triazin-2-yl)amino) carbonyl)benzene)-sulfonamide	
CGA 150829	2-amine-4-methoxy-6-methyl-s-triazine	
PROMETON METABOLITE (GS12853)	2,4-amine-6-methoxy-s-triazine	

ATTACHMENT 1

Metabolism of Metsulfuron Methyl

These data suggest the following routes of metabolism in rats:

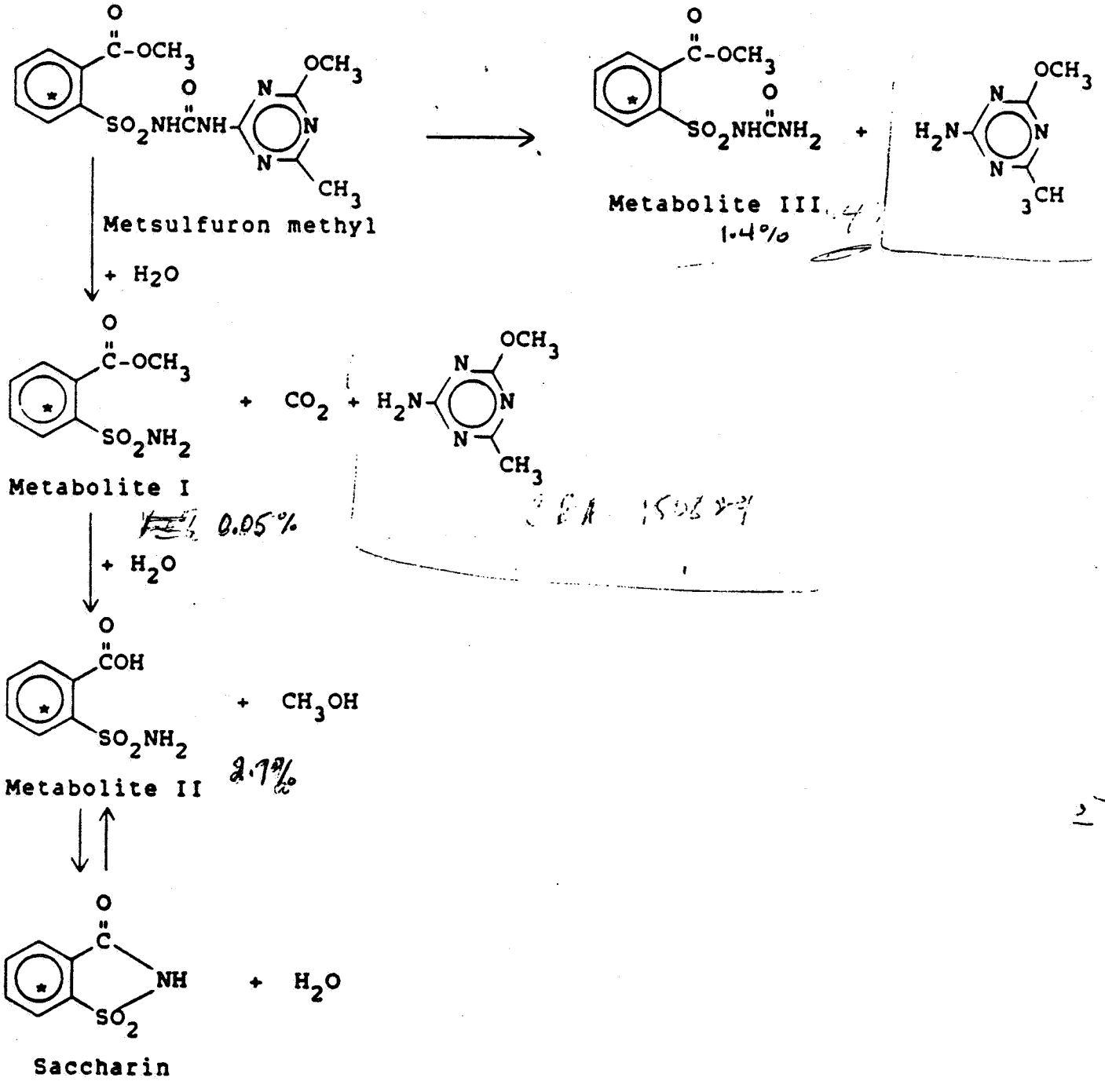


TABLE 1

CHEMICAL INFORMATION FOR CASWELL NUMBER 861C

DATE: 01/24/91 PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Triasulfuron (Amber) Caswell #861C CAS No. 82097-50-5 A.I. CODE: 128985 CFR No. 180.	2yr feeding- mouse NOEL= 1.2000 mg/kg 10.00 ppm LEL= 12.9000 mg/kg 1000.00 ppm ONCO: Negative- 2 species.	Centrilobular hepatocyto-megaly in males. No evidence of carcino-genicity in rats or mice.	PADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.000000	Chronic feed/onco- rat (Current study maybe up-graded).	HED complete 04/11/90. EPA verified 08/22/90.

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
24001AA	BARLEY	8F3658	0.020000		
24007AA	WHEAT-ROUGH	8F3658	0.020000		
24007GA	WHEAT-GERM	8F3658	0.020000		
24007HA	WHEAT-BRAN	8F3658	0.020000		
24007WA	WHEAT-FLOUR	8F3658	0.020000		
50000DB	MILK-NON-FAT SOLIDS	8F3658	0.020000		
50000FA	MILK-FAT SOLIDS	8F3658	0.020000		
50000SA	MILK SUGAR (LACTOSE)	8F3658	0.020000		
53001BA	BEEF-MEAT BYPRODUCTS	8F3658	0.100000		
53001BB	BEEF(ORGAN MEATS)-OTHER	8F3658	0.100000		
53001DA	BEEF-DRIED	8F3658	0.100000		
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	8F3658	0.100000		
53001KA	BEEF(ORGAN MEATS)-KIDNEY	8F3658	0.200000		
53001LA	BEEF(ORGAN MEATS)-LIVER	8F3658	0.100000		
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658	0.100000		
53002BA	GOAT-MEAT BYPRODUCTS	8F3658	0.100000		
53002BB	GOAT(ORGAN MEATS)-OTHER	8F3658	0.100000		
53002FA	GOAT(BONELESS)-FAT	8F3658	0.100000		
53002KA	GOAT(ORGAN MEATS)-KIDNEY	8F3658	0.200000		
53002LA	GOAT(ORGAN MEATS)-LIVER	8F3658	0.100000		
53002MA	GOAT(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658	0.100000		
53003AA	HORSE	8F3658	0.100000		
53005BA	SHEEP-MEAT BYPRODUCTS	8F3658	0.100000		
53005BB	SHEEP(ORGAN MEATS)-OTHER	8F3658	0.100000		
53005FA	SHEEP(BONELESS)-FAT	8F3658	0.100000		
53005KA	SHEEP(ORGAN MEATS)-KIDNEY	8F3658	0.200000		
53005LA	SHEEP(ORGAN MEATS)-LIVER	8F3658	0.100000		
53005MA	SHEEP(BONELESS)-LEAN (W/O REMOVEABLE FAT	8F3658	0.100000		
53006BA	PORK-MEAT BYPRODUCTS	8F3658	0.100000		
53006BB	PORK(ORGAN MEATS)-OTHER	8F3658	0.100000		
53006FA	PORK(BONELESS)-FAT (INCLUDING LARD)	8F3658	0.100000		
53006KA	PORK(ORGAN MEATS)-KIDNEY	8F3658	0.200000		
53006LA	PORK(ORGAN MEATS)-LIVER	8F3658	0.100000		
53006MA	PORK(BONELESS)-LEAN (W/O REMOVEABLE FAT)	8F3658	0.100000		

TABLE 2

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 01/18/91 PAGE: 1

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Triasulfuron (Amber) Caswell #861C CAS No. 82097-50-5 A.I. CODE: 128985 CFR No. 180.	2yr feeding- mouse NOEL= 1.2000 mg/kg 10.00 ppm LEL= 12.9000 mg/kg 1000.00 ppm ONCO: Negative- 2 species.	Centrilobular hepatocyto-megaly in males. No evidence of carcino-genicity in rats or mice.	PADI UF -->100 OPP RfD= 0.010000 EPA RfD= 0.000000	Chronic feed/onco- rat (Current study maybe up-graded).	HED complete 04/11/90. EPA verified 08/22/90.

POPULATION SUBGROUP	TOTAL TMRC (MG/KG BODY WEIGHT/DAY) CURRENT TMRC*	NEW TMRC**	NEW TMRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC	%RFD
U.S. POPULATION - 48 STATES	0.000000	0.000463	4.632670	4.632670		
U.S. POPULATION - SPRING SEASON	0.000000	0.000446	4.462670	4.462670		
U.S. POPULATION - SUMMER SEASON	0.000000	0.000463	4.633430	4.633430		
U.S. POPULATION - FALL SEASON	0.000000	0.000477	4.770670	4.770670		
U.S. POPULATION - WINTER SEASON	0.000000	0.000466	4.664540	4.664540		
NORTHEAST REGION	0.000000	0.000475	4.746590	4.746590		
NORTH CENTRAL REGION	0.000000	0.000484	4.841970	4.841970		
SOUTHERN REGION	0.000000	0.000425	4.247660	4.247660		
WESTERN REGION	0.000000	0.000484	4.840720	4.840720		
HISPANICS	0.000000	0.000563	5.634850	5.634850		
NON-HISPANIC WHITES	0.000000	0.000461	4.606400	4.606400		
NON-HISPANIC BLACKS	0.000000	0.000428	4.283660	4.283660		
NON-HISPANIC OTHERS	0.000000	0.000503	5.034200	5.034200		
NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.000398	3.978770	3.978770		
NON-NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.001543	15.434480	15.434480		
FEMALES (13+ YEARS, PREGNANT)	0.000000	0.000332	3.317490	3.317490		
FEMALES 13+ YEARS, NURSING	0.000000	0.000383	3.828220	3.828220		
CHILDREN (1-6 YEARS OLD)	0.000000	0.001090	10.904990	10.904990		
CHILDREN (7-12 YEARS OLD)	0.000000	0.000734	7.338070	7.338070		
MALES (13-19 YEARS OLD)	0.000000	0.000516	5.157710	5.157710		
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000000	0.000397	3.974550	3.974550		
MALES (20 YEARS AND OLDER)	0.000000	0.000346	3.462170	3.462170		
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000000	0.000283	2.833280	2.833280		

*Current TMRC does not include new or pending tolerances.
**New TMRC includes new, pending, and published tolerances.