

August 14, 2002

Dr. Anne P. LeHuray
Technical Contact
American Chemistry Council
Rubber and Plastic Additives Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Dr. LeHuray:

The Office of Pollution and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Sulfenamide Accelerators category posted on the ChemRTK HPV Challenge Program Web site on December 20, 2002. I commend The Rubber and Plastic Additives Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that The Rubber and Plastic Additives Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Sanders
A. Abramson
C. Auer

**EPA Comments on Chemical RTK HPV Challenge Submission:
Sulfenamide Accelerators Category**

SUMMARY OF EPA COMMENTS

The Sponsor, The Rubber and Plastic Additives Panel for the American Chemistry Council, submitted a test plan and IUCLID data set to EPA for the Sulfenamide Accelerators category on December 3, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on December 20, 2001. Two of the category members, N-oxydiethylenebenzothiazole-2-sulfenamide (MBS) and N-oxydiethylenethio-carbamoyl-N'-oxydiethylenesulfenamide (OTOS), are sponsored chemicals. The remaining three chemicals, N-*tert*-butyl-2-benzothiazolesulfenamide (TBBS), N-cyclohexylbenzothiazole-2-sulfenamide (CBS) and N,N-dicyclohexylbenzothiazole-2-sulfenamide (DCBS), are non-sponsored and used as analogs.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. EPA disagrees with the submitter that MBS/analog and OTOS constitute a category because (1) OTOS contains a thiocarbomoyl moiety that makes it structurally different from other category members that contain a benzothiazole moiety; (2) OTOS can not yield 2-mercaptobenzothiazole upon hydrolysis; thus it does not share a major precursor and degradation product with the other category members; and (3) the physicochemical properties and environmental fate, ecological and toxicological data show differences between OTOS and MBS/analog. Therefore, EPA evaluated OTOS and MBS, the two sponsored chemicals, individually.
2. Physicochemical Properties and Environmental Fate Data. The submitter needs to provide measured data for the octanol/water partition coefficient, water solubility, and stability in water endpoints, and use these data as inputs to the transport and distribution model. A biodegradation test on OTOS needs to be conducted.
3. Health Endpoints. Although data are available for all health effects endpoints on MBS and its three analogs, EPA could not determine the adequacy of these studies because the robust summaries were poorly documented. Similarly, for OTOS, the acute, genetic, repeated-dose, and reproductive toxicity summaries were deficient and poorly documented and EPA could not determine their adequacy. EPA disagrees with the submitter's plan to extrapolate MBS/analog data to OTOS and recommends that the submitter conduct a developmental toxicity study (OECD TG 421) on OTOS.
4. Ecotoxicity. The submitted data on OTOS and MBS/analog are inadequate for all ecotoxicity endpoints. Because MBS hydrolyzes in water under environmental conditions, EPA recommends acute testing in fish, invertebrates, and algae with MBS and/or its hydrolysis products using measured concentrations, identifying the tested product(s) analytically. Depending on the test results for water solubility and stability in water, the same approach may be necessary for OTOS.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON SULFENAMIDE ACCELERATORS CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposes a category of five sulfenamide-containing (= CSNRR') compounds. Two of the category members, N-oxydiethylenebenzothiazole-2-sulfenamide (MBS, CAS No. 102-77-2) and N-oxydiethylenethiocarbamoyl-N'-oxydiethylenesulfenamide (OTOS, CAS No. 13752-51-7), are sponsored chemicals. The remaining three chemicals, N-*tert*-butyl-2-benzothiazolesulfenamide (TBBS, CAS No. 95-31-8), N-cyclohexylbenzothiazole-2-sulfenamide (CBS, CAS No. 95-33-0) and N,N-dicyclohexylbenzothiazole-2-sulfenamide (DCBS; CAS No. 4979-32-2), are non-sponsored chemicals that are intended to provide information in support of the category. These non-sponsored compounds contain a sulfenamide functional group, and also contain a benzothiazole group that is common to only one of the sponsored chemicals, MBS. The other sponsored chemical, OTOS, contains a thiocarbomoyl moiety in addition to the sulfenamide group.

Category Justification

The submitter bases the category on similarities in structure, physicochemical data, and environmental and toxicological properties and points to common synthetic precursors and common degradation (hydrolysis) products as additional supporting evidence. The submitter focuses on the sulfenamide function as the major determinant of properties and concludes that "the physicochemical and toxicological properties of the proposed Sulfenamide Accelerators category members are similar and follow a regular pattern as a result of that structural similarity."

However, EPA believes that the chemicals as a group do not constitute a category and the data do not support the submitter's conclusions for the following reasons:

1. The benzothiazole moiety is common to only four of the five category members and influences the properties of those members that contain this function. The remaining member, OTOS, is a thiocarbomoyl compound and is therefore structurally different from the other members of the category. The data provided by the submitter suggest that these structural differences are also reflected in differences in several physicochemical, environmental, and toxicological properties.
2. OTOS can not yield 2-mercaptobenzothiazole upon hydrolysis; therefore, the evidence does not support the argument for common precursors or degradation products for all the members of the category.
3. The test plan states that "[a]ll members of this category are produced via an oxidation reaction using 2-mercaptobenzothiazole and various primary and secondary amines as starting materials." This statement is incorrect since 2-mercaptobenzothiazole is not a precursor of OTOS.
4. The EPIWIN estimates for OTOS for water solubility and octanol/water partition coefficient suggest that these endpoints for OTOS are significantly different from the other category members.
5. For ecological effects, the submitter proposes to use SAR to estimate acute toxicity. However, pair-wise comparisons of measured and calculated (ECOSAR) values provided by the submitter differ by many orders of magnitude. This may be the result of the uncertainty in the estimated octanol/water partition coefficient noted above. Therefore, the data do not support the use of either a category approach or SAR to estimate the acute ecotoxicity for OTOS.
6. The toxicity data do not indicate common target organs among the five chemicals and genotoxicity results suggest dissimilarities among all five chemicals; therefore, results from the developmental toxicity studies for MBS or its analogs should not be considered applicable to OTOS.

Test Plan

General Comment

In many summaries the test substances were identified by undefined names (Delac Mor, Santacure MOR Accelerator).

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The data for melting point and vapor pressure are adequate for the purposes of the HPV Challenge Program.

Boiling Point. The submitter needs to provide measured boiling or decomposition point data for MBS and OTOS. According to OECD Guideline 103, the boiling point for a chemical substance should be determined experimentally for chemicals with a boiling point less than 300 °C. If a substance decomposes before boiling, the temperature of decomposition should be reported. DCBS decomposes at 200 °C (rubust summary data).

Octanol/water partition coefficient. The submitter needs to revise its data or provide measured data for MBS and OTOS. The Log K_{ow} values provided for TBBS, Santocure MOR, CBS, and DCBS are much higher than the submitted estimated values for OTOS and MBS. EPA believes that these high values can not be extrapolated to OTOS or MBS.

Water solubility. The EPIWIN values calculated by the submitter for MBS (3061 mg/l at 25 °C) and OTOS (62.85 g/l at 25 °C) conflict with the (measured?) value of 32 ppm in the MBS data set and contradict the “negligible water solubility” stated in the test plan. The test plan fails to comment on this significant difference in values in Table 1. Furthermore, according to OECD Guideline 105, the water solubility should be measured unless the value is ≤ 1 µg/L. Therefore, the submitter needs to provide water solubility data for MBS and OTOS to address this endpoint.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Photodegradation. EPA agrees with the submitter that testing for photodegradation is not necessary.

Stability in water. The submitter indicates in its test plan that there are sufficient data for this endpoint and that additional testing is not recommended. In the case of MBS, this conclusion is based on a hydrolysis study for Santocure MOR (composition not given) indicating complete hydrolysis in 7 days at pH 7. However, according to OECD Guideline 111, hydrolysis should be measured for a range of environmentally-related pH values (4 - 9). The submitter presented measured data for an MBS analog, TBBS (Santocure NS) at three different pH values showing that the hydrolysis rate changes with pH. No hydrolysis data were provided for OTOS. OTOS is not a benzothiazole sulfenamide, so hydrolysis data for MBS/analogues can not be used for this chemical. The TBBS data suggest that hydrolysis of these chemicals may be important under environmental conditions. Therefore, the submitter needs to provide measured stability in water data for MBS and OTOS following OECD Guideline 111.

Biodegradation. The submitter did not provide biodegradation data for OTOS. The submitted data for benzothiazole sulfenamides are not applicable to OTOS because it does not have a similar benzothiazole sulfenamide structure. The submitter needs to provide measured biodegradation data for OTOS following OECD guidelines.

Transport and Distribution. The submitter used EPIWIN default values to calculate transport and distribution for MBS and OTOS. The submitter needs to use the measured physicochemical properties and

environmental fate data as inputs to its transport and distribution model. The use of estimated values introduces uncertainties that then become magnified in modeling applications.

When summarizing the fugacity results, the sponsor needs to provide the assumptions and data inputs to the model (see Guidance for Robust Summary preparation). Although EPA had previously recommended the use of EQC Level I, this model is somewhat limited. EPA now recommends a level III analysis, which is more rigorous. The EQC and EPIWIN Level III models are acceptable.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

General Comments. For the reasons given above, EPA considers that MBS, its analogs and OTOS do not comprise a category. Instead, EPA evaluated the sponsored chemicals individually. Data are available for all health effects endpoints on MBS and its three analogs. However, EPA could not determine the adequacy of these studies because the robust summaries were poorly documented. Similarly, for OTOS, the acute, genetic, repeated-dose, and reproductive toxicity summaries were poorly documented and EPA could not determine their adequacy. The submitter did not propose testing for developmental toxicity on OTOS; however, for the reasons given above, EPA disagrees with the submitter's plan to extrapolate MBS/analog data to OTOS. Therefore, EPA recommends that the submitter conduct a developmental toxicity study (OECD TG 421) on OTOS.

Acute Toxicity. The submitter needs to address deficiencies in the robust summaries in order for EPA to determine data adequacy.

Repeated-Dose Toxicity. The adequacy of oral toxicity data for MBS could not be determined because of deficiencies in the robust summaries. Despite omissions in the robust summary, data for repeated inhalation toxicity may be adequate. For OTOS, the submitter needs to address deficiencies in the robust summaries for the two-year chronic toxicity study in order for EPA to determine data adequacy.

Genetic Toxicity. Data for gene mutation and chromosomal aberration exist for both sponsored chemicals. The submitter needs to address deficiencies in the robust summaries in order for EPA to determine data adequacy.

Reproductive Toxicity. For MBS, the adequacy of the two reproductive toxicity studies could not be determined (in one study, a single dose was administered on only two days during estrus; and the design of the other study was not described). The submitter did not assign reliability codes to these studies. In addition, Ref. 45 (Hinderer, 1982) cited for the second summary is that for the mutagenicity evaluation. For OTOS, although the reproductive toxicity data may appear adequate, the submitter needs to address the deficiencies in the robust summaries in order for EPA to determine data adequacy.

Developmental Toxicity. The adequacy of the developmental toxicity study for MBS could not be determined because of deficiencies in the robust summaries. No data were submitted for OTOS and the submitter did not propose testing for this chemical. The submitter proposed bridging data from the other category members to OTOS. However, EPA does not agree that toxicological information for the benzothiazole-type category members is relevant to OTOS because of its differing structure, significantly higher water solubility and lower log K_{OW} value. These differences are likely to result in substantial differences in toxicokinetic and toxicological properties between OTOS and other category members. From the solubility and partitioning properties, both the placental transfer rate and fetal effects of this compound are likely to differ from those of the benzothiazoles. Therefore, a developmental toxicity study (OECD TG 421) is necessary to address this endpoint for OTOS.

Ecotoxicity

EPA considers the submitted data on MBS and its analogs for all ecotoxicity endpoints inadequate. The studies on fish, daphnia, and algae were conducted using nominal concentrations. However, MBS hydrolyzes in water at pH 7 under environmental conditions and as a result, it is likely that the data submitted reflect exposure to the hydrolysis products. The submitter needs to conduct acute testing in fish, invertebrates, and algae with MBS and/or its hydrolysis products using periodic measured concentrations of the chemical species present. In addition, depending on the measured data for water solubility and stability in water, the same approach may be necessary for OTOS.

For both MBS and OTOS, the calculated values are not acceptable because there is no SAR chemical class validated for these chemicals in ECOSAR.

Specific Comments on the Robust Summaries

Health Effects

Many of the robust summaries for the critical studies were incomplete and many were inadequate. EPA could not determine the adequacy of critical or supporting studies because of the deficiencies and a lack of critical information in the robust summaries.

The IUCLID data set for TBBS did not assign reliability codes to studies or identify key studies.

Acute oral toxicity.

OTOS: The omitted information in robust summaries included tested doses, gavage vehicle, length of the observation period, incidence of mortality, systemic toxicity in target organs by dose and sex, and a range or 95% confidence interval for the LD50.

Repeat-dose toxicity

MBS: The omitted information in the oral study summary included the strain and sex of rats, group sizes, the endpoints examined (hematology, clinical chemistry, urinalysis, gross pathology and histopathology), and magnitude of body weight changes. The 4-week inhalation assay omitted the group sizes, the characteristics of the test atmosphere, and the organs that were examined for histopathology. It is unclear whether the NOAEL was properly identified considering effects on nasal turbinates in this study.

OTOS: The following were lacking in the oral study summary: the group sizes, the magnitude of body or kidney weight changes, or the incidences of compound-related lesions by dose and sex. In addition, the EPA guideline cited as number 82-5 should be EPA OPP 83-5.

Genetic toxicity

MBS: The omitted information in the robust summaries for bacterial mutation and chromosomal aberration (SCE) included the positive controls and the source of the metabolic activation system. The summary for the cytogenicity study in CHO cells omitted the name of the test material, concentrations tested, the number of cells examined, the duration of exposure, the criteria for positive and negative results, and the source of the metabolic activation system. In the *in vivo* dominant lethal assay summary the identity of the test material, experimental design, and criteria for evaluating results were not included.

OTOS. Robust summaries for *in vitro* toxicity tests did not provide information on positive controls, the source of the metabolic activation system, and the duration of exposure. In addition, the summaries did not always clearly present the concentrations at which cytotoxicity was observed (non-cytotoxic concentrations reported under the heading for cytotoxic concentrations). Summaries for DNA damage and repair, mutation in mammalian cells, cytogenicity assay (chromosomal aberration) did not adequately describe the experimental design, concentrations tested, time of exposure, number of cells examined, and criteria for evaluating results.

Reproductive toxicity

MBS: Robust summaries for two reproductive toxicity studies did not identify the test material and vehicle, clearly describe the experimental design (especially the group size and the temporal relationship between exposure and mating and termination), or specify the parental and fetal endpoints that were examined.

OTOS: The robust summary of a critical study did not describe the experimental design or indicate whether both sexes were exposed, the timing of exposure with respect to mating and termination, and the parental and fetal endpoints examined were not stated.

Developmental toxicity

MBS: The summaries omitted the group sizes, the purity of the test material, and the maternal and fetal endpoints that were examined.

Ecotoxicity

There were many deficiencies in the robust summaries. The robust summaries for all future ecotoxicity studies should follow the "Guidance on Developing Robust Summaries" at <http://www.epa.gov/opptintr/chemrtk/guidocs.htm>.

Followup activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.