November 1, 2001

MEMORANDUM

SUBJECT: Transmittal of the Final Report of the FIFRA Scientific Advisory Panel (SAP) Meeting Held September 7, 2001

TO: Marcia E. Mulkey, Director
Office of Pesticide Programs

FROM: Paul I. Lewis, Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Larry C. Dorsey, Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Vanessa T. Vu, Ph.D. Director
Office of Science Coordination and Policy

Please find attached the final report of the FIFRA Scientific Advisory Panel open meeting held in Arlington, Virginia, on September 7, 2001. This report addresses a set of scientific issues being considered by the Environmental Protection Agency regarding common mechanism of action of dithiocarbamates and thiocarbamates.

Attachment

cc: Stephen Johnson
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Kendall Wallace, Ph.D.

SAP Report No. 2001-11

REPORT

FIFRA Scientific Advisory Panel Meeting, September 7, 2001, held at the Sheraton Crystal City Hotel, Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Common Mechanism of Action of Dithiocarbamates and Thiocarbamates

NOTICE

This report has been written as part of the activities of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP). This report has not been reviewed for approval by the United States Environmental Protection Agency (Agency) and, hence, the contents of this report do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

The FIFRA SAP was established under the provisions of FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, to provide advice, information, and recommendations to the Agency Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The Panel serves as the primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP) and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. Food Quality Protection Act Science Review Board members serve the FIFRA SAP on an ad-hoc basis to assist in reviews conducted by the FIFRA SAP. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/scipoly/sap/ or the OPP Docket at (703) 305-5805. Interested persons are invited to contact Larry Dorsey, SAP Executive Secretary, via e-mail at dorsey.larry@.epa.gov.

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REPORT:
FIFRA Scientific Advisory Panel Meeting,
September 7, 2001, held at the Sheraton Crystal City Hotel,
Arlington, Virginia

A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding:

Common Mechanism of Action of Dithiocarbamates and Thiocarbamates

Mr. Paul Lewis
Designated Federal Official
FIFRA Scientific Advisory Panel
Date:_____
November 1, 2001

Christopher Portier, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel
Date:_____
November 1, 2001

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 7, 2001

Common Mechanism of Action of Dithiocarbamates and Thiocarbamates

PARTICIPANTS

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PUBLIC COMMENTERS

Oral statements were made by:
David Bower, Ph.D. on behalf of R.T. Vanderbilt Company, Inc. and Ms. Sharen Breyer on behalf of Flexsys
Mr. Timothy Dotson on behalf of UCB Chemicals Corporation
James Lamb, Ph.D. and Janet Ollinger, Ph.D. on behalf of the EBDC/ETU Task Force
Mr. James Markle on behalf of Syngenta Crop Protection, Inc.

Written statements were received
None received

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) has completed its review of the set of scientific issues being considered by the Agency pertaining to common mechanism of action of dithiocarbamates and thiocarbamates. Advance notice of the meeting was published in the *Federal Register* on August 10, 2001. The review was conducted in an open Panel meeting held in Arlington, Virginia, on September 7, 2001. The meeting was chaired by Christopher Portier, Ph.D. Mr. Paul Lewis served as the Designated Federal Official. Randolph Perfetti, Ph.D. (Associate Director, Health Effects Division, Office of Pesticide Programs, EPA) provided opening remarks. Alberto Protzel, Ph.D. (Office of Pesticide Programs, EPA) summarized the grouping of a series of dithiocarbamate pesticides based on a common mechanism of toxicity; Alberto Protzel, Ph.D. (Office of Pesticide Programs, EPA) and Ms. Sheila Piper (Office of Pesticide Programs, EPA) presented the toxicology and exposure considerations, respectively, on a screening level cumulative dietary (food) risk assessment for thiocarbamates.

In preparing this report, the Panel carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This report addresses the information provided and presented within the structure of the charge by the Agency.

CHARGE

I. Dithiocarbamates

1. Issue: The results of metabolism studies submitted to the Agency and of metabolism and mechanistic studies reported in the literature show that carbon disulfide is a common neuropathic metabolite formed by the dithiocarbamates.
Question: Please comment on the evidence supporting the conclusion that carbon disulfide is a common metabolic product of the dithiocarbamates and that carbon disulfide is a neuropathic moiety.

2. Issue: Distal peripheral neuropathy was identified as the most common, sensitive effect for grouping the dithiocarbamates based on the potential to induce a common effect.
Question: Please comment on the evidence supporting the selection of distal peripheral neuropathy as the endpoint of choice for grouping the dithiocarbamates based on the potential to induce a common effect.

3. Issue: Although Na-dimethyldithiocarbamate and ferbam are presumed to form carbon disulfide during metabolism, results of studies with these pesticides have not shown neuropathic effects.
Question: Please comment on the recommendation that Na-dimethyldithiocarbamate and ferbam be excluded from the common mechanism group of neuropathic dithiocarbamates.

II. Thiocarbamates

1. Issue: Although there are data available from the literature and from results of studies submitted to OPP that indicate the thiocarbamate pesticides share a common metabolic profile, there appears to be a lack of information on the specific mechanism of action that can account for the neuropathology that is induced in rats following treatment with a thiocarbamate. Unlike the dithiocarbamates, the thiocarbamates do not undergo conversion to the common metabolite, carbon disulfide.
Question: Please comment on the evidence that supports a presumption that the thiocarbamates may have a common mechanism of toxicity but a common mechanism of toxicity has not been linked to a critical metabolic moiety.

2. Issue: Treatment of rats with a thiocarbamate may result in the formation of neuropathological lesions, developmental/reproductive toxicity, or decrease cholinesterase activity. The current assessment identified distal peripheral neuropathy as the most sensitive, common effect of the thiocarbamates.
Question: Would the panel please comment on the selection of the neuropathological endpoint as the appropriate endpoint for grouping the thiocarbamate pesticides based on the potential to induce a common effect.

3. Issue: The document *Thiocarbamates: A Screening Level Cumulative Dietary (Food) Risk Assessment* presents a step-wise screening process for conducting a cumulative risk assessment. This screening level approach is intended to identify whether there is a need to initiate a more comprehensive cumulative risk assessment for a small group of structurally related pesticides that induce a common effect. It is not intended to identify a level of concern or risk for any one chemical or a group of chemicals that share a common mechanism of toxicity.
Question: Please provide general comments on the overall screening approach used in this preliminary cumulative risk assessment.

DETAILED RESPONSE TO THE CHARGE

The specific issues to be addressed by the Panel are keyed to the Agency's background documents "The Grouping of a Series of Dithiocarbamate Pesticides Based on a Common Mechanism of Toxicity" and "Thiocarbamates: A Screening Level Cumulative Dietary (Food) Risk Assessment", dated August 17, 2001, and are presented as follows:

I. Dithiocarbamates

Although the evidence indicating that CS_2 is neuropathic when administered to laboratory animals is strong, the evidence suggesting that CS_2 is a common metabolic product of dithiocarbamates or that neurotoxicity following exposure to dithiocarbamates results from CS_2 formed *in vivo* is far less convincing. In addition, the data presented do not provide clear evidence that dithiocarbamates produce a distal peripheral neuropathy, as does CS_2. The lesions described in the Agency's report suggest in only a very general way that a common neuropathic effect exists for the dithiocarbamates. The ability to demonstrate a neuropathic effect following dithiocarbamate exposure may have been limited by variability in the quality of the pathology studies such as the level of documentation of the lesions, level of examination, and presentation of the pathology data. Due to these factors, it is suggested that the Agency consider convening a Pathology Working Group when pathology endpoints are an important consideration for grouping chemicals according to common toxic effects. The Panel agreed with the Agency's decision to exclude Na-dimethyldithiocarbamate and ferbam from the grouping of neuropathic dithiocarbamates. The absence of neuropathic changes associated with exposure to these chemicals suggests that their toxicity occurs via some other mechanism; therefore, it is appropriate to exclude them from the common mechanism group. The absence of neuropathic changes following exposure to ferbam calls into question the role of CS_2 in causing the neuropathology changes seen in this group of chemicals.

1. Issue: The results of metabolism studies submitted to the Agency and of metabolism and mechanistic studies reported in the literature show that carbon disulfide (CS_2) is a common neuropathic metabolite formed by the dithiocarbamates.

Question: Please comment on the evidence supporting the conclusion that carbon disulfide is a common metabolic product of the dithiocarbamates and that carbon disulfide is a neuropathic moiety.

Although there exists strong evidence indicating that CS_2 is neuropathic when administered to laboratory animals, the evidence suggesting that 1) CS_2 is a common metabolic product of the dithiocarbamates or 2) neurotoxicity results from CS_2 derived from dithiocarbamates *in vivo* is far less convincing, for the following reasons:

- CS_2 generation *in vivo* has not been demonstrated for any of the ethylene-based dithiocarbamates (EBDCs); nor has the biomarker for CS_2 (TTCA) been detected in the urine following *in vivo* exposures to the EBDCs. The available evidence suggests that it is only at very high dose levels that the EBDCs release detectable CS_2. The only evidence for CS_2 generation by the three EBDCs of concern is inferred from what has been suggested to be a questionable comparison compound, ziram.
- CS_2 generation has been demonstrated *in vivo* only for some of the dimethyl dithiocarbamates (DMDTCs).

The implied link for CS_2 mediating the neurotoxicity of the dithiocarbamates raises several deficiencies:

(1) Although ferbam is reported to generate CS_2 *in vivo* at rates equivalent or higher than thiram and ziram, ferbam exhibits little if any peripheral neuropathy. Thiram and ziram do cause neuropathy.

(2) The *in vitro* acid hydrolysis data suggest that Na-dimethyldithiocarbamate (Na-DMDTC) is a more potent generator of CS_2 than the structurally identical Zn-chelate, ziram. However, ziram is reported to be neuropathic whereas Na-DMDTC is not.

(3) No dose-response relationship is apparent between the amount of CS_2 formed by the various dithiocarbamates and the presence or severity of neuropathic effects.

Data presented in the Agency's report on dithiocarbamates indicate that ziram, ferbam, and thiram release CS_2 *in vivo*. The proportion of the recovered materials that were CS_2 varied between 7.4 and 18.1% for these materials. Truhaut *et al.* (1973) was cited as identifying CS_2 formation after dosing rats with zineb, but the amount excreted was not quantified. There is *in vitro* data demonstrating the acid hydrolysis of Na-diethyldithiocarbamate, an analog of the Na-dimethyldithiocarbamate, produces CS_2; however, the relevancy of *in vitro* hydrolysis conditions to conditions in the stomach is questioned. For mancozeb, maneb, and metiram, there is a presumption that CS_2 is formed; CS_2 release has been reported for zineb, a related EBDC compound. No data are presented that metam sodium is converted to CS_2. The estimated CS_2 formed from mancozeb and metiram are 10% and 11-14%, respectively.

The absence of neurotoxicity following exposure to Na-dimethyldithiocarbamate,

which is the most easily hydrolyzed of the dithiocarbamates, and ferbam, which forms the largest amount of CS_2 *in vivo*, call into question the role of CS_2 as a common metabolite responsible for neurotoxicity of these dithiocarbamates. If the link between CS_2 and the dithiocarbamates is to be made stronger, the lack of neurotoxicity with Na-dimethyldithiocarbamate and ferbam needs to be explained.

There are extensive data on the relationship between CS_2 exposure and neurotoxicity. The primary effects are neurobehavioral changes attributable to alterations in the CNS and distal axonopathy that results in axonal degeneration in the PNS and CNS. Axonal changes are of the "giant axonal" type with secondary demyelination. Cardiovascular and other health effects have also been observed. Exposure to the dithiocarbamates does not elicit these CS_2 effects. As an example, disulfiram, a dithiocarbamate, has been used as a drug for humans. Furthermore, while disulfiram has been shown to produce a peripheral neuropathy in rats following oral dosing, the effects seen are a primary demyelination of peripheral nerves and not a distal axonopathy. This issue is explained in more detail in question #2.

2. Issue: Distal peripheral neuropathy was identified as the most common, sensitive effect for grouping the dithiocarbamates based on the potential to induce a common effect.
Question: Please comment on the evidence supporting the selection of distal peripheral neuropathy as the endpoint of choice for grouping the dithiocarbamates based on the potential to induce a common effect.

These data presented do not provide clear evidence that the dithiocarbamates produce a distal peripheral neuropathy. The lesions described in the Agency's report (Table 1) suggest in a very general way that a common neuropathic effect exists for the dithiocarbamates. It was noted, however, that the ability to demonstrate such an effect was limited by the variability in the quality of the pathology studies, documentation of the lesions, level of examination, and presentation of the pathology data. Due to these factors, it is suggested that the Agency consider convening a Pathology Working Group when such endpoints are an important consideration for grouping chemicals according to common toxic effects.

These summarized data describing the morphology and severity of the peripheral or central nervous system lesions are often lacking in the dithiocarbamate report and need to be summarized more thoroughly by the Agency. For example, the tabulated data for ziram indicates that histopathology of the spinal cord and sciatic nerve was performed, however, morphological descriptions of the lesions were not provided.

If CS_2 were responsible for the neuropathies observed in the dithiocarbamate studies, certain types of lesions would be expected to be present in the CNS and PNS. As indicated in the Agency's report, CS_2 produces a primary axonopathy characterized by "giant" axonal swellings, axonal degeneration, and secondary myelin changes in both CNS and PNS. If the dithiocarbamates produce a neuropathy through a mechanism involving production of CS_2 *in vivo*, lesions similar to those produced by CS_2

administration should be observable.

For mancozeb, degeneration and demyelination of the sciatic and tibial nerves were reported; however, no "giant" axons were reported. Lesions in the distal nerves were not reported; nor were axonal swellings in the CNS (medulla oblongata) reported. For maneb, minimal numbers of digestion chambers were observed in the sciatic, tibial, and peroneal nerves, but distal axonopathic changes typical of CS_2 exposure were not reported. For metiram, decreased myelination was reported in the sciatic and tibial nerves, but no axonopathy was observed. For Na-dimethyldithiocarbamate, no neuropathic changes were observed. For ziram, it is not clear what was observed, Table 3 of the Agency's report refers only to "histopathology of spinal cord and sciatic nerve," presumably without lesions. For thiram, degeneration and demyelination of the sciatic nerve were reported as well as degeneration of the ventral horn of the lumbar cord. Axonal lesions in this case were presumably of the Wallerian type. For ferbam and Na-dimethyldithiocarbamate, no neuropathic changes were observed. For metam sodium, no results were reported.

The pathology presented does not support: 1) a consistent form of pathology for the dithiocarbamates; 2) a distal neuropathy; 3) a central-peripheral neuropathy; or 4) "giant" axonal changes all of which are seen with CS_2 exposure. If the changes are correctly reported in Table 1 by the Agency, it would appear that some of these chemicals produce axonal lesions, some primary demyelination, and others neuronal changes suggesting differing mechanisms of action. While there is a level of concern that peripheral neuropathy is produced by some of these chemicals, the data do not support CS_2 production as the common mechanism.

The Agency did not discuss in its background document whether the neuropathological evaluations are adequate for evaluating whether neurofilamentous axonal swellings consistent with CS_2 exposure occurred. While the Agency cited information suggesting that disulfiram, like CS_2, produces a distal axonopathy, recent data suggests this might not be correct. A case in point is the recent study by Tonkin *et al.* (2000) who demonstrated that disulfiram, a dithiocarbamate drug used for alcohol aversion therapy, induces a schwannopathy rather than an axonopathy. This study and a companion study by Johnson suggest that some dithiocarbamates may result in CS_2 formation, yet do not induce neuropathy through CS_2 formation. This observation further suggests that a common mechanism of toxicity may not be present for the dithiocarbamates.

The Panel concluded that the evidence is equivocal as to whether neuropathy is the most appropriate endpoint of choice for grouping the dithiocarbamates based on the potential to induce a common effect. In many cases, thyroid effects are actually more sensitive. The Agency should more clearly indicate that thyroid effects are being considered in detail.

The Panel recommends that the Agency consider:

1) If possible, using a Pathology Working Group to provide input on the

similarity of pathology effects caused by different dithiocarbamates.

2) Presenting dose-response data for CS_2 in units of mg/kg/day along with the effects data so that dose-response relationships can be more easily assessed.

3) Providing an assessment of the strength of evidence supporting its conclusion on common site of toxicity as well as common mechanism of action.

4) Continuing to evaluate the thyroid effects of the dithiocarbamates as a possible most sensitive site of toxicity.

3. Issue: Although Na-dimethyldithiocarbamate and ferbam are presumed to form carbon disulfide during metabolism, results of studies with these pesticides have not shown neuropathic effects.
Question: Please comment on the recommendation that Na-dimethyldithiocarbamate and ferbam be excluded from the common mechanism group of neuropathic dithiocarbamates.

The Panel agreed with the Agency's decision to exclude Na-dimethyldithiocarbamate and ferbam from the grouping of neuropathic dithiocarbamates. The absence of neuropathic changes associated with exposure to these chemicals suggests that their toxicity occurs via some other mechanism; therefore, it is appropriate to exclude them from the common mechanism group. The absence of neuropathic changes following exposure to ferbam calls into question the role of CS_2 in causing the neuropathology changes seen in this group of chemicals as ferbam had the highest conversion rate to CS_2 yet was not neurotoxic.

The Agency has set forth what appears to be a very cogent argument that the dithiocarbamates should be grouped as a set of compounds that produce a neuropathy (i.e., a distal axonopathy) due to their ability to generate (CS_2). While the argument is set forth in a logical fashion, there are numerous limitations as noted in this report. CS_2 is considered a known neuropathic agent. The Agency has gathered evidence that suggests most of the seven compounds to be grouped can generate or would be expected to generate CS_2 in either an *in vitro* or *in vivo* situation. However, there is very little *in vivo* evidence for generation of CS_2 for most of the compounds. Also, data are limited showing that these compounds result in the excretion of TTCA in the urine of treated animals. TTCA is considered a biomarker of cumulative CS_2 exposure. The failure of ferbam and Na-dimethyldithiocarbamate to exhibit neuropathy while producing CS_2 presents some very real limitations for the Agency's main argument, that dithiocarbamates produce neuropathy through their ability to produce CS_2.

Because ferbam is demonstrated to produce CS_2 *in vivo* and Na-dimethyldithiocarbamate would be expected to produce CS_2 *in vivo,* but neither compound produces a neuropathy, the Agency's is really left with no recourse but to exclude them from the common neuropathic mechanism group. The Agency has argued that CS_2 production is the common mechanism and these compounds do or are expected to produce CS_2. The Agency really provides no reason for the failure to find neuropathy despite the production of CS_2. The Agency could possibly have argued more convincingly that the failure to observe neuropathy with the two compounds was due to

some aspect of the dosing regimen. Ferbam in cited references, albeit old ones (Hoge, *et al.*, 1956; Lee and Peters, 1976; Lee, *et al.*, 1978), was reported to produce ataxia and paralysis in some treated rats but no lesions were revealed by histological evaluation. This would at least suggest that under some circumstances the clinical signs of axonopathy have been reported. The two MRID reports (Table 1) cited in the document concerning ferbam and Na-dimethyldithiocarbamate make no mention of clinical signs. It is difficult to know if none were observed or if the animals were not observed for clinical signs although it would be assumed if these were done under the existing neurotoxicology guidelines, observations of treated animals would have been conducted.

The generally limited nature of the results of the MRIDs presented in the report precluded a thorough evaluation by SAP members. Although the Agency's report cites LoPachin's work, it does not use the author's arguments concerning the possibility of a particular hallmark of distal axonopathy only being produced by a certain type of dosing regimen. The author had argued for other agents producing distal axonopathies, (i.e., acrylamide and 2,5-hexanedione) that depending on the route and dosing regimen, not all hallmark signs may be present. Thus, for acrylamide, a high acute dosing regimen can produce clinical signs of neuropathy without histological evidence of neurodegeneration, while a subacute, low-dose regimen is necessary to produce axon swelling and degeneration. This does raise the issue as to whether other dosing schedules would allow ferbam or Na-dimethyldithiocarbamate to produce axonopathies, although the MRID studies were apparently conducted over a long period of time (two years). This highlights the difficulty of comparing studies which have different dosing schedules. Further, this hampers the Agency in having a thorough scientific database to prepare a risk assessment.

Some argument can also be made that not enough information was provided in the report concerning the dithiocarbamates to even know if they produce the same distal axonopathy that CS_2 does. Certainly the descriptions provided do not mention axonal swellings, one of the hallmarks of CS_2 axonopathy. Disulfiram, not one of the candidate compounds but a neuropathic dithiocarbamate, is reported to produce axonal swellings in exposed humans but axonal swelling have not been reported in animal studies.

Chemical	Table 1: Neuropathy Observed Following Dosing with Dithiocarbamates[1]
Mancozeb	- 8.2/49.7; Degeneration/demyelination of sciatic, tibial nerves, etc. 90-day rat neurotoxicity. MRID 42034101 - Rats developed paresis in the hind limbs at 3 months, progressing to complete paralysis. Oral doses of 700 or 3500 mg/kg, twice a wk. [1969 study; EHC 78, WHO, 1988]
Maneb	23/100; Digestion chambers in tibial, sciatic, peroneal nerves (minimal response) - 90-day rat neurotoxicity. Decreased fore and hind-limb grip strength at HDT females. MRID 439477603
Metiram	- 27.3/88.8; Decreased myelination of sciatic and tibial nerves - 90-day rat. Decreased cross-sectional areas of myelinated axons in sciatic and tibial nerves (3 rats/dose level) MRID 40290601, decreased in hand-limb grip strength. 42539101 - atrophic lesions of high muscle seen in males at 900 ppm and in females at 300 or 900 ppm.
Na-DMDTC	No neuropathology up to 98.75 - 90-day rat neurotoxicity. MRID 435550501
Ziram	10.2/34.6; Histopathology of spinal cord, sciatic nerve - 2 yr rat. Dose-related increase in axonal degeneration: in females 3/50, 5/50, 4/50, and 16**/50 at 3.4, 10.2, 34.6 mg/kg/day. Narrowing of muscle fibers at mid- and high-dose. NTE inhibited 47% in males and 38% in females. MRID 43404201
Thiram	25.5/66.9; Degeneration/demyelination of the sciatic nerve and the axis cylinders; degeneration of the ventral horn of the lower lumbar region of the spinal cord of rats - 80 week rat (Lee, C.C. and P.J. Peters, 1976).
Ferbam	No evidence of neuropathology up to a dose of 100 mg/kg/day in a 90-day neurotoxicity study or a two-year study.

1. Data provided by the USEPA at the SAP meeting

II. Thiocarbamates

The Panel agreed with the Agency that there was insufficient evidence to suggest an identified common mechanism of toxicity of the thiocarbamates. In addition, questions remain as to whether a common metabolic product exists. The Panel evaluated the overall screening approach within the framework of the process only as an example, not as it applies to thiocarbamates. The Panel did not recommend the use of this approach for the preliminary cumulative risk assessment for thiocarbamates.

1. Issue: Although there are data available from the literature and from results of studies submitted to OPP that indicate the thiocarbamate pesticides share a common metabolic profile, there appears to be a lack of information on the specific mechanism of action that can account for the neuropathology that is induced in rats following treatment with a thiocarbamate. Unlike the dithiocarbamates, the thiocarbamates do not undergo conversion to the common metabolite, carbon disulfide.
Question: Please comment on the evidence that supports a presumption that the thiocarbamates may have a common mechanism of toxicity but a common mechanism of toxicity has not been linked to a critical metabolic moiety.

The Panel agreed with the Agency that a common mechanism of action has not been demonstrated for the thiocarbamates considered in the current grouping exercise. It is not unusual for a common toxic effect to suggest a common mechanism of action while a common critical metabolite has not been identified. However, grouping of the chemicals based upon peripheral nerve damage is hindered by the quality of the available data, i.e., limited sample size, lack of consistent pathological examination and documentation of the lesions across studies and chemicals.

For example, the similarity in the neurotoxicities observed following exposure to n-hexane or methyl n-butyl ketone suggested a common metabolite might be responsible for the similar effects; however, it was some time before a common metabolite was actually identified. Thus in a research environment, recognition of similarities can lead to testable hypotheses that can be addressed. However, it remains a question as to how such observations can contribute to the risk assessment process. With regard to the thiocarbamates, it is not clear that a common effect has been identified for the chemicals under consideration. For EPTC, axonal degeneration in the sciatic nerve was observed and neuronal necrosis in the brain was noted. This raised a question as to whether the axonal damage that was observed is related to a mechanism of action involving axonal damage or one involving neuronal damage. For molinate, degeneration (presumably axonal damage) and demyelination were observed. For thiobencarb, no neuropathic changes were observed. For pebulate, triallate, butylate, and cycloate, varying degrees of sciatic nerve degeneration were seen. Pebulate also induced some sort of spinal cord lesion in addition to sciatic nerve damage. CNS lesions commonly seen with distal axonopathies were not reported for any of the chemicals under consideration. None of the data presented clearly identify this class of chemicals as causing a distal axonopathy. At best, these lesion descriptions suggest that Wallerian degeneration was the only

common lesion seen for this grouping of chemicals. However, Wallerian degeneration is a common endpoint for many different processes that damage axons.

2. Issue: Treatment of rats with a thiocarbamate may result in the formation of neuropathological lesions, developmental/reproductive toxicity, or decrease cholinesterase activity. The current assessment identified distal peripheral neuropathy as the most sensitive, common effect of the thiocarbamates. Question: Would the panel please comment on the selection of the neuropathological endpoint as the appropriate endpoint for grouping the thiocarbamate pesticides based on the potential to induce a common effect.

The Panel complimented the Agency on its approach to the grouping of thiocarbamate pesticides. It appears that the Agency first used chemical structure (structure activity) as the basis for grouping the candidate group. This is a reasonable method for the initial evaluation. They then investigated commonalties of toxic response in various tissues and selected the neuropathological endpoint as the most appropriate for a variety of reasons. This also appears reasonable based on the available data. However, data does not currently exist to support grouping of the thiocarbamate pesticides based upon the potential to produce neuropathology.

The Panel cautioned that a common effect does not necessarily indicate a common mechanism. They are entirely different concepts and since the FQPA clearly refers to common mechanism and not common effect, the former is the concept that has to be supported by definitive data. Therefore, the Agency would, for any group of chemicals, need to show that the common effects are orchestrated via a common mechanism and this has not been done in this case. While neuropathic changes frequently occurred at relatively low doses, the data provided do not convincingly demonstrate that the lesions may occur by a common mechanism. The Panel noted that the Agency appears to agree with this conclusion.

A pattern of common neuropathology does not appear to exist. Five of seven of the candidate thiocarbamates induce some type of neuropathology. However, the Panel is unable to determine whether the thiocarbamate pesticides induce a consistent morphological response in exposed animals. There is some evidence that some of the thiocarbamates induce central neuropathy whereas other thiocarbamates induce sciatic nerve degeneration. The character of the sciatic nerve degeneration (e.g., axonopathy vs myelinopathy) is not described. There is some concern that the data for cycloate may be confounded by a high incidence of neuropathology in control animals. Neuropathology was not the most sensitive effect for two of the seven candidate thiocarbamates. The Agency should provide an assessment of whether the available data are suitable for this evaluation. For example, the toxicity data are not very consistent among the different cited studies. Could there be strain effects or other experimental differences that could account for this variability?

It was suggested that the Agency should consider whether the selection of a different endpoint (e.g., developmental toxicity) could have resulted in a more

conservative risk assessment than did peripheral neuropathy.

In the process of making such a selection, the following series of steps is suggested. In looking at a common endpoint, susceptibility should be logical for the effect and is common to all chemicals. If so, what would be the proposed mechanism of action. Is that mechanism common to all chemicals in the class? If not, a rationale is needed. Is there a dose response? If there is a common toxicity endpoint, are the effects seen across sex, species, and route of exposure? Are there any other explanations for the results? At this point, there should be a body of evidence with a logical progression that could allow for the determination of an appropriate endpoint.

3. Issue: The document *Thiocarbamates: A Screening Level Cumulative Dietary (Food) Risk Assessment* presents a step-wise screening process for conducting a cumulative risk assessment. This screening level approach is intended to identify whether there is a need to initiate a more comprehensive cumulative risk assessment for a small group of structurally related pesticides that induce a common effect. It is not intended to identify a level of concern or risk for any one chemical or a group of chemicals that share a common mechanism of toxicity.
Question: Please provide general comments on the overall screening approach used in this preliminary cumulative risk assessment.

The Panel evaluated the overall screening approach within the framework of the process. The Panel did not recommend the use of this approach for preliminary cumulative risk assessment for thiocarbamates. Comments were raised with regard to the process only as noted below:

(1) The Panel concluded that the Agency had made a significant effort toward identifying issues of concern and determining a process of logical series of steps for conducting such a screening evaluation. The actual approach of the screening process as presented appeared to be sound and highly conservative. However, all of the caveats associated with use of the methodology were not clearly stated. The lack of a discussion on uncertainty was raised as a major problem with the current document. The purpose and use of this cumulative risk assessment is based on the assumption that the effect is by a common mechanism or common lesion. This was clearly not identified for the thiocarbamates.

(2) The Panel believed that the use of the NOAEL as a method for determining potency may not be appropriate. Because the NOAEL is highly dependent on the process used to select dose levels for studies, the potency calculation is more a reflection of the method of dose selection than a true estimate of relative potency. This approach also does not allow for the trend in the data to be included in the process. In addition, the approach does not allow for the ability to determine if there are any changes that occur in the system rather than relying on a statistical yes/no determination. A question was raised as to how the Agency would chose a NOAEL in the case of multiple studies. The document needs to discuss and articulate the procedure recommended for use to derive a NOAEL in the absence of such data.

(3) While the issue of using data from studies of various duration in determining relative potencies was addressed in the document, concern was raised about how the Agency would determine the "most" sensitive endpoint under such conditions using NOAELs. The issue of the quality of the data was raised with regard to determining the most sensitive endpoint. This issue would be addressed in the process of setting a RfD. Thus, the Panel recommended that the Agency consider conducting an abbreviated RfD determination prior to comparing toxicity endpoints. In addition, questions were raised as to how the Agency would compare a group of chemicals for which a RfD had been determined for a subset.

(4) The process as outlined gave the suggestion that one would examine data within each "type" of endpoint independent of the others to determine the sensitive endpoint. It was suggested that the guidance for this process be more accurate to take into consideration that an underlying mechanism may be identified or supported when effects across all types of toxicities are compared.

(5) The Agency's approach rests on the assumption that a common mechanism will be identified for the identified toxic response within a set of candidate chemicals. This in fact dictates the selection of the toxic response. In the case of thiocarbamates, the developmental toxicity was not selected due to the lack of an identified common toxic mechanism. The necessity of identifying a common toxic mechanism may be an untenable assumption for many sets of candidate chemicals.

(6) It was not clear how the data from this screening assessment would be used. What criteria would be considered to determine whether or not a more comprehensive cumulative risk assessment would be completed?

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