December 19, 2001

MEMORANDUM

SUBJECT: Thiocarbamates: A Determination of the Existence of a Common Mechanism of Toxicity and A Screening Level Cumulative Food Risk Assessment .

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This memorandum summarizes the position of the Office of Pesticide Programs (OPP) with respect to the grouping of the thiocarbamate pesticides based on a common mechanism of toxicity and the results of a screening level cumulative risk assessment (final position document *Thiocarbamates: A Determination on the Existence of a Common Mechanism of Toxicity and a Screening Level Cumulative Food Risk Assessment* attachment A). The results of the screening level cumulative risk assessment are intended to provide direction to the Special Review and Reregistration Division (SRRD) as it proceeds in conducting the reassessment of tolerances for these pesticides and to the Registration Division (RD) as it considers any tolerance actions involving these pesticides. This memorandum describes the information considered by scientists, the process followed in developing a position on the thiocarbamates, and the conclusions regarding this scientific issue.

The group of registered thiocarbamate pesticides covered in this review includes EPTC, Molinate, Pebulate, Triallate, Butylate, Cycloate, and Thiobencarb.

Background

The Food Quality Protection Act (FQPA) amended the laws under which EPA evaluates the safety of pesticide residues in food. Among other types of information EPA is to weigh when making safety decisions, the new amendments direct EPA to consider "available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity." Sec. 408(b)(2)(D)(v) of the Federal Food Drug and Cosmetic Act. FQPA also directs EPA to apply the new safety standard to tolerances established prior to the passage of FQPA. Further, in carrying out the tolerance reassessment provisions of FQPA, EPA "shall give priority to review of the tolerances or exemptions that appear to pose the greatest risk to public health." Sec. 408(q)(2).

The carbamate pesticides represent a class of food use pesticides that have been given high priority by OPP for the reassessment of tolerances in accordance with the mandates FQPA. Within the class, there are three distinct subgroups: N-methyl carbamates, thiocarbamates, and dithiocarbamates. As part of the reassessment, OPP scientists considered whether it would be appropriate to group the thiocarbamate pesticides because the thiocarbamates operate by a common mechanism of toxicity. In reviewing this issue, OPP scientists were guided by several relevant science policies, including:

- *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (issued for public comment in August 1998; issued in revised form in February 1999, Attachment B). [http//www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf **or** Document No. 6055, Fax-on-Demand, (202) 401-0527].

- *Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity*, USEPA, January 22, 2000, Attachment C. Internet: http://www.epa.gov/fedrgstr/EPA-PEST/2000/June/Day-30/6049.pdf

- *A Science Policy on a Common Mechanism of Toxicity: The Carbamate Pesticides and the Grouping of Carbamate with the Organophosphorus Pesticides*, Attachment D. Internet: http://www.epa.gov/scipoly/sap/1999/September/carbam.pdf

Review of the thiocarbamate pesticides

EPA's Office of Pesticide Programs (OPP) prepared the document *Thiocarbamates: A Screening Level Cumulative Dietary (Food) Risk Assessment* in response to a September 1999 recommendation from the FIFRA Scientific Advisory Panel (SAP Report No. 99-05, November, 1999) that the Agency specifically address effects other than acetyl cholinesterase inhibition reported in studies conducted on the thiocarbamates before initiating a cumulative risk assessment.

The approach in the initial assessment was to identify a common effect of the thiocarbamates that might be attributable to a common mechanism and to conduct a screening level cumulative food assessment to determine if grouping the thiocarbamates based on a common effect and concurrent exposures to the group would suggest a potential for cumulative dietary risks.

A review of data provided in studies submitted by registrants and in studies reported in the literature suggested that the thiocarbamate pesticides share a common metabolic profile and induce a common effect, neuropathy of the sciatic nerve. However, a common mechanism of toxicity could not be established for the common effect. Some thiocarbamates (EPTC, molinate, pebulate, and cycloate) share a common mechanism of toxicity for acetylcholinesterase inhibition (ChEI) but, in general, ChEI is produced by these pesticides at higher dose levels than is neuropathy. As a screening level exercise, a cumulative risk assessment was conducted using the assumption that the neuropathy induced by the thiocarbamates could be attributed to a common mechanism of toxicity. The screening approach also assumed treatment of 100% of crops with each thiocarbamate registered for use on a crop and used tolerance levels for the exposure component of the assessment, rather than a more refined estimate of actual residue levels.

On September 7, 2001, the Agency presented to the FIFRA Scientific Advisory Panel (SAP) the draft cumulative risk assessment of the thiocarbamates. The SAP commented that it agreed with the Agency that there was insufficient evidence that the thiocarbamates induce neuropathology via a common mechanism of toxicity and questioned whether a common metabolic product exists even though results of studies submitted to OPP indicate thiocarbamate pesticides share a common metabolic profile (SAP Report No. 2001-11 dated November 1, 2001, Attachment E). Further, the SAP opined that a pattern of common neuropathology does not appear to exist but pointed out that lack of consistent pathological examinations hindered the evaluation of common neuropathology effects. The SAP also questioned the use of a screening approach for the thiocarbamates because a common mechanism of toxicity could not be established. and suggested that the Agency consider whether the selection of other toxicity

endpoints could result in a more conservative risk assessment than did neuropathology. Finally, the panel raised concerns that the use of a NOAEL as a method for determining potency may not be appropriate.

OPP has considered the recommendations of the SAP and believes that the overall process described in the document*, Thiocarbamates: A Determination on the Existence of a Common Mechanism of Toxicity and a Screening Level Cumulative Dietary (Food) Risk Assessment* (Attachment A), provides a reasonable approach to for a small group of structurally related pesticides where data suggest, but are not sufficient to establish, a common mechanism of toxicity. The results of such a screening approach are useful in several respects. First, a screening assessment can inform the risk assessor of deficiencies in the hazard and exposure components of the data base that would need to be addressed if it is later determined that a common mechanism is present. Secondly, a decision may be made by a risk manager that the results of a screening level assessment show that there is a reasonable certainty that food exposure to the group of pesticides, were they found to share a common mechanism of toxicity, will not result in harm to the human population. If such is the case, there would be little value in obtaining additional information on the potential for the candidate group of chemicals to induce a common effect by a common mechanism and the resources required for the preparation of a comprehensive cumulative risk assessment could be devoted to issues of higher concern. In contrast, if concerns are raised by the screening level assessment that there could be a potential for adverse effects in humans who may be exposed to the group of pesticides should they be determined to share a common mechanism of toxicity, OPP would initiate a comprehensive cumulative risk assessment when data were made available that supported the grouping of the candidate pesticides based on an established common mechanism of toxicity, as required by the provisions of FQPA.

The Agency has considered the potential that the selection of an endpoint other than neuropathology (e.g., acetylcholinesterase inhibition, developmental/reproductive effects; see Attachment A, Section III, C, 5) would result in a more conservative risk assessment and concluded that the neuropathology effects of the thiocarbamates is the most sensitive endpoint.

Regarding the use of NOAELs to estimate potencies, it should be noted that OPP recognizes that the use of benchmark doses or other modeling approaches of dose response data is preferred. OPP has calculated the lower limit for benchmark doses ($BMDL_{10}$) for those thiocarbamates for which adequate dose response data are available and modified the attached document accordingly. As discussed in the attached document (See Section V-B), the use of NOAEL's would not lead to underestimates of potential risks because: a) the $BMDL_{10}$ for the index chemical, Cycloate is almost equal to the NOAEL and b) the use of NOAEL's overestimates the

potencies of the major contributor to the cumulative risk assessment, Molinate, by almost 10-fold. The potency of Triallate is underestimated by 1.5-fold but this thiocarbamate is a minor contributor to the estimates of cumulative risk. Thus, the use of NOAEL's to compare potencies, when considered together with the use of tolerance level residues and the assumption of treatment with 100% of crops each thiocarbamate, is unlikely to lead to an underestimate of potential cumulative food risks from exposures to the common assessment group of thiocarbamate pesticides.

Conclusion

In conclusion, OPP has determined that some thiocarbamates (EPTC, Molinate, Pebulate, and Cycloate) share a common mechanism of toxicity, the inhibition of acetylcholinesterase. It is OPP's position, however, that there is insufficient evidence for grouping the thiocarbamate pesticides based on a common mechanism of toxicity for effects other than acetyl cholinesterase inhibition. Although, structural and metabolic similarities exist among the thiocarbamates and there is evidence that the thiocarbamates may produce a common effect (neuropathology), this evidence is not definitive.

In addition to making the determinations regarding the existence of a common mechanism of toxicity, OPP also conducted a preliminary screening level cumulative food risk assessment for this group of pesticides. The screening level cumulative risk assessment incorporates a number of very conservative assumptions, i.e. assumptions which overstate significantly the actual level of potential risk. Among the effects induced by the thiocarbamates (i.e., acetylcholinesterase inhibition, reproductive/developmental, and neuropathology), neuropathology was identified as the most sensitive effect. Even though a common mechanism of toxicity could not be established for neuropathology, the effect was selected as the endpoint for use in a screening level cumulative risk assessment to assure that risks would not be underestimated. Results of the screening level cumulative food risk assessment are intended to provide guidance to risk managers regarding the need to acquire and evaluate additional data on a common mechanism of toxicity for the thiocarbamates and to initiate a comprehensive cumulative risk assessment.

OPP will place this memorandum and its attachments in a public docket and will post the memorandum on OPP's website. In addition, OPP will notify its stakeholders of this determination using the Pesticide Program Update messaging system and will announce the availability of these documents to the media. Further, OPP will invite the public to submit comments on this determination, as well as any relevant new data or analyses over the next 60 days. Finally, as OPP moves ahead, the Office will consider fully all comments and information submitted by the public.

Attachments

A: *Thiocarbamates: A Determination on the Existence of a Common Mechanism of Toxicity and a Screening Level Cumulative Food Risk Assessment*. December 1, 2001

B: *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity.* January 29, 1999

C: Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity. June 22, 2000.

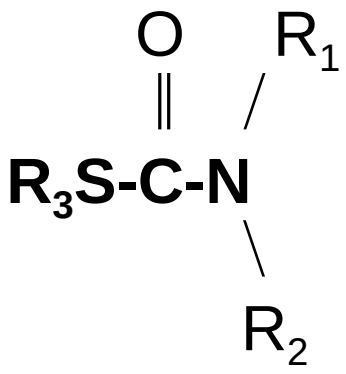
D: *A Science Policy on a Common Mechanism of Toxicity: The Carbamate Pesticides and the Grouping of Carbamate with the Organophosphorus Pesticides*. August 30, 1999

E. SAP Report No. 2001-11, FIFRA Scientific Advisory Panel September 7, 2001; Report Issued November 1, 2001

Attachment A

THIOCARBAMATES:

A Determination of the Existence of a Common Mechanism of Toxicity and a Screening Level Cumulative Food Risk Assessment



U.S. EPA Office of Pesticide Programs
Health Effects Division
December 1, 2001

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Acronyms and Abbreviations

ALDH aldehyde dehydrogenase

BEAD Biological and Economic Analysis Division

CAG cumulative assessment group

ChE cholinesterase

ChEI acetylcholinesterase inhibition

CMG common mechanism group

CNS central nervous system

COS carbonyl sulfide

DEEM™ Dietary Exposure Evaluation Model

ED_{50} effective dose causing a toxic response in 50 percent of the animals treated

GSH glutathione

FMO flavin monoxygenase

FQPA Food Quality Protection Act of 1996

HED Health Effects Division

i.p. intraperitoneally

LD_{50} lethal dose expected to cause death in 50 percent of the animals treated

LOAELs lowest observed adverse effect level

MOE margins of exposure

NOAELs no observed adverse effect level

PAD population adjusted dose

RfD reference dose

RPFs relative potency factors

SAP FIFRA Scientific Advisory Panel

Executive Summary

A cumulative risk assessment begins with the identification of a group of chemicals, a common mechanism group (CMG), that induce a common toxic effect(s) by a common mechanism. The Office of Pesticide Programs (OPP) has determined that certain members of the thiocarbamate pesticides, a subgroup of the larger group of carbamate pesticides, share a common mechanism of toxicity - the inhibition of acetyl cholinesterase. The specific thiocarbamates found to share this common mechanism are EPTC, molinate, pebulate, and cycloate. Acetylcholesterase inhibition is, however, not the most sensitive endpoint for these thiocarbamates. While the thiocarbamates also produce a range of other toxic effects, OPP has determined there is no definitive evidence that any of the other endpoints is produced by a common mechanism of toxicity.

OPP considered particularly carefully those thiocarbamates which induce a common effect, neuropathy of central or peripheral nerves. Formation of a reactive sulfoxide metabolite is a plausible common critical event that may be associated with the neuropathologic effects of the thiocarbamates. However, available data are not sufficient to link the formation of a sulfoxide metabolite with the induction of neuropathy. Furthermore, the morphological descriptions of the neuropathy seen in sciatic nerve tissue (degeneration) can be attributed to different processes that damage neurons. The thiocarbamate pesticides are also metabolized to carbonyl sulfide (COS) and isocyanate but data are also not sufficient to evaluate the role these moieties may have in inducing neuropathy. In sum, the evidence does not show that it is more probable than not that thiocarbamates share a common mechanism of toxicity for the common toxic effect, neuropathology.

In addition, OPP also conducted a preliminary, screening level cumulative risk assessment of the thiocarbamates which assumed the existence of a common mechanism of toxicity. The screening level assessment incorporates a number of very conservative assumptions, i.e., assumptions which overstate significantly the actual level of risk. For example, some thiocarbamates share the common effect of inhibiting cholinesterase (ChE) and induce common developmental effects (e.g., effects on skeletal development), but these effects are generally induced at higher dose-levels than neuropathy and, in the case of developmental toxicity, the mechanism of toxicity is unknown. The neuropathy induced by the thiocarbamates was identified as the most sensitive common endpoint and this endpoint was used as the basis for the screening level cumulative risk assessment of potential chronic food risks. OPP's screening level assessment also made conservative assumptions with respect to potential food exposure. A Dietary Exposure Evaluation Model (DEEM^{TM}) preliminary screening analysis used tolerance levels and assumed treatment of 100% of crops with each member of the thiocarbamates.

OPP's screening level assessment shows that the cumulative margins of exposure (MOE) for population subgroups are greater than 1000, with the exceptions of infants less than one year of age, children one to six years of age, and children seven to 12 years of age (MOEs - 310, 517, and 783, respectively). Removal of molinate from the thiocarbamates, which were grouped together as a potential CAG, results in MOEs greater than one thousand for all population subgroups.

I. Introduction

A. Background

EPA's Office of Pesticide Programs (OPP) has prepared this document in response to a September 1999 recommendation from the FIFRA Scientific Advisory Panel (USEPA, 1999c) that the Agency specifically address effects of concern other than cholinesterase inhibition reported in studies conducted on the thiocarbamates. At the Panel meeting, EPA had solicited the Panel's advice on guidance document regarding the evaluation of a common mechanism of toxicity of the carbamate pesticides. That document, *Thiocarbamates: A Screening Level Cumulative Dietary (Food) Risk Assessment*, also described the results of EPAs *screening level* cumulative risk assessment of a common assessment group of thiocarbamates.

The approach to the initial assessment was to identify a common effect of the thiocarbamates that might be attributable to a common mechanism. OPP also decided to conduct a screening level cumulative food assessment to determine if grouping the thiocarbamates based on a common effect and concurrent exposures to the group would reveal the potential for cumulative risks. This assessment was conducted using the assumption that the neuropathological effects induced by the thiocarbamates may be attributed to a common mechanism of toxicity. The screening approach also assumed treatment of 100% of crops with each thiocarbamate registered for use on a crop and used tolerance levels for the exposure component of the assessment rather than a more refined estimate of actual residue levels.

The consideration of the need for a cumulative risk assessment on the thiocarbamates is consistent with the mandates of The Food Quality Protection Act (FQPA) of 1996[1]. FQPA specifies, among other things, that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk on: aggregate (i.e., total dietary (food and water), residential, and other non-occupational) exposure. EPA is also required to consider available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposures to pesticides and other substances that have a common mechanism of toxicity. In effect, the FQPA directs OPP to consider the possibility that low-level exposures to multiple substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the chemicals individually. Individuals, including infants and children, exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of

[1]For details see The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Federal Food, Drug, and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 3, 1996; U.S. Environmental Protection Agency, Office of Pesticide Programs, document # 730L97001, March, 1997.

the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

To this end, OPP has developed several science policy documents to be used when performing cumulative hazard and risk assessments. The science policy documents include:

- ❏ Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999a)

- ❏ A Science Policy on a Common Mechanism of Toxicity: The Carbamate Pesticides and the Grouping of Carbamate Pesticides with Organophosphorus Pesticides (USEPA, 1999b)

- ❏ Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity (USEPA, 2000b).

The document on the evaluation of a common mechanism of toxicity of the carbamate pesticides laid the groundwork for evaluating whether or not the thiocarbamates should be grouped on the basis of inducing a common effect by a common mechanism(s) of toxicity. This document was presented at a meeting of the FIFRA Scientific Advisory Panel (SAP) meeting held on September 22, 1999. The SAP concluded that those carbamates that inhibit ChE should be considered for grouping in a cumulative risk assessment (USEPA, 1999c).

The document on the common mechanism of toxicity of the carbamates also contained a discussion of effects other than ChEI that might have a bearing on whether all carbamates should be grouped based on the potential to inhibit ChE. Depending on the particular carbamate, other effects may result including reproductive or developmental effects, thyroid toxicity and neuropathic effects.

The dithiocarbamates and thiocarbamates are two subgroups of carbamates whose toxicities are characterized principally by effects other than ChEI. The SAP stated in their report that “groupings of carbamates based on non-cholinergic endpoints such as reproductive, thyroid, developmental, and broad-spectrum neurotoxicity could possibly be appropriate for certain carbamates, especially the low-potency, thio- and di-thiocarbamate fungicides and herbicides, whose ability to inhibit acetylcholinesterase is weak or absent.”

On September 7, 2001, the Agency presented to the FIFRA Scientific Advisory Panel (SAP) a paper containing an evaluation of the evidence concerning potential mechanisms of toxicity other than cholinesterase inhibition, as well as a draft screening level cumulative risk assessment of the thiocarbamates. The SAP commented in their report that it agreed with the Agency that there was insufficient evidence that the thiocarbamates induce neuropathology via a common mechanism of toxicity and questioned whether a common metabolic product exists even though results of studies submitted to OPP indicate thiocarbamate pesticides share a

common metabolic profile (USEPA, 2001). Further, the SAP opined that a pattern of common neuropathology does not appear to exist but pointed out that lack of consistent pathological examinations hindered the evaluation of common neuropathology effects.

The SAP also questioned the use of a screening level cumulative risk assessment of the thiocarbamates because a common mechanism of toxicity had not been established. However, the Agency believes that the results of such a screening approach are useful in several respects. First, a screening assessment can inform the risk assessor of deficiencies in the hazard and exposure components of the data base that need to be addressed if the Agency later concluded that there is a common mechanism. Secondly, a decision may be made by a risk manager that the results of a screening level assessment show that there is a reasonable certainty that food exposure to the candidate group were they found to share a common mechanism will not result in harm to the human population. If such is the case, there would be little value in obtaining additional information on the potential for the candidate group of chemicals to induce a common effect by a common mechanism and the resources required for the preparation of a comprehensive cumulative risk assessment could be devoted to issues of higher concern. In contrast, if concerns are raised by the screening level assessment that there could be a potential for adverse effects in humans who may be exposed to the group of pesticides, should they be determined to share a common mechanism of toxicity, OPP would initiate a comprehensive cumulative risk assessment at such time as data were made available that supported the grouping of the candidate pesticides based on an established common mechanism of toxicity, as required by the provisions of FQPA.

B. Purpose

This document is intended to describe the evidence evaluated and the findings regarding the potential for two or more thiocarbamates to induce toxicity via a common mechanism using the principles described in the document *"Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity,* January 29, 1999 [http//www.epa.gov/fedrgstr/EPA-PEST/1999/February/Day-05/6055.pdf **or** Document No. 6055, Fax-on-Demand, (202) 401-0527].

The information contained herein also shows the results of EPA's preliminary screening level food cumulative risk assessment of registered thiocarbamate pesticides. Assumptions in this assessment were that 100% of crops are treated with each thiocarbamate registered for use on a crop and that tolerance levels of residues occur on commodities from the crops. Neuropathology was identified as a common toxicity endpoint for use in the preliminary, screening level food cumulative risk assessment.

The preliminary screening level cumulative risk assessment is intended to illustrate the **process** that may be followed as a first step in evaluating the need for

a more refined cumulative risk assessment of a group of chemicals that may share a common mechanism of toxicity. The cumulative risk assessment presented in this document is not intended to identify a level of concern or risk for any one chemical or group of chemicals included in the assessment.

II. Thiocarbamate Pesticides: Properties, Uses and Structures

Thiocarbamates are volatile compounds that will evaporate from soil; they may also leach and move laterally because of their water solubility. Their half-life in moist soil ranges from one to >four weeks and in heavy clay from one to 12 weeks. The thiocarbamates' herbicidal activity is believed to be due to their metabolism to reactive sulfoxide intermediates. The acute lethal doses (LD_{50}) of the thiocarbamates, with the exception of molinate and diallate (LD_{50}'s 369 and 395 mg/kg, respectively) exceed 1000 mg/kg. Lethality is a result of respiratory paralysis (WHO, 1988).

Currently, there are seven thiocarbamates registered for use as pesticides. The thiocarbamates are used only as herbicides in agriculture; there are no residential uses.

Figure 1 shows the general structure of the currently registered thiocarbamates included in this cumulative dietary risk assessment. The formulas for each of the registered thiocarbamates follow.

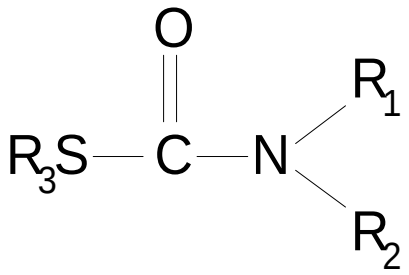
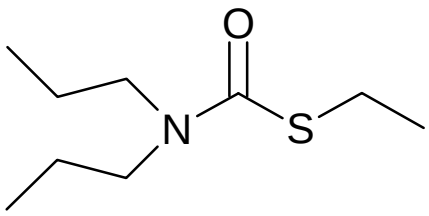


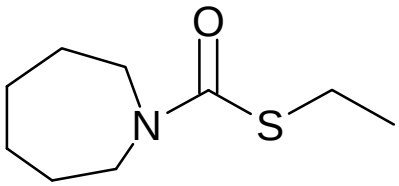
Figure 1. General Structure of Thiocarbamates

A. Structures of the Registered Thiocarbamates Pesticides

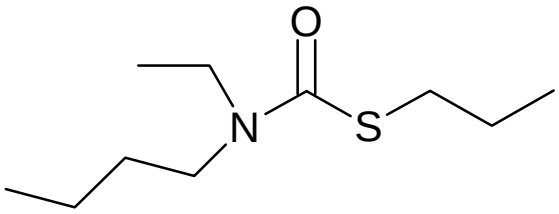
1. EPTC (CAS NO. 759-94-4)



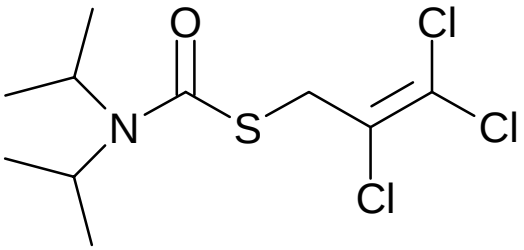
2. Molinate (CAS NO. 2212-67-1)



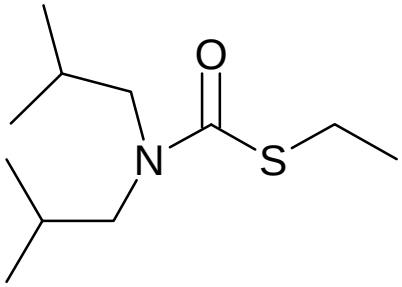
3. Pebulate (CAS NO. 1114-71-2)



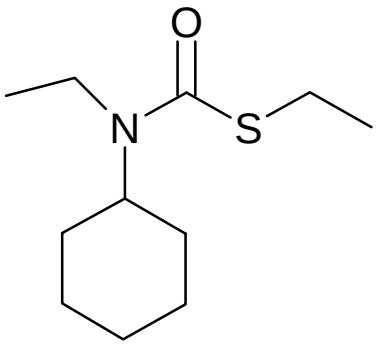
4. Triallate (CAS NO. 2303-17-5)



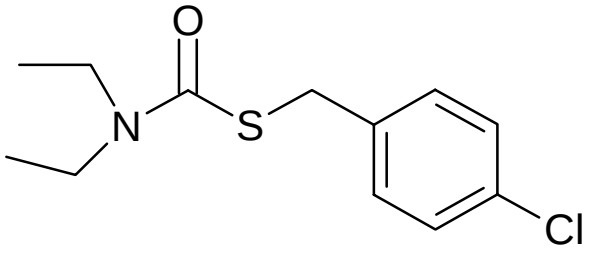
5. **Butylate (CAS NO. 2008-41-5)**



6. **Cycloate (CAS NO. 1134-23-2)**



7. **Thiobencarb (CAS NO. 28249-77-6)**



III. Lines of Evidence

In this section, the various available lines of evidence used in the evaluation of the common mechanism of toxicity of the thiocarbamates under consideration is presented.

A. Structure Activity Considerations

In general, based on structure-activity relationships (SAR), the pesticides in a given class may be grouped according to their likelihood to generate a common type of toxic molecule or reactive intermediate or their ability to mimic a common biologically active molecule that interferes with the normal homeostasis of the cell (e.g., via receptor binding, enzyme induction, etc.).

It was concluded by the FIFRA SAP following the meeeting of September 22, 1999, that those carbamates that inhibit cholinesterase (ChE), associated with the carbamate ester linkage (-OC=O), should be considered for grouping based on a common mechanism of the toxicity. For those carbamates in which carbamate ester linkage has been changed to thiolo (-SC=O), thiono (-OC=S) or dithio (SC=S), the ChE inhibitory property may be considerably diminished or absent, and thus the grouping based on other endpoints was also evaluated.

For the candidate group of thiocarbamates, subject of this paper, at least three reactive moieties capable of eliciting toxic action, other than ChE inhibition, should be considered 1. a sulfoxide ; 2. carbonyl sulfide; 3. an S-methyl-ester.

1. Sulfoxide generation

As illustrated in Figure 2 for molinate, sulfoxidation of the molecule renders the carbonyl more electrophilic, facilitating its reaction with glutathione to the extent that 35-40% of the urinary radioactivity consists of molinate mercapturate.

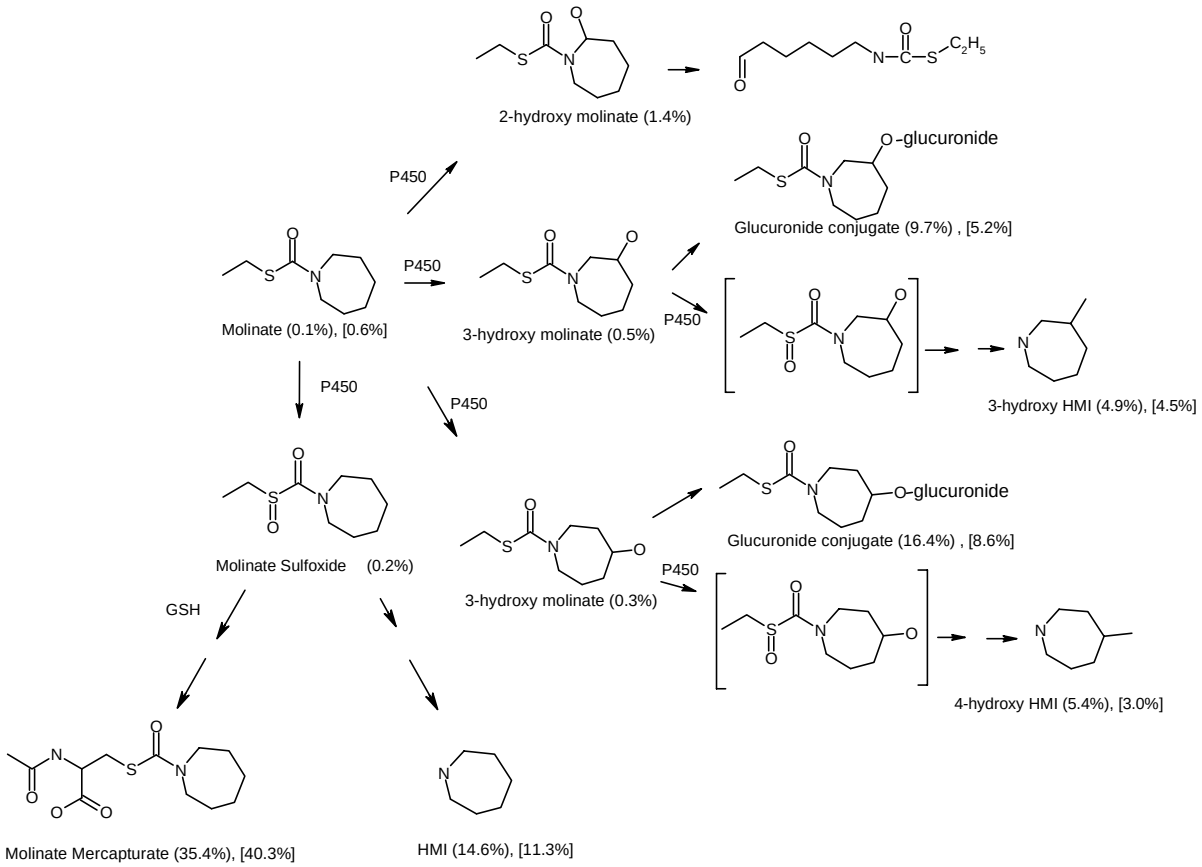


Figure 2. The biotransformation of [ring-^{14}C] molinate in the rat. Adapted from DeBaun et al. (1978) and from MRID 41781804. Percentages are percent of urinary radioactivity; values in parenthesis are from DeBaun et al. (1978) , and values in brackets are from MRID No. 41781804.

There is interest in the thiocarbamate sulfoxides because of their possible role in toxic reactions. Jewell and Miller (1998) implicated molinate sulfoxide in testicular toxicity in rats by binding a carboxylesterase required for mobilization of cholesterol required in testosterone synthesis. Schuphan et al.(1979) postulated that a rearrangement of diallate sulfoxide produces an unstable intermediate that subsequently generates the mutagen 2-chloroacrolein. Hart and Faiman (1995) reported that five thiocarbamate herbicides (EPTC, molinate, butylate, vernolate and ethiolate) inhibited rat liver low K_m aldehyde dehydrogenase ($ALDH_2$), probably via their sulfoxides. The authors speculated on the basis of the $ALDH_2$ inhibition, that workers exposed to ethanol after the use of the above pesticides may exhibit a reaction like that experienced by individuals treated with disulfiram, which is used in alcohol aversion therapy.

2. Carbonyl sulfide generation

As illustrated in Figure 3 for EPTC, α-oxidation of the S-alkyl chain will result in release of the the thiocarbamate as a free thiol, which, in addition to other reactions, will be cleaved to give carbonyl sulfide (COS). As shown in Figure 3, at least 7% of EPTC is metabolized to COS. This value is probably an underestimate since up to 17% of the amount mtabolized is attributable to acetaldehyde (presumably produced in equimolar amounts with COS and the amine). The work of Peffer et al (1991) on butylate (Figure 4) indicates that about 51% of the urinary radioactivity excreted by rats dosed with [[^{14}C-isobutyl]butylate appears as diisiobutyl amine. By analogy with the work shown in Figure 3, one may speculate that a comparable amount of COS has been produced, but is undetected because of the label used. Although at this time there is no data on the chronic toxicity of COS, interest in this compound arises because of its potential conversion to an isocyanate, a protein-chain crosslinker from Graham et al. (1995).

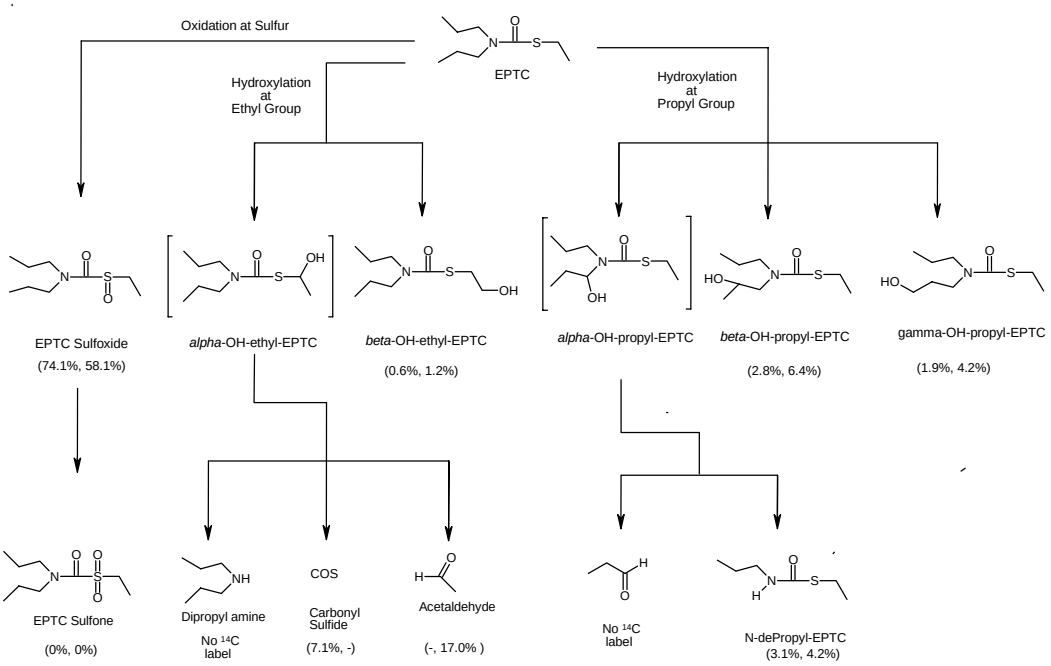


Figure 3. Metabolic pathways for EPTC in a mouse liver microsome-NADPH system. Numbers in parenthesis are normalized yields for each metabolite from [^{14}C=O] and [ethyl-^{14}C]EPTC, respectively, calculated as metabolite amount relative to totall metabolized EPTC. Unstable intermediates are shown in brackets. This microsomal system lacks phase II detoxication enzymes such as GSH S-transferase components. It illustrates some oxidative reactions in the metabolism of EPTC. Adapted from Chen and Casida (1978).

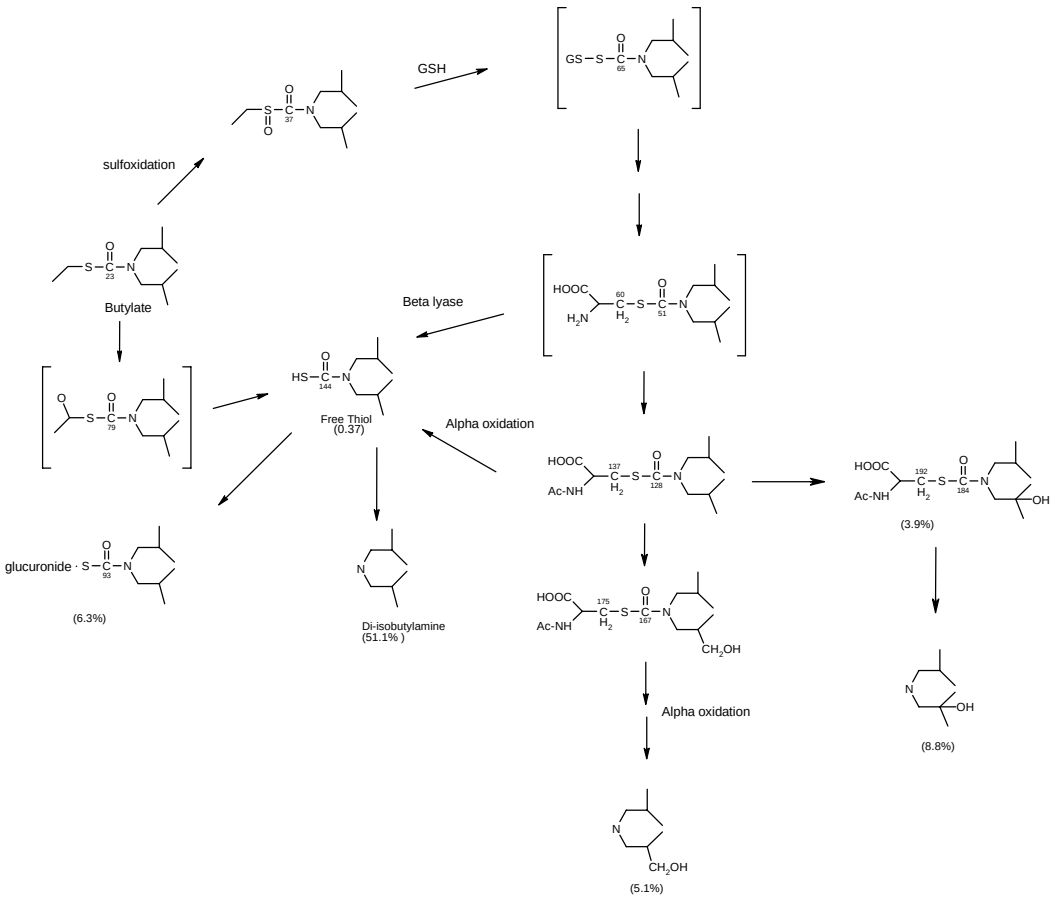


Figure 4. Major metabolic pathways of butylate in the rat. Adapted from Peffer et al (1991). Values in parenthesis are percent of urinary radioactivity expressed as mean of males and females.

Graham et al. (1995) presented a scheme describing reactions and intermediates that could lead to protein cross-linking by molecules such as CS_2 and COS (Figure 5). Although cross-linking by CS_2 is being intensively studied as a mechanism for CS_2-induced neuropathies, no mechanism exists at this time for thiocarbamate induced neuropathies. Whether or not COS plays any role in the induction of neuropathies is not known at this time.

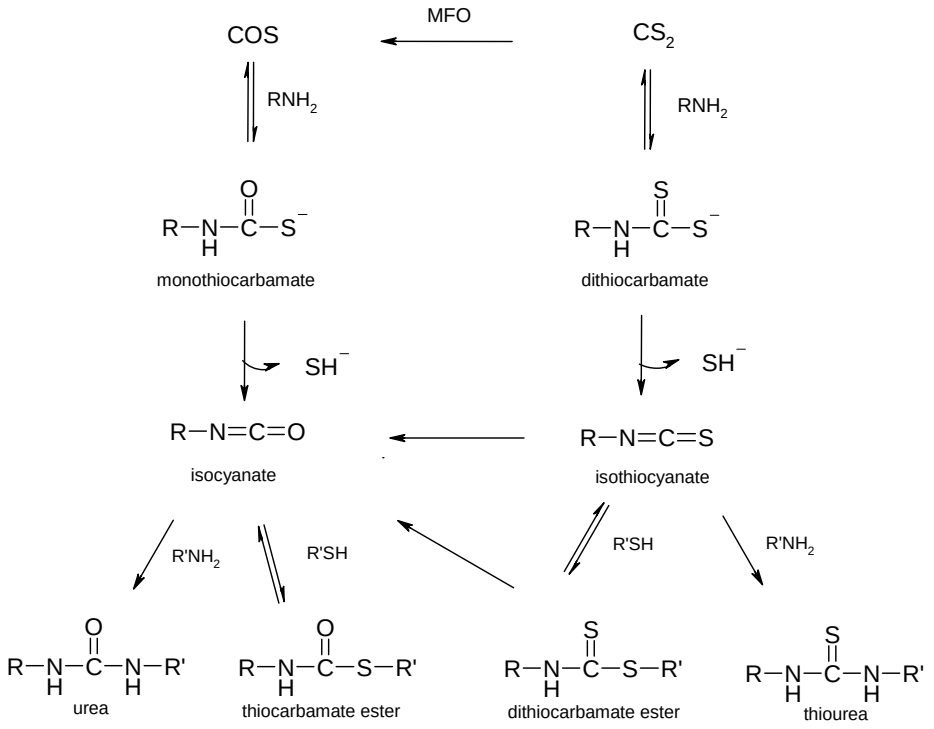


Figure 5. Cross linking reactions resulting from COS and CS_2 exposure. RNH_2 and R'NH_2 are different protein backbones being crosslinked. Likewise, RNH_2 and R'SH are different protein backbones being crosslinked. In this diagram, crosslinking may occur via an isothiocyanate originated from CS_2 or via an isocyanate originated from COS. (Adapted from Graham et al. 1995)

3. Formation of an S-methyl ester

Staub et al (1995) studied the formation of S-methyl esters of thiocarbamates as a bioactivation mechanism in mice for thiocarbamates. After intraperitoneal injection of EPTC, molinate, butylate, vernolate, pebulate, diallate, triallate, liver extracts contained the S-methyl derivatives of the respective parents. Additionally, when the dosing was conducted with the glutathione (GSH) conjugate of molinate, the liver extract contained methyl molinate ester. Thus, methylation appears to be a way to reactivate molecules such as the GSH-conjugates of thiocarbamates. The methylated thiocarbamate can be released again into circulation as a molecule that can undergo additional reactions such as sulfoxidation.

B. Metabolism

Figure 6 summarizes the key metabolic products that may be formed by the thiocarbamates. Metabolism may proceed by a major pathway involving initial oxidation of the sulfur to a sulfoxide followed by further metabolism, including conjugation with glutathione. In another pathway, the thiocarbamate may undergo hydroxylation at the S- or N-alkyl side chains. Both pathways may result in formation of a thiocarbamic acid that can be further metabolized to COS (Staub *et al.,* 1995; WHO, 1988).

As discussed earlier, there are several metabolic pathways that are thought to be affected by treatment of laboratory animals with thiocarbamates. A thiocarbamate may selectively inhibit aldehyde dehydrogenase (ALDH), ATPase activity, and lipid metabolism (Staub *et al.*, 1999 ; Staub *et al.*, 1995; Pentyala and Chetty, 1993). The potential to inhibit ALDH has led to the use of disulfiram, a dithiocarbamate, as an alcohol-aversion drug. The thiocarbamate herbicides and their metabolites have been shown to be similar to the disulfiram metabolites, S-methyl N,N-diethylthiocarbamate and its sulfoxide, in their potency range as ALDH inhibitors (Quistad *et al*., 1994). For example, EPTC administered intraperitoneally (i.p.) to mice (4 mg/kg) inhibits liver ALDH activity by 50% and leads to an elevation of acetaldehyde levels in blood and brain. Metabolism of COS by carbonic anhydrase leads to the formation of hydrogen sulfide, which is implicated as the causative agent responsible for respiratory depression in rats treated acutely with COS (Chengelis and Neal, 1980). Thiocarbamates may also have ChEI activity (see Section 3b).

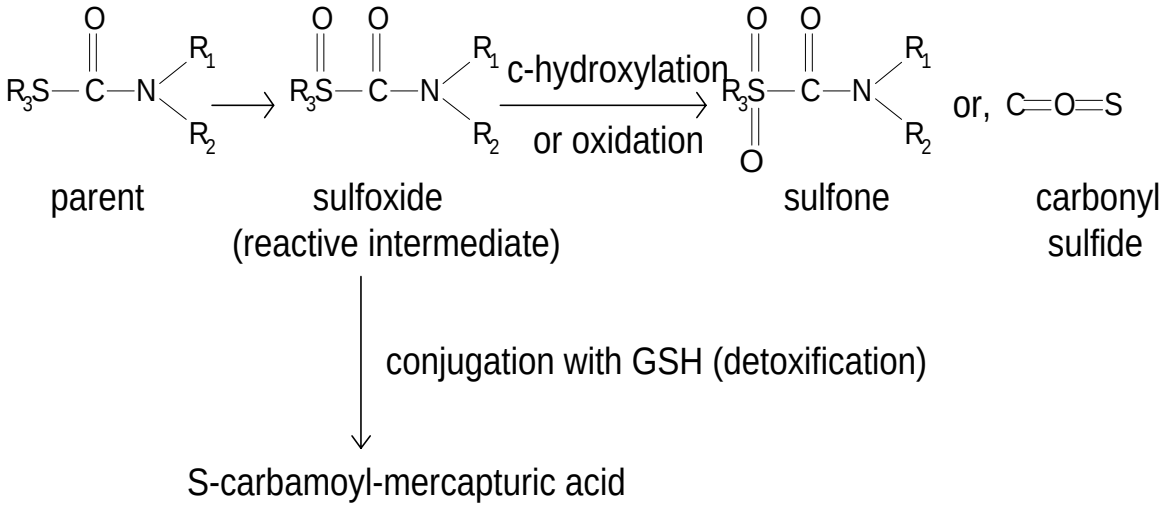


Figure 6. General Activation and Detoxification Pathways of Thiocarbamates

C. Critical Effects

The identification of a candidate group of chemicals for a cumulative risk assessment involves, as an initial step, an evaluation of the effects that may be common to the group of chemicals under review. Following is a discussion of the types of effects reported to be induced by treatment of laboratory animals with thiocarbamates and an evaluation of the extent to which the effects are common to this group of chemicals.

1. Neuropathological Effects

Studies submitted to OPP report that neuropathology is a characteristic, common effect in studies conducted with thiocarbamates. (Table 1). They provide evidence that administration of six of seven of these compounds to rats leads to lesions of brain, spinal cord, or peripheral neurons in rats. The neuropathological effect most common to the thiocarbamates reviewed is degeneration and demylination of the sciatic nerve. Table 1 shows the dose responses and the incidences reported for this lesion and the type study from which the data were extracted.

NOAELs for neuropathological effects in studies with EPTC, molinate, pebulate, triallate, butylate, and cycloate range from <0.3 to 600 mg/kg/day. LOAELs for these same thiocarbamates are three to six orders of magnitude higher with the exception of molinate (NOAEL not established) and the incidences (% of rats with a lesion) at a LOAEL ranges from 13 to 65%. The neuropathological effect was seen only at the high dose for pebulate and butylate and at the low dose for molinate, thus limiting an evaluation of the dose-response characteristics of these three thiocarbamates. No evidence of neuropathology was observed in studies conducted with thiobencarb. Treatment of rats with butylate resulted in neuropathology at an acute dose of 2000 mg/kg; no neuropathology was reported in a two-year rat study up to a dose of 400 mg/kg/day. Given the high dose required to provide evidence of neuropathological potential and the questionable significance of the solitary finding in a single study conducted with butylate, it is unlikely butylate would contribute to any cumulative dietary risk that might result from dietary exposure to two or more thiocarbamates.

Table 1. Dose-Response for Neuropathological Effects of the Thiocarbamates in Rats

Chemical and Study	Dose Response (mg/kg/day)	Comments
EPTC–two-year MRID 00145004, 00146311	0 5 **25**[a] 125 7/46[b] 4/42 32/49 33/43 (15)[c] (10) (65) (76)	Sciatic nerve-axonal degeneration (no grading); 90-day neurotoxicity study shows neuronal necrosis in brain at 39.4 mg/kg/day; NOAEL 7.9 mg/kg/day
Molinate – two-year MRID 41815101	0 **0.3** 1.8 13 2/69 8/60 9/60 38/60 (3) (13) (15) (63)	Degeneration and demyelination of sciatic nerve; Grades 3, 4, and 5
Pebulate–90-day neurotoxicity MRID 43221001	0 4.5 22 **85** 1/6 0/6 0/6 2/6 (17) (0) (0) (33)	Sciatic nerve degeneration; effect graded minimal. Moderate degenerative changes in spinal cord and peripheral nerves in one-year dog study at 100 mg/kg/day. No effect on sciatic nerve in two- year rat study up to 75 mg/kg/day
Triallate – 90-day neurotoxicity MRID 43021601	0 8.1 **38.9** 146.6 0/5 0/5 2/5 4/5 (0) (0) (40) (80)	Sciatic nerve degeneration–minimal and mild
Butylate–acute neurotoxicity MRID 43514101, 43967901	0 200 600 **2000** 0/5 0/5 0/5 2/5 (0) (0) (0) (40)	Sciatic nerve degeneration. No neuropathology up to a dose of 400 mg/kg/day in a two-year rat study or a one-year dog study up to a dose of 100 mg/kg/day
Cycloate – two-year MRID 00137735	0 0.1 0.5 **3.1** 16.8 5/29 5/22 6/24 17/37 31/33 (17) (23) (25) (46) (94)	Sciatic nerve degeneration, all grades; average grade increased at 3.1 mg/kg/day
Thiobencarb MRID 43001001, 00154506	--------	No evidence of neuropathology up to a dose of 100 mg/kg/day in a 90-day neurotoxicity study or a two-year study

a = LOAEL in **bold**; b = incidence; c = percent response

2. Activity as Cholinesterase Inhibitors

Data submitted to OPP show that at least four of the thiocarbamates inhibit ChE, an effect which is generally accepted as being a common mechanism of toxicity. Table 2 shows ChEI NOAELs and LOAELs for five of the seven thiocarbamates; ChEI measurements were not performed in studies with triallate and thiobencarb. No ChEI was reported when butylate was administered to rats up to a dose of 383 mg/kg/day for 90 days. The dose needed to induce ChEI in dogs by EPTC was 60 mg/kg/day (NOAEL 8 mg/kg/day). NOAELs for EPTC, molinate, pebulate, and cycloate are 8, 1.8, 4, and <8 mg/kg/day, respectively; corresponding LOAELs are 60, 13, 19, and 8 mg/kg/day. ChEI is induced at relatively low doses following treatment of rats with EPTC, molinate, pebulate, and cycloate but at higher doses than doses that induce neuropathy (as discussed later in Section 4).

Table 2. Thiocarbamates: NOAELs and LOAELs for ChEI in Rat Studies

Chemical	Study	ChEI NOAEL/LOAEL (mg/kg/day)	Chemical	Study	ChEI NOAEL/LOAEL (mg/kg/day)
EPTC MRID 40442301	one-year dog	8/60 male and female plasma	Butylate MRID 43452201	90-day rat neurotoxicity	No ChEI up to 383 mg/kg/day
Molinate MRID 41815101	two-year rat	1.8/13 male RBC	Cycloate MRID 00077787	two-year rat	<8/8 P, RBC, & brain
Pebulate MRID 43231001	90-day rat neurotoxiciy	4/19 8% in male brain; 19/78 13% male brain; 22/85 23% female brain	Thiobencarb	------	Not measured
Triallate	----	Not measured			

3. Developmental Toxicity

Results from developmental studies submitted to OPP show that a common effect of treatment of rats with a thiocarbamate is a delay or defect in ossification of the sternebrae (Table 3). For the most part, the developmental effects were observed at maternally-toxic doses. Malformations in fetuses from dams treated with a thiocarbamate are uncommon effects. The NOAELs for the effects on skeletal development range from 5 mg/kg/day to 100 mg/kg/day. Frank malformations were not reported in developmental neurotoxicity studies conducted with triallate or molinate but a decrease in thickness of tissues in brain areas was observed following treatment of rats with molinate.

Table 3. Results from Developmental Toxicity Studies of Thiocarbamates

Chemical	Species	NOAEL/LOAEL (mg/kg/day)	Developmental and Maternal Effects
EPTC MRID 00138919, 40442302	Rat	100/300 (D)* 100/300 (M)**	Decreased litter size, increased resorptions, increased incidence of omphalocele and unossified sternebrae at maternally-lethal dose Mortality
	Rabbit	300/>300 (D)	No effects
Molinate MRID 41473401, 44079201, 14021015	Rat	2.2/35 (D) 35/140 (M)	Increased incidence of runting Decreased body weight, salivation, and dehydration
	Rabbit	20/200 (D) 20/200 (M)	Reduced ossification of sternebrae Decreased body weight and abortions
	Rat***	<1.8/1.8 (D) 1.8/6.9 (D) 6.9/26.1 (M)	Reductions in startle amplitude Reductions in morphometric measurements in areas of brain Decreased body weight gain
Pebulate MRID 40033301, 40033201	Rat	30/200 (D)	Decreased body weight, increased incidence of unossified sternebrae
	Rabbit	30/200 (M) 150/>150	Decreased body weight gain No effects
Triallate MRID 00114260, 41706906, 00114261, 43315001, 4471050	Rat	30/90 (D) 10/30 (M)	Decreased fetal body weight, protruding tongue, and malaligned sternebrae Decreased body weight
	Rabbit	5/15 (D) 15/45 (M)	Decreased fetal body weight and fused sternebrae Decreased body weight and clinical signs
	Rat ***	30/60 (D) 30/60 (M)	Increased motor activity, decrease in passive avoidance Decreased body weight
Butylate MRID 00131032, 40389102	Rat	40/400 (D)	Decreased body weight, increased incidence of misaligned ' sternebrae
	Rabbit	40/400 (M) 500/>500	Decreased body weight and increased liver weight No effects
Cycloate 00146659, 42694901	Rat	400/>400 (D)	No effects
	Rabbit	300/>300 (D)	No effects
Thiobencarb MRID 00086873, 00093691, 00115248	Rat	25/150 (D) 25/150 (M)	Reduced ossification and increased incidence of runts Decreased body weight gain

*D = developmental NOAEL/LOAEL; **M = maternal NOAEL/LOAEL; *** rat developmental neurotoxicity study

4. Reproductive Effects

Table 4 shows results reported in one- or two-generation reproduction studies submitted to OPP. With the exception of molinate, treatment of rats with a thiocarbamate is not generally associated with reproductive effects. No evidence of reproductive effects was reported in studies with EPTC, butylate, pebulate, cylcloate, or thiobencarb. Decreased body weights and increased mortality was the most common effect on offspring and in all cases where these effects were reported, the effect occured at maternally-toxic doses.

Table 4. Results from Rat Toxicity Studies Evaluating the Reproductive Effects of Thiocarbamates

Chemical	NOAEL/LOAEL (mg/kg/day)	Reproductive and Developmental Effects
EPTC MRID 00121284	<2/2 (P)* 50/>50 (R)** 10/40 (D)***	Cardiomyopathy and renal tubule degeneration No effects Decreased body weights
Molinate MRID 44403201	<0.4/0.4 (P and D) 0.4/0.8 (R) Males 1.9/4.7 (R) Females 0.4/0.8 (D) Males 1.9/4.7 (D) Females	Reduced brain weights Abnormal sperm, decreased cauda weight, increase in interstitial tissue Ovarian lesions and cystic follicles Decreased testes and spleen weights, decreased litter size and live pups Delayed vaginal opening, decreased litter size and live pups.
Pebulate MRID 40970001	0.8/6 (P) 50/>50 (R) 6/50 (D)	Decreased body weights, decreased hemoglobin and hematocrit, increased platelet count No effects Decreased survival
Triallate MRID 00114308, 00132880	7.5/30 (P) 7.5/30 (R) 7.5/30 (D)	Neurotoxic clinical signs Reduced pregnancy rates, shortened gestation lengths Reduced weights, increased mortality
Butylate MRID 00160548, 00155519	10/1000 (P) 1000/>1000 (R) 10/1000 (D)	Decreased body weights and increased liver weights No effects Decreased body and brain weights
Cycloate MRID 41691901	2.5/20 (P) 2.5/20 (D)	Decreased body weight gain Decreased body weight gain and survival
Thiobencarb	Not applicable	No developmental or reproductive effects up to 100 mg/kg/day

* P = parental; **R= reproductive; ***D= Developmental

5. Relative Sensitivity of Common Effects

When evaluating the potential of the seven neuropathic thiocarbamates reviewed to pose a cumulative risk, a conservative approach is to identify the common effect that is the most sensitive indicator of toxicity. One approach to comparing relative sensitivities among several effects is to compare the NOAEL for each effect to the NOAEL used to select a reference dose (RfD).

Table 5 shows the NOAELs and LOAELs for effects used to establish chronic RfDs for the thiocarbamates. Critical effects that are the basis for NOAELs/LOAELs are variable among the chemicals and include decreased organ or body weights, cardiomyopathy, and neuropathy. The NOAELs range from <0.3 to 5 mg/kg/day and indicate that the thiocarbamates are relatively toxic chemicals. Only molinate and cycloate have an RfD that is based on one of the common endpoints, neuropathy.

Table 6 shows the relative sensitivity of NOAELs and LOAELs for neuropathology, ChEI, and developmental endpoints based on comparison to NOAELs and LOAELs for effects that were used to establish chronic RfDs. For two of the six neuropathic thiocarbamates (molinate and cycloate), the NOAEL for neuropathological effects is the NOAEL used as the basis for the RfD. The NOAELs for neuropathological effects of EPTC, pebulate, triallate and butylate, are, respectively, three, thirty, three and one hundred and twenty times greater than the NOAELs used to establish an RfD for the chemicals. Because the NOAEL for butylate is substantially higher than the NOAEL used to establish an RfD and because neuropathology was observed at a dose of 2000 mg/kg/day, a limit dose, it is unlikely that butylate would contribute to potential cumulative risks of the thiocarbamates.

Table 5. Thiocarbamates: NOAELs and LOAELs Used to Establish RfDs for Chronic Effects

Chemical	Study	Chronic RfD NOAEL/LOAEL (mg/kg/day)	
EPTC	two-generation reproduction	2.5/10 RfD 0.025	Cardiomyopathy
Molinate	two-year rat	<0.3/0.3 RfD 0.001	Degeneration and demyelination of sciatic nerve
Pebulate	two-year rat	0.74/7.12 RfD 0.007	Decreased body weight and cataracts
Triallate	two-year rat	2.5/12.5 RfD 0.025	Decreased body and adrenal weights
Butylate	12-month dog	5/25 RfD 0.05	Increased relative liver weights
Cycloate	chronic rat	0.5/3 RfD 0.005	Distended myelin sheath, demyelination, atroph, nerve fiber loss
Thiobencarb	two-year rat	1/5 RfD 0.01	Decreased body weight gains, food consumption, and increased BUN

Table 6. Comparisons of NOAELs (mg/kg/day) for Neuropathy, ChEI, or Developmental Toxicity and NOAELs for Chronic Toxicity

Chemical	Chronic RfD NOAEL	Neuropathic NOAEL/ RfD NOAEL	ChEI NOAEL/ RfD NOAEL	Developmental NOAEL/ RfD NOAEL	ChEI NOAEL/ Neuropathic NOAEL	Developmental NOAEL/ Neuropathic NOAEL
EPTC	2.5	5/2.5 = 2	8/2.5 = 3.2	100/2.5 = 40	8/5 =1.6	100/5=25
Molinate	<0.3	<0.3/<0.3 = 1	1.8/<0.3 = >6	20/<0.3 = 67	1.8/<0.3 = >6	20/<0.3=>67
Pebulate	0.74	22/0.74 = 30	4/0.74 = 5.4	30/0.74 = 41	4/22=0.2	30/22=1
Triallate	2.5	8.1/2.5 = 3	NM*	30/2.5 = 12	NA**	30/8.1=4
Butylate	5	600/5 = 120	No ChEI up to 383 mg/kg/day	40/5 = 8	NA	40/600=0.1
Cycloate	0.5	0.5/0.5 = 1	<8/0.5 = <16	No developmental effects	<16	NA
Thiobencarb	1	NA	NM	25/1 = 25	NA	NA

*= ChEI not measured; **NA=not applicable

The ability to inhibit ChE is not the most common sensitive endpoint exhibited by the thiocarbamates because for most, the dose required to inhibit ChE is above the doses that lead to neuropathology or other toxic effects. The neuropathology NOAELs for EPTC, molinate, and cycloate are, respectively, 1.6 , >6, and <16 times lower than the NOAELs for ChEI. Butylate does not inhibit ChE up to a dose of 383 mg/kg/day. Pebulate is the only thiocarbamate reviewed that appears to have more activity as a ChEI than as a neuropathic agent (Table 6). Given the reduced sensitivity of ChEI as a toxicological endpoint when compared to effects selected as endpoints for establishment of RfDs and the neurotoxicity that has been shown to be associated with the treatment of laboratory animals with this group of chemicals, ChEI would not seem to be as conservative as the neuropathy endpoint for use in a screening level cumulative risk assessment of the thiocarbamates.

The NOAEL dose-levels for developmental effects (delayed or absence of ossification) are from eight to 67 times higher than the NOAEL dose-levels used to establish RfDs, about the same magnitude of difference between these parameters as for ChEI (Table 6). However, the LOAELs for the developmental effects in rats of pebulate and triallate were 200 and 90 mg/kg/day, respectively (Table 3), as compared to LOAELs of 85 and 39 mg/kg/day for the neuropathological effects of the same chemicals (Table 1). Assessing the potential cumulative risk of the thiocarbamates based on developmental effects would not be as conservative as using neuropathological effects when consideration is given to differences in both NOAELs and LOAELs. In addition, there are no data available that show a linkage between the developmental effects induced by the thiocarbamates and an underlying mechanism.

The results of the comparisons of doses that induce neuropathological, ChEI, and developmental effects show that neuropathy generally is induced at lower doses, relative to the other effects. Furthermore, the doses that induce neuropathy are at or near the RfD NOAEL for most of the thiocarbamates.

6. Grouping of Thiocarbamates That Are Toxic by a Common Mechanism

OPP has determined that four thiocarbamates - EPTC, molinate, pebulate, and cycloate - share a common mechanism of toxicity, the inhibition of cholinesterase. Inhibition of acetylcholinesterase is, however, not the most sensitive endpoint for these four thiocarbamates. While the thiocarbamates also produce a range of other toxic effects, OPP has determined that there is no definitive evidence that any of the other endpoints is produced by a common mechanism of toxicity.

The common, sensitive effect among the thiocarbamates reviewed is the potential to produce neuropathological lesions of central nervous system (CNS) or peripheral neurons. The precise biochemical mechanism associated with the neurotoxic effects of the thiocarbamates has not been firmly established but the formation of sulfoxide derivatives that can react with sulfhydryl groups of amino acids and proteins is a common metabolic step. Graham *et al.* (1995) have postulated a mechanism for induction of axonopathies after exposure to CS_2, a product of dithiocarbamate metabolism. This mechanism involves cross-linking of axonal proteins via reaction of CS_2 with axonal proteins and formation of dithiocarbamate derivatives leading to cross-linking. These authors also suggest that COS, a product of oxidation of CS_2 could serve as a source of isocyanates that would also result in cross-linking of proteins. One may speculate that COS, formed from metabolism of the thiocarbamates, might be a component of the pathway leading to axonal protein cross-linking resulting in the production of nerve degeneration as shown in Table 1.

Although it has been postulated that COS may contribute to thiocarbamate-induced lesions of nervous tissue, some evidence suggests that metabolism to COS is not involved. In a one-generation reproduction study in which male and female rats were exposed via inhalation with up to 180 ppm COS (six hours a day, five days a week for 13 weeks), no lesions were observed in brain tissues or the sciatic nerve of the adult animals or offspring (Reyna and Ribelin, 1987). OPP acknowledges that a common mechanism or a common neuropathology effect can not be established for the thiocarbamate group of pesticides at this time.

Given that the data from the reproduction studies do not indicate a potential for the carbamates to induce a common reproductive effect and that developmental effects reported in reproduction and developmental toxicity studies are non-specific in nature and cannot be attributed to an underlying mechanism of toxicity, use of data from the reproductive or developmental studies for the identification of a common mechanism assessment group is not supported.

7. Uncertainties

Metabolism to intermediates that have the potential to react with nervous tissue is a common feature of the thiocarbamates but there are uncertainties that bear on inferences regarding the extent to which two or more thiocarbamates may interact and induce effects at a dose-level below dose-levels that produce the same effect with the individual chemicals. Thiocarbamates share structural similarities but there are differences in substituent groups that can be expected to affect relative rates of absorption, distribution, metabolism and excretion. The thiocarbamates have also been reported to form reactive intermediates by several pathways and it is not known to what degree a specific intermediate is responsible for the neuropathological effects of a particular thiocarbamate or whether different reactive intermediates would interact with the same molecular site. Pharmacokinetic and mechanistic data that would address these issues are not available.

As pointed out by the SAP, there is a question regarding whether the thiocarbamates induce a common neuropathology effect. The common description of neuropathololgy reported in studies with the thiocarbamates is sciatic nerve degeneration, a lesion that is a common endpoint for many different processes that damage axons.

IV. Summary: Grouping of Thiocarbamate Pesticides Based on a Common Mechanism of Toxicity

Initiation of a cumulative risk assessment begins with the identification of a group of chemicals that produce a common toxic effect by a common mechanism. OPP has determined that four of the thiocarbamates, EPTC, molinate, pebulate, and cycloate share a common mechanism of toxicity, the inhibition of cholinesterase. As stated in the introduction to this review, one goal of the current document is to provide a scientific basis for determining if the carbamates may be subgrouped based on the characteristic of some to produce effects unrelated to ChEI. The subgroup of the carbamates, the thiocarbamates, were postulated to have a common effect, neuropathology of peripheral nerves. Formation of a reactive sulfoxide metabolite is a plausible common critical event that may be associated with the neuropathologic effects of the thiocarbamates. However, the specific mechanism for the induction of neuropathy by the thiocarbamates has not been established. The thiocarbamate pesticides can also be metabolized to COS and isocyanate but data are not sufficient to evaluate the role these two moieties may have in inducing neuropathy. For those thiocarbamates that inhibit ChE, NOAELs for neuropathology are consistently, although not exclusively, below the NOAELs for ChEI. Developmental effects of the thiocarbamates are also induced at dose-levels above those that induce neuropathy and there is no known mechanism for the induction of the developmental effects.

In summary, OPP finds that the lines of evidence relevant to the evaluation of whether the thiocarbamates have a common mechanism of toxicity other than cholinesteras inhibition is limited and essentially unclear. Although the potential to produce a common toxic effect, neuropathy, and the similarities in structure and metabolism are suggestive of a common mechanism, other information raises questions about whether the common effect is produced by a common mechanism. Based on currently available evidence, OPP concludes that four thiocarbamates, EPTC, molinate, pebulate, and cycloate, share a common mechanism of toxicity, cholinesterase inhibition. However, among the effects induced by the thiocarbamates (i.e., acetyl cholinesterase inhibition, reproductive/developmental, and neuropathology), neuropathology (sciatice nerve degenration) was identified as the most sensitive common effect

As discussed in the next Section, a screening level cumulative (food) risk assessment was conducted using the assumption that the neuropathy produced by the thiocarbamates may be attributed to a common mechanism of toxicity. The results of such a screening approach are useful in several respects. First, a screening assessment can inform the risk assessor of deficiencies in the hazard and exposure components of the data base that would need to be addressed if the Agency decided to prepare a refined cumulative risk assessment. Secondly, a decision may be made by a risk manager that the results of a screening level assessment show that there is a reasonable certainty that food exposure to the group of pesticides, were they found to share a common mechanism of toxicity pesticides, will not result in harm to the human population. If such is the case, there would be little value in obtaining additional information on the potential for the candidate group of chemicals to induce a common

effect by a common mechanism and the resources required for the preparation of a comprehensive cumulative risk assessment could be devoted to issues of higher concern. In contrast, if concerns are raised by the screening level assessment that there could be a potential for adverse effects in humans who may be exposed to the group of pesticides should they be determined to have a common mechanism of toxicity, OPP would initiate a comprehensive cumulative risk assessment when data were made available that supported the grouping of the candidate pesticides based on an established common mechanism of toxicity, as required by the provisions of FQPA.

V. Cumulative Food Risk Assessment of the Thiocarbamates

OPP conducts cumulative food risk assessments using DEEM™ Version 7.73. The DEEM™ software incorporates consumption data generated by USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For cumulative chronic risk assessments, the average cumulative residue estimates for all chemicals in a cumulative assessment group (CAG) that occur in or on a commodity of interest are multiplied by the averaged consumption estimate of that commodity for each population subgroup. The resulting residue consumption estimate for each food/food use form is summed with the residue consumption estimates for all other food/food forms on the commodity residue list to arrive at the total estimated exposure. Exposure estimates are expressed as mg/kg/body weight/day. Cumulative exposure assessments are also expressed as MOEs using one member of the CAG as an index chemical and using relative potency factors (RPFs) to express the contribution of all members of the CAG in equivalents of the index chemical. The point of departure (POD) used to estimate risk can be the NOAEL for the index chemical. The cumulative MOE is determined as the ratio of the POD to the estimated cumulative exposure (MOE=POD/Exposure).

This assessment was used here as a screening level assessment designed to help determine whether thiocarbamates may pose a cumulative dietary risk. There are no residential uses for the thiocarbamates. The following conservative assumptions used in the screening assessment were:

Food exposures were based on tolerance levels for all registered uses of each thiocarbamate.

Treatment of crops with a thiocarbamate registered for use on that crop was considered to be 100%.

RPFs were determined by comparing the NOAELs of each thiocarbamate to the NOAEL of a reference thiocarbamate, cycloate. NOAELs were used to determine RPFs because of the lack of robust dose-response data that would support estimating ED_{50} or other doses that would induce a quantitatively similar response among the thiocarbamates.

The NOAEL for cycloate was used as the POD in the cumulative food risk assessment. Because the NOAEL of cycloate is six-fold less than the LOAEL and because there are good dose response data for cycloate, selection of cycloate NOAELs for the POD for a cumulative risk assessment is likely to result in an estimate of potential cumulative food risks that would not underestimate potential food risks.

A. Selection of a CAG of Thiocarbamates

Once a CMG of chemicals is identified, the next step in the cumulative risk assessment process is to identify those chemicals that should be included in a CAG. Evaluation of the toxicological profiles of the thiocarbamates showed that six induce neuropathological effects. Four of the thiocarbamates inhibit cholinesterase, one, butylate does not, and cholinesterase measurements have not been taken for triallate and butylate. As discussed in Section IIIC5, the neuropathy induced by the thiocarbamates was identified as the most sensitive endpoint. OPP recognizes a common mechanism can not be established for the neuropathological effects of the thiocarbamates. However, because the current assessment is a screening level cumulative risk assessment, OPP selected the most sensitive endpoint, neuropathy, in order to assure that potential risks are not understated.

When identifying members of a CAG, consideration is also given to the potential of a chemical to contribute to a cumulative risk, based on the potency of the chemical compared to other members of the group, and the likelihood of dietary exposure to the chemical in amounts that would contribute to a potential cumulative risk. Among the six thiocarbamates identified as inducing neuropathy, one, butylate, induces neuropathy at a dose substantially higher than the other thiocarbamates. However, because the current assessment is a screening assessment and because butylate is applied to large acreages of corn, butylate is included in the current screening level cumulative food risk assessment.

B. Relative Potencies of the Thiocarbamates

Table 7 shows the NOAELs and LOAELs for the common effect, neuropathy, of each of the thiocarbamates reported to induce this effect. Table 6 also shows the RPFs of each thiocarbamate when cycloate is used as the reference chemical. RPFs were estimated using doses that induce no observed adverse effects (NOAELs). *For comparison, RPFs based on the use of a lower limit on a benchmark dose ($BMDL_{10}$) are shown for those thiocarbamates that have dose response data* that are amenable to modeling.

Table 7. RPFs for the Neuropathology of Six Thiocarbamates

Chemical	Neuropathology NOAEL/LOAEL (mg/kg/day)	Neuropathology $BMDL_{10}$/p-value[1]	RPFs[2] (using NOAEL)	RPFs (using $BMDL_{10}$)
Cycloate[3]	0.5	0.511/0.149	1	1
EPTC	7.9[4]	Goodness of fit not achieved	0.06	Not applicable
Molinate	0.1[5]	1.11/0.906	5	0.460
Pebulate	22	Goodness of fit not achieved	0.02	Not applicable
Triallate	8.1	5.15/0.762	0.06	0.099
Butylate	600	Goodness of fit not achieved	0.001	Not applicable

[1] Lower limit on benchmark dose and p-value where goodness of fit achieved if $p \geq 0.1$; [2]With cycloate as index chemical; [3]Index chemical; NOAEL of cycloate divided by NOAEL of each thiocarbamate; [4]NOAEL from 90-day neurotoxicty study; [5]LOAEL divided by three for lack of a NOAEL

Regarding the use of NOAELs to estimate potencies, it should be noted that OPP recognizes that the use of benchmark doses or other modeling approaches of dose response data is preferred. OPP calculated the lower limit for benchmark doses ($BMDL_{10}$) for those thiocarbamates for which adequate dose response data are available (Table 7). The use of NOAELs would not lead to underestimates of potential risks because a) the $BMDL_{10}$ for the index chemical, cycloate is almost equal to the NOAEL, b) the use of NOAELs overestimates the potencies of the major contributor to the cumulative risk assessment, molinate, by almost 10-fold. The potency of triallate is underestimated somewhat (1.5-fold) but, as will be shown below, this thiocarbamate is a minor contributor to the estimates of cumulative risk. Thus, the use of NOAELs to compare potencies, when considered together with the use of tolerance level residues and the assumption of treatment with 100% of crops each thiocarbamate, would not lead to an underestimate of potential cumulative risks from exposures to the common assessment group of thiocarbamate pesticides.

Ideally, determinations of relative potencies among a group of chemicals that are toxic by a common mechanism should be made using data from studies of similar duration. As shown in Table 1, Section III, data on the neurotoxicological effects of the thiocarbamates were extracted from studies of varying duration. Data were extracted from two-year studies on EPTC, molinate, and cycloate and from 90-day neurotoxicity studies on pebulate and triallate. This approach was necessary because neural tissues were not examined in two-year studies conducted with some of the thiocarbamates or doses administered to the animals in two-year studies did not achieve a level that induced neuropathology. The use of data from studies of varying duration introduces uncertainty when relative potencies are determined for the thiocarbamates.

C. Estimates of Cumulative MOEs

Using RPFs and tolerance levels, estimated cumulative residues range from 0.001 ppm to 3.75 ppm (Table 8). The major contributors to the cumulative residues are from uses of molinate on rice (3.75 ppm), cycloate on spinach (0.5 ppm), and cycloate on sugar beets (tops and roots, 1 and 0.5 ppm, respectively). Residues on all other crops are less than or equal to 0.017 ppm.

Table 8. Cumulative Residues of Thiocarbamates with Cycloate Used as Index Chemical and RPFs Based on NOAELs

Commodity	Chemical	Tolerance (ppm)	Tolerance x RPF	Residues[1] (ppm)	Cumulative Residues[2] (ppm)
Almond/Walnut	EPTC	0.08	0.08 x 0.06	0.005	0.005
Beans (dry/succl)	EPTC	0.08	0.08 x 0.06	0.005	0.005
Bean/peas	EPTC	0.08	0.08 x 0.06	0.005	0.017
	Triallate	0.2	0.2 x 0.06	0.012	
Beets, garden (top)	Cycloate	1.0	1.0 x 1	1.00	1.03
	EPTC	0.5	0.5 x 0.06	0.03	
Beets, garden (roots)	Cycloate	0.5	0.5 x 1	0.5	0.506
	EPTC	0.1	0.1 x 0.06	0.006	
Beets, sugar (top)	EPTC	0.5	0.5 x 0.06	0.03	1.03
	Pebulate	0.05	0.05 x 0.02	0.001	
	Cycloate	1.0	1.0 x 1	1.00	
Beets, sugar (roots)	EPTC	0.1	0.1 x 0.06	0.006	0.507
	Pebulate	0.05	0.05 x 0.02	0.001	
	Cycloate	0.5	0.5 x 1	0.5	
Citrus	EPTC	0.1	0.1 x 0.06	0.006	0.006
Corn	EPTC	0.08	0.08 x 0.06	0.005	0.005
	Butylate	0.10	0.1 x 0.001	0.0001	
Cotton	EPTC	0.1	0.1 x 0.06	0.006	0.006
Flaxseed	EPTC	0.1	0.1 x 0.06	0.006	0.006
Potato/Sweet	EPTC	0.1	0.1 x 0.06	0.006	0.006
Rice	Molinate	0.75	0.75 x 5	3.75	3.75
Safflower/ Sunflower seed	EPTC	0.08	0.08 x 0.06	0.005	0.005
Spinach	Cycloate	0.5	0.5 x 1	0.50	0.50
Strawberries	EPTC	0.1	0.1 x 0.06	0.006	0.00
Tomato	Pebulate	0.05	0.05 x 0.02	0.001	0.001
Wheat/Barley	Triallate	0.05	0.05 x 0.06	0.003	0.003

[1]Residues = Tolerance x RPF; [2]Cumulative residues = sum of the residues

Table 9 lists the cumulative chronic food exposure for thiocarbamates. Based on residue data using tolerance levels and assuming 100% of registered crops are treated with each thiocarbamate, estimated MOEs range from 310 to 1,696 (Table 9). The largest contributor to the cumulative risks for all population subgroups is the use of molinate on rice. For example, the MOEs for exposure of infants when residues of all thiocarbamates on all crops are accumulated is 310 versus an MOE of 1016 when the use of molinate on rice is excluded from the cumulative assessment (Table 11). Table 10 also shows that cereal grains (rice) and sugar beets are the highest percentage of total exposure for all population subgroups.

Table 9. Cumulative Dietary Exposure Summary for Thiocarbamates: Tolerance Levels and RPFs Based on NOAELs

Population Subgroup	Exposure (mg/kg/day x 10^{-3})	
U.S. Population	0.473	1,058
All infants (<1 yr)	1.615	310
Children (1-6 yrs)	0.968	517
Children (7-12 yrs)	0.638	783
Females (13-50 yrs)	0.383	1,307
Males (13-19 yrs)	0.401	1,246
Males (20+ yrs)	0.398	1,257
Seniors (55+)	0.295	1,696

Table 10. Commodity Contribution Analysis for Population Subgroups

Population Subgroup	Commodity	% of Total Exposure
U.S. Population	Cereal Grains- rice-milled (white) Sugar-beet	66.12 26.54
All Infants (< 1yr)	Cereal Grains- rice-milled (white) Sugar-beet	70.53 26.74
Children (1-6 yrs)	Cereal Grains- rice-milled (white) Sugar-beet	63.84 28.06
Children (7-12 yrs)	Cereal Grains- rice-milled (white) Sugar-beet	61.26 30.27
Females (13-50 yrs)	Cereal Grains- rice-milled (white) Sugar-beet	67.17 25.37
Males (13-19 yrs)	Cereal Grains- rice-milled (white) Sugar-beet	54.21 39.50
Males (20+ yrs)	Cereal Grains- rice-milled (white); rice-rough (brown) Sugar-beet	70.91 22.37
Seniors (55+)	Cereal Grains- rice-milled (white); rice-rough (brown) Sugar-beet	63.11 24.36

D. Residue Levels from Field Trial Data and Tolerances

In the past, because of the establishment of tolerances based on negligible residues, USDA monitoring for residues of the thiocarbamates was not performed. For the cumulative risk assessment, PDP monitoring data was not available for the thiocarbamate pesticides. FDA monitoring data was found on potatoes (595 samples) and rice (169 samples) with no detectable residues. In the absence of FDA monitoring data, field trial data were evaluated for the frequency and levels of the thiocarbamates found on food commodities.

The cumulative food risk assessment discussed above was conducted using tolerance levels as the residue levels for the thiocarbamates. Actual residue data indicate exposures to the thiocarbamates would be less than tolerance levels, as discussed below.

Table 11 is a summary of detectable residues found for each thiocarbamate reviewed and the food commodity on which residues were found. A discussion of the analyses for both detectable and nondetectable residues on various food commodities follows Table 11.

Table 11. Highest Residues and Tolerances (ppm) of Thiocarbamates Detected in Field Trials

Chemical	Food Commodity	Residues	Residue Level (ppm)	
EPTC	Corn and commodities processed from corn	ND	<0.05	0.1
	Snap beans	ND	<0.05	0.08
	Citrus	ND	<0.05	0.1
	Almond and walnut nutmeat	ND	<0.05	0.08
	Potatoes	N-2-hydroxy-propyl EPTC ; N-3-hydroxy-propyl EPTC	0.03 0.02	0.1
Molinate	Rice grain	4-OH-molinate	0.56	0.75
Pebulate	Sugar beets and tomatoes	ND	<0.05	0.05
Triallate	Peas (succl)	TCPSA*	0.06-0.11	0.2
	Wheat	TCPSA	<0.01-0.03	0.05
	Barley	ND	<0.01	0.05
Butylate	Corn	ND**	<0.05	0.10
Cycloate	Garden beets	t-3HC, c-3HC, or t-4HC	0.11(roots); 0.44, 0.3, 0.11(tops)	0.05 & 1.0 (roots and tops)
	Spinach	c-4HC	0.11	0.5
	Sugar beets	ND	<0.05	0.5
Thiobencarb	Rice	ND	<0.05	0.2

ND- Non-detects
* trichloroallyl sulfonic acid (TCPSA)
** Residues were not found in 250 corn samples but registrant required to submit additional information on sample storage conditions and intervals (USEPA, 1993)

1. EPTC

No detectable residues were found for EPTC or its hydroxy metabolites on field corn grain treated at an exaggerated rate (3X) with ERADICANE 6.7E or on all processed commodities of grits, meal, starch, refined oil, crude oil, or flour from field corn grain. No detectable residues of EPTC, N-2-hydroxypropyl EPTC, N-3-hydroxypropyl EPTC and 2-hydroxyethyl EPTC were detected in or on snap bean pods and seeds, vines, hay, almond nutmeats, walnut nutmeats, or cotton seed. In potato tubers, EPTC and 2-hydroxyethyl EPTC were nondetectable but N-2-hydroxypropyl and N-3-hydroxypropyl EPTC were detected. The maximum total residues of EPTC and its metabolites were <0.09 ppm. The EPTC Guidance document (9/30/83) concluded that the available data pertaining to grapefruits and lemons support the established group tolerance of 0.1 ppm for residues of EPTC on citrus fruits.

2. Molinate

No detectable residues of the parent chemical were found in or on rice grain. Residues of 4-hydroxy molinate found in or on field trial samples ranged from 0.05 ppm to 0.56 ppm and molinate acid was found in or on one sample (0.12 ppm).

3. Pebulate

No detectable residues were found in/on eight samples of mature sugar beet roots and tops or 14 samples of tomatoes.

4. Triallate

No detectable residues of triallate or its metabolite trichloroallyl sulfonic acid (TCPSA) were found in/on barley commodities in field trials. Detectable residues (0.06 ppm to 0.11 ppm) of TCPSA, but not triallate, were found in/on beans or succulent green peas. Detectable residues of TCPSA (<0.01 ppm to 0.03 ppm), but not triallate, were found on wheat grain.

5. Butylate

No detectable residues of butylate or its metabolites were found in or on corn.

6. Cycloate

Residues of the cycloate metabolites, t-3HC, c-3HC, or t-4HC, but not the parent chemical, were found on roots or tops of garden beets (0.11 ppm to 0.44 ppm) in field trials from California but not New York, Oregon, Texas, or Wisconsin. No detectable residues of cycloate or its metabolites were found in/on field trials involving sugar beets.

7. Thiobencarb

No detectable residues of thiobencarb were found in or on rice in field trials.

E. Summary of Field Trial or FDA Residue Data

No residues of the parent thiocarbamate were detected for those thiocarbamates for which field trial or FDA monitoring data were available. Hydroxy metabolites and acid metabolites of the parent thiocarbamate compound were detected in or on some commodities in field trials as shown in Table 11. Tolerance levels (based on reassessments) for each of the thiocarbamates exceed the residue levels of metabolites found in all cases, with the exception of residues of cycloate on garden beet roots. Commodities in or on which metabolites of one or more thiocarbamates were found are potatoes, rice grain, fresh beans and peas, wheat, barley, garden beets, and spinach. No residues of any thiocarbamate were found on corn, nutmeats, sugar beets, barley, or tomatoes. As noted above, the use of molinate on rice is the major contributor to cumulative residues of the thiocarbamates. Field trial data indicate that average residues of molinate are below tolerance levels.

The data from field trials and FDA monitoring suggest that the use of tolerance level residues would overestimate the exposure component of this screening level cumulative risk assessment.

F. Potential Chronic Food Risks When the Use of Molinate on Rice Is Excluded from the Cumulative Food Assessment

Evaluation of the potential for the thiocarbamates to induce toxicity if humans are exposed through the diet to two or more of the chemicals shows that one member of the group, molinate, is the major contributor to estimates of cumulative food risks. Table 12 shows the cumulative MOEs for population subgroups when tolerance level residues of molinate on rice are excluded from the cumulative food assessment. As shown in Table 12, exclusion of these residues results in MOEs of 1000 or more for all population subgroups.

Table 12. Cumulative Chronic Food Exposure Summary for Thiocarbamates Excluding Residues of Molinate on Rice

Population Subgroup	Exposure (mg/kg/day x 10^{-3})	MOEs
U.S. Population	0.170	2,938
All Infants (< 1 yr)	0.492	1,016
Children (1-6 yrs)	0.373	1,340
Children (7-12 yrs)	0.264	1,891
Females (13-50 yrs)	0.133	3,755
Males (13-19 yrs)	0.196	2,552
Males (20+)	0.123	4,051
Seniors (55+)	0.115	4,349

VI. Thiocarbamates: Summary of Screening Level Estimates of Cumulative Food Risks

Estimates of potential cumulative food risks for the cumulative exposures to six thiocarbamates show that MOEs are 310 or more. MOEs were determined using tolerance levels and using the assumption that 100% of crops are treated with each thiocarbamate registered for use on that crop. Data provided from field trials and FDA monitoring studies show tolerance levels of thiocarbamate residues are unlikely to be reached and, for many commodities, residues of a thiocarbamate are absent or well below established tolerance levels.

Molinate was identified as the major contributor in the screening level cumulative food risk assessment. The lowest MOE identified, 310 for infants less than one year of age, is attributable to the use of molinate on rice. MOEs are 500 or greater for all other population subgroups. When the use of molinate on rice is excluded from the cumulative food risk assessment, MOEs for all population subgroups, including infants less than one year of age, are 1000 or greater.

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