13544

041403 0014000 112399 TX013864 R000783

Chemical:	**Pebulate**
PC Code:	**041403**
HED File Code	**14000 Risk Reviews**
Memo Date:	**11/23/99**
File ID:	**TX013864**
Accession Number:	**412-01-0045**

HED Records Reference Center
11/13/2000

Microfiche

013864

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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

11/23/99

MEMORANDUM

SUBJECT: **Pebulate Revised Human Health Risk Assessment. HED Chapter for the Reregistration Eligibility Decision (RED) Document.** P.C.Code 041403. Case No. 2500. DP Barcode D261243.

FROM: William J. Hazel, Ph.D.
Reregistration Branch 1
Health Effects Division (7509C)

THRU: Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

TO: Philip Poli/Betty Shackleford
Reregistration Branch 3
Special Review and Reregistration Division (7508C)

Please find attached the Revised Human Health Risk Assessment for the **Pebulate** Reregistration Eligibility Decision Document (RED). This revised HED assessment supersedes the 6/7/99 assessment (D256012) and reflects a more recent HIARC report and reconsideration of the plantback interval for rotational crops. The HED chapter includes the Hazard Assessment from Yung Yang in Toxicology Branch 1 (Attachment 1), Product and Residue Chemistry Assessments from William Hazel in Reregistration Branch 1 (Attachment 2), Dietary Exposure Analysis from Christina Swartz in Reregistration Branch 1 (Attachment 6), and Occupational and Residential Exposure Assessment from Susan Hanley in Reregistration Branch 1 (Attachment 3). Other attachments are: 12/7/98 HIARC memorandum (Attachment 4), the FQPA Safety Factor Committee memorandum (Attachment 5), and the 9/2/99 HIARC report reassessing dermal endpoints (Attachment 7). Information was also drawn from EFED's Draft Water Resource Assessment. This risk assessment or its components have been evaluated within HED by the following peer review committees: HIARC, FQPA SFC, MARC, ChemSAC, ExpoSAC, DE SAC, and the RARC.

PEBULATE

HED'S HUMAN HEALTH RISK ASSESSMENT

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a human health risk assessment for the active ingredient **Pebulate** (S-propyl butylethylthiocarbamate) for the purpose of making a reregistration eligibility decision.

Pebulate is a thiocarbamate herbicide used for preemergence control of germinating seeds of broadleaf and grassy weeds in sugar beet, tobacco, and tomato. Pebulate inhibits the growth of seedling shoots and roots via alteration of plant metabolism, particularly through inhibition of lipid synthesis. There are no registered uses of pebulate in a residential setting. There is one registered end-use product: the 6 lb ai/gal emulsifiable concentrate (EC), EPA Reg. No. 10182-158. Pebulate is typically applied preplant once per season using ground or irrigation equipment and is soil-incorporated immediately after application to prevent loss via volatilization.

HED evaluated the toxicology, residue chemistry, and occupational exposure databases for pebulate and determined that the data are adequate to support a reregistration eligibility decision. Acute and chronic dietary risk assessments were conducted as was a qualitative assessment of the potential exposure to pebulate through drinking water. Since pebulate is not used in a residential setting, an assessment of residential exposure was not conducted. As a result, the quantitative assessment of aggregate risk includes only dietary exposure. HED also considered dermal and inhalation exposure to occupational handlers as well as to workers reentering treated fields.

Pebulate is a herbicide in the class of thiocarbamates, which includes molinate, EPTC, butylate, vernolate, and cycloate, and is a reversible cholinesterase inhibitor. As with other chemicals in this class, neurotoxicity is the major toxic effect of pebulate; however, other toxic effects were also observed in the toxicology studies. No significant differences were observed in the toxicology studies with regard to gender.

The acute toxicity data demonstrate that Pebulate has low acute oral, dermal, and inhalation toxicity. It is slightly to mildly irritating to the eye and skin. Pebulate is not a skin sensitizer. Neurotoxic signs were found in both dogs and rats fed pebulate. Serum cholinesterase inhibition was observed in the one-year dog study at doses as low as 25 mg/kg/day, but clinical signs, such as ataxia and severe convulsions, were seen at doses as low as 5 mg/kg/day in males. Inhibition of brain cholinesterase activity and decreased brain weight were observed in rats fed pebulate for 90 days at doses as low as 19 mg/kg/day. Histological findings showed that pebulate induced a minimal sciatic nerve fiber degeneration in rats and moderately severe Wallerian-type degenerative changes in the spinal cord and peripheral nerves in dogs. There is no indication of carcinogenicity. The details of the toxicological data are presented in the Toxicology Chapter of

the RED (Attachment 1).

Briefly, the doses and endpoints selected by the HED Hazard Identification Assessment Review Committee (12/7/98 and 9/2/99) for the following risk assessments were:

- Acute dietary - NOAEL = 50 mg/kg/day based on decreased motor activity at the LOAEL of 150 mg/kg/day in an oral acute rat neurotoxicity study;
- Chronic dietary - NOAEL = 0.74 mg/kg/day based on decreased body weight and increased cataract incidence at the LOAEL of 7.12 mg/kg/day in an oral chronic rat study;
- Short-term and intermediate-term dermal - NOAEL = 100 mg/kg/day (highest dose tested) from a 21-day dermal rat study in which no systemic toxicity was observed at the highest dose tested;
- Short-term and intermediate-term inhalation - NOAEL = 0.0034 mg/L (equivalent to 0.89 mg/kg/day) based on prolonged coagulation time and degenerative kidney effects at the LOAEL of 0.016 mg/L (4.2 mg/kg/day) observed in a 90-day rat inhalation study.

All doses for risk assessment purposes were assessed the conventional safety factors of 10x for interspecies extrapolation and 10x for intraspecies variability. In addition, HED's FQPA Safety Factor Committee (FQPA SFC) considered the increased susceptibility of infants and children (1/26/99). The FQPA safety factor of 10x was retained for pebulate due to (i) the severe neuropathology exhibited in studies with adult animals, (ii) the structural similarities to other thiocarbamates for which increased susceptibility of developing fetuses has been demonstrated, and (iii) the outstanding requirement for a developmental neurotoxicity study. In the current analysis, the 10x safety factor was applied to the various populations of infants and children as well as to females (13-50 years, i.e., females of childbearing age). The reason for this is that the Agency is concerned about potential developmental (*in utero* exposure) effects of pebulate. The 10x FQPA factor is not applied to the general population when it is appropriate only to apply the factor to portions of the population. In the case of pebulate, it is not appropriate to apply the factor to males or to the general population due to the *in utero* nature of the effect.

A reference dose (RfD) which includes the FQPA safety factor (10X, 3X or 1X) is defined as the Population Adjusted Dose (PAD). In the case of pebulate, the acute and chronic PADs for adults are equivalent to the acute and chronic RfDs selected by the HIARC (i.e. FQPA factor for adults = 1X). For populations which include infants, children, and females 13-50, the acute and chronic PADs include the FQPA safety factor of 10X, and are therefore equivalent to the acute and chronic RfDs/10, respectively.

Dietary risk assessments reflected highly refined exposure assessments; anticipated residues and percent-crop-treated figures were incorporated. Refinements were conducted in anticipation of a cumulative risk assessment being conducted in the future (possibly on the thiocarbamates as a class). Refinements also permit a more realistic comparison of Drinking Water Levels of Comparison (DWLOC) with estimates of potential drinking water concentrations provided by the Environmental Fate and Effects Division (EFED). A probabilistic/Monte Carlo type of acute dietary assessment was conducted using an acute population adjusted dose (aPAD) of 0.5

mg/kg/day for adults and 0.05 mg/kg/day for infants, children, and females (13-50 yr); **acute risks to all population subgroups were <1% of the aPAD.** Chronic risks were calculated using a chronic PAD (cPAD) of 0.007 mg/kg/day for adults and 0.0007 mg/kg/day for infants, children, and females (13-50 yr); **chronic dietary risks to all population subgroups were <1% of the cPAD.**

The Draft EFED water resouce assessment included residues of parent pebulate and its major soil/water degradate pebulate sulfoxide. Pebulate sulfoxide is not regulated in plant or livestock commodities because it is not a significant residue in these matrices. However, because pebulate sulfoxide is a major soil/water degradate, the MARC determined that HED would be interested in modeling of this metabolite. Although there are no toxicity data involving testing of pebulate sulfoxide, analogous metabolites are considered to be of toxicological concern for other thiocarbamates and there is no basis to determine that pebulate sulfoxide would not have similar toxicity to pebulate per se.

Conservative Tier II (PRZM-EXAMS) modeling provided by EFED indicates that pebulate concentrations (pebulate + pebulate sulfoxide) in surface water are not likely to exceed 40 ppb pebulate equivalents for peak (acute) exposure and 2.6 ppb pebulate equivalents for mean (chronic) exposure. Pebulate *per se* is not expected to be a commonly detected ground water contaminant, based on its chemical properties. However, conservative estimates of ground water concentrations provided by EFED using the SCI-GROW model vary considerably with the assumptions made regarding the mobility of pebulate sulfoxide. If the mobility is assumed to be equivalent to that of molinate sulfoxide (for which soil binding affinity data are available), then ground water modeling predicts peak and annual concentrations of 1.8 ppb. However, if pebulate sulfoxide is assumed to have much greater mobility than molinate sulfoxide (no binding to soil), then the model predicts peak and annual concentrations of 44 ppb in groundwater. The latter scenario is clearly a conservative estimate that could be refined by the availability of additional environmental fate property data on pebulate sulfoxide.

Large amounts of ambient water monitoring data are available suggesting that pebulate *per se* is rarely detected in either surface or ground water, and, when detected, it is present at very low levels. For example, the STORET database indicates that only 2 of 5387 samples of surface water collected in Kentucky contained detectable levels of pebulate (at 0.02-0.04 ppb). Also, out of a combined total of 6220 groundwater samples in the USGS NAWQA and STORET databases, only four samples contained detectable levels of pebulate *per se* ($\leq$0.005 ppb); of these, 407 were collected in GA and KY, states in which pebulate is used. Pebulate sulfoxide was not sought in monitoring programs. USGS NAWQA monitoring of residues in surface waters from 1991-1995 revealed the maximum concentration of pebulate detected to be 0.8 ppb.

With the exception of the conservative estimated environmental concentrations, calculated by assuming a total lack of pebulate sulfoxide soil binding, estimated water concentrations of pebulate + pebulate sulfoxide do not exceed the acute and chronic Drinking Water Levels of Comparison (DWLOCs). The available monitoring data, although not targeted to

pebulate, support this.

Occupational risks associated with dermal and inhalation exposure were calculated separately for the following reasons: (i) exposure via both routes was expected to be potentially important based on the use pattern and properties of pebulate; (ii) route-specific toxicity studies were available reflecting administration via the dermal and inhalation routes; and (iii) toxic effects resulting from dermal and inhalation exposure are different (see Table 1). No respiratory protection is required for most workers using pebulate; MOEs for these workers range from 110 to 350, i.e., less than the Agency's level of concern. Organic vapor respirators **are** required for people who use chemigation to treat large acreage and those who prepare spray solutions for applications to tomatoes at very high rates in the western region of the United States; use of respirators results in MOEs for these people ranging from 250 to 640. The preparation of large quantities of dry bulk fertilizer impregnated with pebulate requires the use of a closed loading system; MOEs for these workers using closed loading range from 230 to 470. This label modification is thought to be very practical considering the nature of how pebulate is used in these settings and the equipment that is typically required for preparation of bulk quantities of fertilizer.

For occupational handler dermal exposures, the results of this risk assessment indicate that concerns for worker exposure can be addressed by the use of personal protective equipment (PPE) in all of the worker scenarios. Risks were below the Agency's level of concern (MOE >100) for all pebulate scenarios involving loading groundboom equipment with the use of PPE (i.e., long pants, long sleeved shirt, chemical resistant gloves, coveralls): the MOEs were 200 to 1700. The MOEs for the pebulate applicator exposures are greater than 100 at baseline (range is 350 to 2200). The remaining scenario, mixing and loading emulsifiable concentrate for impregnation of dry bulk fertilizer with a closed mixing system, has an MOEs greater than 100 (range is 250 to 510).

One mixer/loader and two applicator scenarios were not represented by corresponding surrogate exposure unit values in the Agency's library of actual exposure monitoring data known as Pesticide Handlers Exposure Database (PHED) or any pebulate-specific study data. Consequently, these scenarios were not evaluated in this risk assessment (mixing/loading pebulate with fluid fertilizer, applying pebulate impregnated onto bulk fertilizer with specialized equipment, and soil injection applications). Based on the calculations for the other scenarios, the mixing and loading of large quantities (≥800 lb ai) and the application of high rates (10 lb ai/A) would likely result in worker exposure above the Agency's level of concern.

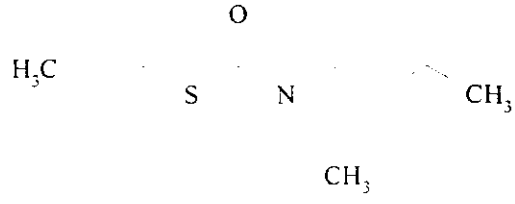
The Agency does not believe that there are any post-application exposure concerns over the use of pebulate on sugar beets. The Agency did not complete a risk assessment on tomatoes and tobacco because there are no major activities that contribute to post-application exposure. However, there are some types of tomato and tobacco transplanting that may involve human contact with freshly treated soil even though the process is described as being mechanical in nature. Additional information is needed to demonstrate how transplanting in tobacco and

tomatoes occurs in relation to pebulate use: if re-entry concerns are not satisfactorily addressed by this cultural practices information, label changes to eliminate this possible exposure are required.

Although the pebulate database is sufficient to render a reregistration eligibility decision, **a deficiency exists for developmental neurotoxicity**. Additional information is required to elucidate potential postapplication exposure to workers transplanting tobacco and tomatoes; label restrictions or exposure data are also alternatives. Other labeling changes are also required: (i) increasing the preharvest interval for tomatoes from 8 days to 30 days and (ii) establishment of a 4-month plantback interval (PBI) for all rotational crops including crops on the label unless data are submitted to demonstrate that a shorter PBI is sufficient.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Pebulate [S-propyl butylethylthiocarbamate] is a preplant selective herbicide used for control of grassy and broadleaf weeds in sugar beets, tobacco, and tomatoes.



Empirical Formula:	$C_{10}H_{21}NOS$
Molecular Weight:	203.36
CAS Registry No.:	1114-71-2
Chemical I.D. No.:	041403

Pebulate technical is an amber liquid with a boiling point of 142 C at 21 mm Hg, a density of 0.9552 g/mL at 20 C, an octanol/water partition coefficient (K_{ow}) of 9.6×10^3 at 25 C, and a vapor pressure of 8.9×10^{-3} mm Hg at 25 C. Pebulate is slightly soluble in water (60 ppm at 20 C), and is miscible with acetone, benzene, isopropanol, methanol, and xylene. No impurities of toxicological concern have been identified. Since pebulate is fairly volatile, exposure by the inhalation route is expected.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Although a developmental neurotoxicity study was identified by the HED Hazard Identification Assessment Review Committee (HIARC) as a data gap (Attachment 4), the toxicology database for pebulate is adequate to assess its toxicity and permits a reregistration eligibility decision to be made. A more recent HIARC report dated 9/2/99 presents the outcome of a 5/26/99 meeting to reassess dermal endpoints. Tables 1 and 2 present HIARC toxicity endpoints and doses for risk assessment and the toxicity profile for pebulate, respectively.

Pebulate is an herbicide in the class of thiocarbamates, which includes molinate, EPTC, butylate, vernolate, and cycloate, and is a reversible cholinesterase inhibitor. As with other chemicals in this class, neurotoxicity is the major toxic effect for pebulate; however, other toxic effects described below were also observed in the toxicology studies. No significant differences were observed in the toxicology studies with regard to gender.

Neurotoxic signs were found in both dogs and rats fed pebulate. Serum cholinesterase inhibition was observed in the one-year dog study at doses as low as 25 mg/kg/day, but clinical signs, such as ataxia and severe convulsion, were seen at doses as low as 5 mg/kg/day in males. Inhibition of brain cholinesterase activity and decreased brain weight were observed in rats fed pebulate for 90 days at doses as low as 19 mg/kg/day. Histological findings showed that pebulate induced a minimal sciatic nerve fiber degeneration in rats and moderately severe Wallerian-type degenerative changes in the spinal cord and peripheral nerves in dogs. The details of the toxicological data are presented in the Toxicology Chapter of the RED (Attachment 1).

The acute toxicity data showed that Pebulate had low acute oral, dermal, or inhalation toxicity. It was a slight to mild irritant to the eye or skin. It was not a skin sensitizer. Toxicity Categories were either 3 or 4.

Although there are no subchronic oral toxicity studies submitted, information from chronic toxicity studies in rats and dogs is available. In a subchronic inhalation study, rats exposed to pebulate aerosol at higher doses for 14 weeks showed prolongation of the blood coagulation time, histological changes in kidney, and increased incidence of mucigenic epithelial hyperplasia of the nasal turbinates in both sexes. In a 21-day dermal toxicity study in rats, significant decrease in body weight gains and food utilization and a reduction in neutrophil counts were seen.

At the higher doses of the dog chronic feeding study, pebulate induced clinical signs which included abnormal behavior, gait, and posture, a decrease in serum cholinesterase activity, and neuropathology characterized by Wallerian-type degenerative changes in the spinal cord and peripheral nerves. Although this type of neuropathology was not seen in the two-year study in rats, sciatic nerve fiber degeneration was observed in a subchronic neurotoxicity study in rats. In

the two-year chronic feeding study in rats, ophthalmological effects (zonal disjunction, retinal degeneration and cataracts) were observed at doses as low as 0.7 mg/kg/day.

There was no evidence of increased tumor incidence in the carcinogenicity studies in rats and mice, and the mutagenic test battery also indicated that pebulate was not mutagenic. Therefore, pebulate was classified as "Not Likely" to be a human carcinogen.

The developmental toxicity studies in rats and rabbits and a reproductive study in rats indicated that pebulate did not cause significant developmental or reproductive effects. The data also demonstrated no increased sensitivity of rats or rabbits to in utero or early post-natal exposure to pebulate. There was no evidence of endocrine disruption. However, both the developmental and reproductive toxicity studies did not measure developmental neurotoxicity of pebulate. HED's HIARC (Attachment 4) determined that a developmental neurotoxicity study was required for pebulate based on the following reasons: (1) brain weight decrements were observed in a subchronic neurotoxicity study in rats, (2) neuro-histopathologic findings (e.g., degeneration in the sciatic nerve fibers) were observed in rats and dogs, (3) pebulate is a thiocarbamate and is structurally related to molinate, cycloate, EPTC, and vernolate all of which were shown to produce neurotoxicity/neuropathology; molinate was shown to produce developmental neurotoxic effects. A developmental neurotoxicity study would provide additional data regarding functional parameter development, potential increased susceptibility of the offspring, and the effects of pebulate on the development of the fetal nervous system.

Pebulate did not cause delayed neurotoxic signs in hens. In the acute neurotoxicity screening study in rats, pebulate produced neurotoxic effects which included clinical signs (decreased activity, hunched posture, splayed gait, decreased visual placement response, piloerection, irregular breathing, ptosis, chromodacryorrhea, rigidity during handling, and signs of salivation and urinary incontinence), and increased incidence of neuronal cell necrosis in the brain. Some of these signs were observed at doses as low as 150 mg/kg. The clinical signs were observed 5-6 hours after dosing and disappeared within 1-2 days. There was no observed effect on cholinesterase activity; however, it should be noted that cholinesterase activity was not measured at an optimal time in this study. In a subchronic neurotoxicity screening study in rats, pebulate inhibited brain cholinesterase activity at doses as low as 19.4 mg/kg/day and a minimal sciatic nerve fiber degeneration at a dose of 78.4 mg/kg/day.

In the rat, pebulate was readily absorbed, distributed, metabolized and eliminated, primarily in urine, feces and CO_2. Less than 3% was detected in total tissues. Major metabolites were identified in the urine as pebulate mercapturate, hydroxylated pebulate, butylamine and ethylbutylamine, hydroxyethylbutylamine, hydroxylated pebulate mercapturate.

3.2 FQPA Considerations

The HIARC recommended that the **FQPA safety factor of 10X** for protection of infants and children (as required by FQPA) be **retained** (Attachment 4). This recommendation was subsequently affirmed by the HED FQPA Safety Factor Committee (HED DOC# 013704; Attachment 5).

The rationale for **retention of the FQPA safety factor** was due to concern for:

- the data gap for a pebulate developmental neurotoxicity study in rats. A developmental neurotoxicity study will provide additional data regarding functional parameter development, potential increased susceptibility, and the effects of pebulate on the development of the fetal nervous system.

- the severe neuropathology exhibited in studies with adult animals (subchronic neurotoxicity study in rats and one-year dog study indicate exposure to pebulate produced neuropathologic findings);

- the structure activity relationship to molinate and other thiocarbamates known to produce neurotoxicity/neuropathology;

- molinate induction of neurotoxicity/neuropathology after single and multiple exposures *via* the oral, dermal, and inhalation routes across species. There is clear evidence of increased susceptibility in rat fetuses following *in utero* exposure to molinate in the prenatal developmental study. Increased susceptibility was demonstrated in the developmental neurotoxicity study in rats. Molinate was also found to be a reproductive toxicant (mice, rats, and dogs); and

The FQPA Safety Factor Committee determined that the 10x FQPA safety factor is applicable to the following subpopulations:

Acute Dietary Assessment: All populations which include Infants and Children. The FQPA factor is appropriate for these populations due to the uncertainty regarding the effects on the developing fetal nervous system after a single exposure to pebulate. This uncertainty is being addressed by the requirement of a developmental neurotoxicity study in rats.

Chronic Dietary Assessment: All populations which include Infants and Children. The FQPA factor is appropriate for these populations due to the uncertainty regarding the effects on the developing fetal nervous system after repeated exposures to pebulate. This uncertainty is being addressed by the requirement of a developmental neurotoxicity study in rats.

In the current analysis, the 10x safety factor was applied to the various populations of infants and children as well as to females (13-50 years, i.e., females of childbearing age). The reason for this is that the Agency is concerned about potential developmental (*in utero* exposure) effects of pebulate. **The 10x FQPA safety factor is not applied to the general population when it is appropriate only to apply the factor to portions of the population.** In the case of pebulate, it is not appropriate to apply the factor to males or to the general population due to the *in utero* nature of the effect.

3.3 Dose Response Assessment

The strengths and weaknesses of the pebulate toxicology database were considered during the process of toxicity endpoint and dose selection. In general, all the required guideline studies on pebulate were available and provided reasonable confidence when the toxicity endpoints and doses for risk assessment were selected. The HIARC recommended that a developmental neurotoxicity study be conducted for pebulate because decreased brain weight and degeneration in the sciatic nerve fibers were seen in adult test animals and due to the structural relationship of pebulate to other neurotoxins (Molinate and EPTC). Therefore, it was important to explore the possible neurologic effects of pebulate in developing animals.

All of the toxicity endpoints and doses for risk assessment were selected based upon the most sensitive toxic effect and derived from studies which used similar routes of exposure as those expected in possible human exposure scenarios. For pebulate, several studies showed that cholinesterase inhibition occurred at dose levels higher than those for clinical signs characteristic of cholinesterase inhibition. This could be due to the facts that pebulate is a reversible cholinesterase inhibitor and the time for cholinesterase activity measurement in certain studies was not optimal.

The 21-day dermal rat toxicity study was selected as the source of dose and endpoint for short-term and intermediate-term dermal risk assessments because its duration and route of exposure are appropriate for short- and intermediate term-dermal exposure. Slight to moderate dermal irritations were observed at mid- and high-dose groups. Systemic effects were similar to those observed in other studies. Although there were some body weight gain decrements and decreased food utilization in females at 100 mg/kg/day, they were judged to be confounded by the following data: (1) there were no differences in absolute body weight; (2) the decreased body weight gain was equivocal at all doses in the females; (3) the decreases were significant only on sporadic days and did not exhibit any consistency over time; and (4) decreased body weight gain can be attributed to the dermal irritation which was severe in the high-dose groups. Based on these factors, the HIARC concluded that the 100 mg/kg/day dose is the NOAEL (not the LOAEL) and this value should be used for risk assessment.

Table 1. Doses and Toxicological Endpoints Selected for Various Exposure Scenarios[a]

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL=50	Decreased motor activity at 150 mg kg/day	Acute Neurotoxicity-Rat
	(UF=100) [FQPA UF=10]	**Acute RfD = 0.5 mg/kg/day** FQPA acute population adjusted dose (aPAD) for infants, children, and females (13-50 yr) = 0.05 mg/kg/day aPAD for adults other than females (13-50 yr) = 0.5 mg/kg/day	
Chronic Dietary	NOAEL=0.74	Decreased body weights and increased incidence of cataracts in both sexes	Chronic Toxicity -Rat (1 year)
	(UF=100) [FQPA UF=10]	**Chronic RfD = 0.007 mg/kg/day** FQPA chronic population adjusted dose (cPAD) for infants, children, and females (13-50 yr) = 0.0007 mg/kg/day cPAD for adults other than females (13-50 yr) = 0.007 mg/kg/day	
Carcinogenicity (Dietary)	Not Applicable	Pebulate was not mutagenic and did not result in increased tumor incidence in rats or mice. Pebulate was classified as "Not Likely" to be a human carcinogen.	
Short-Term (Dermal)	NOAEL=100 (HDT) (*MOE of concern* = 100)	No systemic toxicity was observed at the highest dose tested	21-Day Dermal Toxicity- Rats
Intermediate-Term (Dermal)			
Long-Term (Dermal)	Not Applicable	Based on the use pattern, no long-term dermal exposure is expected to occur. Risk assessment is not required.	
Short-term (Inhalation)	NOAEL=0.003 mg/L (0.89 mg/kg/day)[b] (MOE of concern = 100)	Prolonged coagulation time, degenerative effects in kidneys of both sexes.	Subchronic Inhalation-(90 days) Rats
Intermediate-term (Inhalation)			
Long-term (Inhalation)	Not Applicable	Based on the use pattern, no long-term inhalation exposure is expected to occur. *Risk assessment is not required.*	

[a]Table was adapted from the HED HIARC report (Attachment 4) and HED FQPA Safety Factor Committee report (Attachment 5); the table is excerpted from the Pebulate Toxicology Chapter (Attachment 1) as modified by the 5/26/99 HIARC decision regarding the NOAEL for dermal scenarios (Attachment 7).

[b]Inhalation dose calculation is detailed in Attachment 3; *the equation included the* Sprague-Dawley rat mean respiratory volume of 10.26 L/hr (at rest) and mean body weight of 0.236 kg.

Occupational risks associated with dermal and inhalation exposure were calculated separately (and not combined) for the following reasons: (i) exposure via both routes was expected to be potentially important based on the use pattern and properties of pebulate: (ii) route-specific toxicity studies were available reflecting administration via the dermal and inhalation routes; and (iii) toxic effects resulting from dermal and inhalation exposure were different (see Table 1).

Table 2. Toxicity Profile of Pebulate Technical

Guideline	MRID#	Type of Study	Results	Tox. Cat.	Core Grade
Acute Toxicity					
§81-1 870.1100	41591701	Acute Oral-Rat	LD_{50}= 1750(♂)/1550(♀) mg/kg	3	Acceptable
§81-2 870.1200	41591701 41677301	Acute Dermal-Rabbit Acute Dermal- Rat	LD_{50} >2000 mg/kg (Rabbit or Rat)	3	Acceptable
§81-3 870.1300	00143575	Acute Inhalation-Rat	LC_{50}= 3.7(♂)/3.5(♀)mg/L	4	Acceptable
§81-4 870.2400	41591703	Eye Irritation-Rabbit	Mild eye irritant	3	Acceptable
§81-5 870.2500	41591702	Skin Irritation-Rabbit	Slight dermal irritant	4	Acceptable
§81-6 870.2600	41614808	Dermal Sensitization-Guinea pig	Not a skin sensitizer	N/A	Acceptable
Subchronic Toxicity					
§82-1(a) 870.3100	N/A	90-day feeding-Rat	N/A		Waived*
§82-1(a) 870.3100	N/A	90-day feeding-Mouse	N/A		Waived*
§82-1(b) 870.3150	N/A	90-day feeding-Dog	N/A		Waived*
§82-2 870.3200	41920701	21-day dermal- Rat	NOAEL= 100 mg/kg/day (HDT)		Acceptable
§82-3 870.3465	00143576	90-day Subchronic Inhalation-Rat	NOAEL=0.0034 mg/L LOAEL=0.016 mg/L		Acceptable
Chronic Toxicity					
§83-1(b) 870.4100	40969701	1-year Chronic oral-Dog	NOAEL= <5(♂)/5(♀)mg/kg/day LOAEL= 5(♂)/25(♀)mg/kg/day		Acceptable
§83-2(b) 870.4200	41920705	Carcinogenicity-Mouse (18 months)	NOAEL= 34(♂)/47(♀) mg/kg/day LOAEL= 116(♂)/161(♀) mg/kg/day No evidence of Carcinogenicity		Acceptable

§83-5 870.4300	41213001	Combined Chronic/Oncogenicity -Rat (2 years)	NOAEL= 0.74(♂)/1.85(♀) mg/kg/day LOAEL= 7.12(♂)/9.49(♀) mg/kg/day No evidence of Carcinogenicity	Acceptable
Developmental / Reproductive Toxicity				
§83-3(a) 870.3700	40033301	Developmental-Rat	*Maternal* NOAEL= 30 mg/kg/day LOAEL= 200 mg/kg/day Developmental NOAEL= 30 mg/kg/day LOAEL= 200 mg/kg/day	Acceptable
§83-3(b) 870.3700	40033201	Developmental-Rabbit	Maternal NOAEL= 30 mg/kg/day LOAEL= 150 mg/kg/day *Developmental* NOAEL= 150 mg/kg/day (HDT)	Acceptable
§83-4 870.3800	40970001	Two-generation Reproduction-Rat	Parental NOAEL= 0.8 mg/kg/day LOAEL= 6 mg/kg/day Offspring NOAEL= 6 mg/kg/day LOAEL= 50 mg/kg/day Reproductive NOAEL= 50 mg/kg/day (HDT)	**Unacceptable** (Not required to repeat the study)
Neurotoxicity				
§81-7 870.6100	00067869 92138016	Acute delayed Neurotox- Hen	Negative	Acceptable
§81-8ss 870.6200	43217401	Acute neurotoxicity-Rat	NOAEL= 50 mg/kg LOAEL= 150 mg/kg	Acceptable
§82-7 870.6200	43231001	Subchronic neurotoxicity- Rat	Neurotoxicity NOAEL= 3.9(♂)/4.5(♀) mg/kg/day LOAEL= 19.4(♂)/21.5(♀)mg/kg/day ChE inhibition:Brain, plasma, RBC NOAEL= 3.9(♂)/4.5(♀) mg/kg/day LOAEL= 19.4(♂)/21.5(♀)mg/kg/day	Acceptable
Mutagenicity				
§84-2 870.5100	**41556803**	Ames Assay (S. typhimurium)	Not mutagenic	Acceptable
§84-2 870.5375	**41556802**	In vitro mammalian cytogenetics -*human lymphocytes*	No induction of chromosomal aberrations	Acceptable
§84-2 870.5550	41614809	Unscheduled DNA synthesis in rat hepatocyte treated in vivo	No conclusion can be reached	**Unacceptable**
Metabolism				

§85-1 870.7485	42215201 42482501 42482502 42482503	Metabolism	Pebulate was readily absorbed, distributed, metabolized and excreted, primarily in urine (59-76%), feces and CO_2 (4-14% and 13-16%, respectively.) Very little (0.4-1.0%) was detected in tissues. Major metabolites were identified in the urine as pebulate mercapturate, hydroxylated pebulate, butylamine and ethylbutylamine, hydroxyethylbutylamine, hydroxylated pebulate mercapturate. The data suggested that metabolism of pebulate does not appear to be sex- or dose- related and does not bioaccumulate.	Acceptable

* There are no subchronic oral toxicity studies submitted; however, information from chronic toxicity studies in rats and dogs is available.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Pebulate is a thiocarbamate preplant selective herbicide used for control of grassy and broadleaf weeds in sugar beets, tobacco, and tomatoes. There is one registered end-use product, the 6 lb/gal emulsifiable concentrate (EC), which is applied once per season via ground equipment and which is immediately soil-incorporated. Registered uses are not expected to result in residential exposure.

Application rates range from 3-6 lb ai/A except for plug-planted tomatoes for which a maximum application rate of 10 lb ai/A may be used (California only).

4.2 Dietary Exposure

Potential exposure to pebulate residues in the diet occurs through food and water. Data supporting food exposure are adequate and are summarized in the Residue and Product Chemistry Chapters (Attachment 2). Exposure to pebulate residues in ground and surface water was estimated using conservative modeling techniques; available modeling data were assessed but were not considered adequate for quantitative risk assessment purposes.

4.2.1 Food Exposure

Pebulate has an early season soil-incorporated application with extensive soil degradation/ dissipation and plant metabolism. No parent compound is identified in plant metabolism studies. Major metabolites found in plants are a series of three different butylamine compounds resulting from hydrolysis of the thiocarbamate moiety; these metabolites are not of toxicological concern at the concentrations expected from registered uses of pebulate (HED Metabolism Committee,

5/19/92, C. Olinger). The bulk of the remaining radioactivity is incorporated into natural plant consituents. Pebulate residues were below the limit of quantitation in all field trials and processing studies.

Pebulate *per se* was identified at low levels in milk and fat in livestock metabolism studies using greatly exaggerated doses (up to 223x). However, livestock dietary exposure is expected to be negligible even using conservative assumptions for livestock diets, i.e., that sugar beet tops, dried sugar beet pulp, and sugar beet molasses are all fed simultaneously at the maximum feeding levels; livestock diets were calculated based on Table 1 of OPPTS 860.1000. These are the only potential feed items that may bear pebulate residues. Residues were nonquantifiable (<0.05 ppm) in all samples of sugar beets and its processed products. Therefore, there is no reasonable expectation of secondary residues in livestock commodities [40 CFR 180.6(a)(3)], and tolerances for pebulate residues in livestock commodities are not required (HED Metabolism Assessment Review Committee, 4/21/99, W. Hazel).

Tolerances are established for residues of pebulate *per se* in tomatoes and sugar beet roots and tops at 0.1 ppm (40 CFR 180.238). Based on field trial data, HED recommends reassessment of all tolerances to the limit of quantitation of the analytical method, 0.05 ppm, because all residues were consistently less than the limit of quantitation. HED has high confidence in the available geographically representative field trial data.

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with residues in commodities to determine average exposure in mg/kg/day. For acute dietary risk assessments, the entire distribution of single day food consumption events is combined with either a single residue level (deterministic analysis) or a distribution of residues (probabilistic analysis, referred to as "Monte Carlo") to obtain a distribution of exposure in mg/kg/day. For deterministic (Tier 1) analyses, the Agency regulates at the 95th percentile of exposure; when probabilistic assessments are conducted, the Agency regulates at the 99.9th percentile of exposure.

Acute and chronic dietary exposure to pebulate result in risk estimates that are significantly below the Agency's level of concern (the aPAD and cPAD, respectively) at all tiers of analysis (i.e., using existing tolerances, reassessed tolerances, and incorporating residue refinements). Residue refinements included anticipated residues from field trials, adjustments for percent crop treated, and a probabilistic/Monte Carlo acute analysis. No Pesticide Data Program/USDA (PDP) or Food and Drug Administration (FDA) monitoring data have been generated for pebulate. Even though dietary risk was below the Agency's level of concern based on existing tolerances, the maximum level of refinement was used in the likely event that a cumulative risk assessment is required for pebulate and other chemicals having a similar mechanism of toxicity (perhaps the class of thiocarbamate pesticides). **Applying all of these refinements, acute and chronic dietary risk estimates were calculated to be <1% of the acute and chronic**

population adjusted doses (aPAD and cPAD, respectively) for adults and infants/children (Table 3). Details of the dietary risk assessment are provided in Attachment 6.

Table 3. Acute and Chronic Dietary Exposure and Risk Estimates for Pebulate.[1]

Population Subgroup	Acute Exposure/Risk Using Anticipated Residues/Monte Carlo		Chronic Exposure/Risk Using Anticipated Residues	
	Exposure (mg/kg/day) 99.9th %-ile	%aPAD	Exposure (mg/kg/day)	%cPAD
General US Population	0.000134	0.03	0.000003	0
Females 13-50	0.000099	0.20	0.000002	0.3
Males 13-19	0.000087	0.02	0.000003	0
Males 20+	0.000098	0.02	0.000002	0
All Infants <1yr	0.000107	0.21	0.000001	0.2
Nursing Infants <1yr	0.000050	0.10	0.000001	0.1
Non-Nursing Infants <1yr	0.000126	0.25	0.000001	0.2
Children (1-6 years)	0.000197	0.39	0.000005	0.7
Children (7-12 years)	0.000200	0.40	0.000004	0.6

[1] The acute population adjusted dose (aPAD) is 0.5 mg/kg/day for adults, and 0.05 mg/kg/day for infants, children and females 13-50. The chronic PAD (cPAD) is 0.007 mg/kg/day for adults and 0.0007 mg/kg/day for infants, children, and females 13-50.

4.2.2 Water

The Draft EFED water resource assessment included residues of parent pebulate and its major soil/water degradate pebulate sulfoxide. Pebulate sulfoxide is not regulated in plant or livestock commodities because it is not a significant residue in these matrices. However, because pebulate sulfoxide is a major soil/water degradate, the MARC determined that HED would be interested in modeling of this metabolite. Although there are no toxicity data involving testing of pebulate sulfoxide, analogous metabolites are considered to be of toxicological concern for other thiocarbamates and there is no basis to determine that pebulate sulfoxide would not have similar toxicity to pebulate per se.

Based on aerobic soil metabolism data and modeling, pebulate initially comprises the majority of the total pebulate + pebulate sulfoxide residue in water, as expected, but the relative concentration of the sulfoxide appears to increase with time. Since direct drinking water monitoring data were not available for pebulate, the surface and ground water assessments were based on modeling predictions and, qualitatively, on available ambient water monitoring data. Uncertainty in modeling predictions of ground and surface water residues was due primarily to a lack of environmental fate data (including organic matter partitioning coefficient and solubility of the sulfoxide metabolite) and the inability to accurately estimate the influence of volatilization of the parent on dissipation. Since conservative input parameters were used for both ground and surface water, modeling of ground and surface water (including Tier II) residues is considered to be conservative.

The modeling procedures were conducted for the tobacco use pattern because this use is expected to contribute most to pebulate loading into surface waters due to the large geographical extent of the tobacco growing region.

4.2.2.1 Surface Water

Tier II PRZM-EXAMS modeling provides upper-bound predictions of pebulate concentrations in surface water when 4 lb ai/A of pebulate and 0.732 lb ai/A of pebulate sulfoxide are applied to a sandy loam soil in NC, a major tobacco-growing state. Concentrations of pebulate + pebulate sulfoxide in surface water are not likely to exceed 40 ppb pebulate equivalents for peak (acute) exposure and 2.6 ppb pebulate equivalents for mean (chronic) exposure. USGS NAWQA monitoring was not targeted to pebulate, and therefore could not be used for quantitative estimates of residues in surface waters. However, the data show that from 1991-1995, the maximum concentration of pebulate detected was 0.8 ppb. Pebulate was detected in 21 of 1000 samples taken from agricultural streams, with a maximum concentration of 0.24 ppb. STORET surface water monitoring data collected by the Kentucky Department of Natural Resources and Environmental Protection indicated pebulate detects in only 2 of 5387 samples, at concentrations of 0.02 to 0.04 ppb; these data were generated in areas of known pebulate usage, but were not necessarily timed to pebulate application. None of the monitoring programs included analysis for residues of pebulate sulfoxide.

4.2.2.2 Ground Water

Pebulate *per se* is not expected to be a commonly detected ground water contaminant, based on its chemical properties. However, the SCI-GROW model was used to estimate ground water concentrations using the same site, soil, and application rate input data as was used for PRZM/EXAMS. Concentrations of pebulate + pebulate sulfoxide vary considerably with the assumptions made regarding the mobility of pebulate sulfoxide. If the mobility is assumed to be equivalent to that of molinate sulfoxide, then ground water modeling predicts peak and annual concentrations of 1.8 ppb. However, if pebulate sulfoxide is assumed to have negligible binding

affinity for soil (Koc = 0), then the model predicts peak and annual concentrations of 44 ppb; this is an extremely conservative assumption that could be refined by the submission of environmental fate data (eg., Koc data on pebulate sulfoxide). The registrant must provide information to permit refinement of the ground water exposure estimates, particularly of pebulate sulfoxide, so that assumptions regarding the environmental fate properties need not be used.

The NAWQA database had only 4 pebulate detections in 3023 samples collected, with a maximum concentration of 0.005 ppb. In 3197 samples in the STORET database, no pebulate residues were detected. Out of the 3197 samples, 2790 were collected by the USGS NAWQA program, while 2 were collected in Kentucky and 405 were collected in Georgia in the early 1990s. Both of the states are areas of known pebulate usage, but the sample collection was not necessarily timed to pebulate application.

4.2.2.3 Acute and Chronic DWLOCs

Drinking Water Levels of Comparison (DWLOCs) represent the maximum contribution to the human diet, in mg/kg/day, that may be attributed to residues of a pesticide in drinking water after dietary exposure and, in the case of chronic exposure, residential exposure are subtracted from the aPAD or cPAD. In the case of pebulate, there is no residential exposure. Acute and chronic DWLOCs for pebulate were calculated using anticipated residues in food. These are presented in Tables 4 and 5. Comparisons are made between DWLOCs and the estimated concentrations of pebulate + pebulate sulfoxide in surface water and ground water generated via PRZM/EXAMS and SCI-GROW, respectively. Note that the contribution of residues in food are extremely small in comparison to the aPAD and cPAD, in effect rendering the available water exposure identical to the aPAD or cPAD.

Table 4. Summary of Chronic DWLOC Calculations.

Population Subgroup	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	SCI-GROW (μg/L)[a]	PRZM/ EXAMS (ppb)	DWLOC (μg/L)
U.S. Population	0.007	0.000003	0.007	44/1.8	2.6	245
Females 13-50 yr	0.0007	0.000002	0.0007	44/1.8	2.6	21
All infants[b]	0.0007	0.000001	0.0007	44/1.8	2.6	7
Children 1-6 yr	0.0007	0.000005	0.0007	44/1.8	2.6	7

Population Subgroup	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	SCI-GROW (μg/L)[a]	PRZM/ EXAMS (ppb)	DWLOC (μg/L)
Children 7-12 yr	0.0007	0.000004	0.0007	44/1.8	2.6	7

[a]The figure 44 ug/L assumes greater soil mobility (Koc = 0) than molinate sulfoxide whereas 1.8 ug/L assumes that the mobilities of pebulate sulfoxide and molinate sulfoxide are the same.
[b]All infants includes the population subgroups: All infants <1 yr, Nursing infants <1 yr, and Non-nursing infants <1 yr. Food exposure was the same for all three infant population subgroups.

Table 5. Summary of Acute DWLOC Calculations.

Population Subgroup	aPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	SCI-GROW (μg/L)[a]	PRZM/ EXAMS (ppb)	$DWLOC_{acute}$ (μg/L)
U.S. Population	0.5	0.000134	0.5	44/1.8	40	17500
Females 13-50 yr	0.05	0.000099	0.05	44/1.8	40	1500
All infants[b]	0.05	0.000126	0.05	44/1.8	40	500
Children 1-6 yr	0.05	0.000197	0.05	44/1.8	40	500
Children 7-12 yr	0.05	0.000200	0.05	44/1.8	40	500

[a]The figure 44 ug/L assumes greater mobility than molinate sulfoxide whereas 1.8 ug/L assumes that the mobilities of pebulate sulfoxide and molinate sulfoxide are the same.
[b]All infants includes the population subgroups: All infants <1 yr (0.000107), Nursing infants <1 yr (0.000050), and Non-nursing infants <1 yr (0.000126); parenthetic numbers are food exposure in mg/kg/day). The highest food exposure is presented in the table.

Chronic DWLOCs. Upon comparison of the chronic DWLOCs with the environmental concentrations of pebulate + pebulate sulfoxide estimated using conservative modeling, surface water concentrations are less than the DWLOCs (Table 4). If mobility is assumed to be equivalent to molinate sulfoxide, ground water concentrations are also estimated to be less than the chronic DWLOCs. However, if the mobility is assumed to be much greater (conservative

assumption of Koc = zero), then the estimated concentration of pebulate + pebulate sulfoxide in ground water exceeds the chronic DWLOC for infants, children, and females (13-50 yr). Thus, there appears to be the slight potential for pebulate residues in ground water to occur at levels of concern, i.e., >DWLOC of 7 or 21 ppb (see Table 4). However, residues this high are not supported by extensive ambient water monitoring data (see 4.2.2.1 and 4.2.2.2 above). Uncertainties in the water assessment include lack of knowledge of the environmental fate properties of pebulate sulfoxide and inability to accurately estimate the volatilization rate of pebulate. Environmental fate properties of pebulate sulfoxide (such as Koc) would permit refinement of these conservative modeling estimates

Acute DWLOCs. Acute DWLOCs greatly exceed even the most conservative estimated environmental concentrations in both surface water and ground water (Table 5). This indicates that there is no acute dietary concern for pebulate residues in drinking water.

4.3 OCCUPATIONAL EXPOSURE

Pebulate, a single use pre-plant/pre-emergent herbicide, is formulated only as an emulsifiable concentrate containing 6 pounds of active ingredient per gallon as indicated in Table 6 It is only used in agriculture to control germinating weeds on tobacco, sugar beets, and tomatoes. There are no residential uses or products available for sale to homeowners.

Applications are made using common ground-based agricultural equipment. Aerial application is not allowed. If pebulate is applied using common groundboom equipment, it must be incorporated into the soil during or immediately after application to prevent volatilization and ensure efficacy as the vapor pressure is relatively high (8.9×10^{-3} mm Hg at 25°C). It can be also applied below the surface of the soil to prevent volatility using subsurface sweeper application (tobacco only) or using soil injection methods. Applications of pebulate in irrigation water are also allowable (referred to as chemigation). If pebulate is applied during irrigation, it must be watered in with approximately ½ inch of water (per the label) to ensure that it penetrates the surface of the soil to depths between 2 to 4 inches. Pebulate can also be mixed and applied along with fluid fertilizer to tomatoes and tobacco or it can be impregnated on dry bulk fertilizer for application to tobacco. Soil incorporation is also required after the application of pebulate in either liquid or dry fertilizers. The addition to dry bulk fertilizer is an allowable, but uncommon practice. In this case, pebulate is added to the fertilizer with a "closed rotary-drum mixer or a similar type of closed blender equipped with suitable spray equipment."

The Agency believes that those involved in the application can be exposed. These people are generically referred to as handlers and represent those who prepare spray solutions and fertilizer mixtures for use (i.e., referred to as mixer/loaders) and those who actually make the applications by driving the groundboom tractor or other piece of application equipment (referred to as applicators). Worker exposures are not thought to occur to pebulate in any agricultural setting after application because it is soil incorporated and because there are no apparent cultural

practices in the treated crops that are thought to lead to exposures. According to the label, workers can re-enter a pebulate treated field 12 hours after application. Any worker entering the field before that time must wear personal protective equipment if coming in contact with treated soil (i.e., hoeing tomatoes or plug planting into treated soil).

Table 6. Summary of Use Patterns/Formulations Information Relevant to Occupational Exposure/Risk Assessment

Formulation Type, % ai range in product	Equipment used for mixing/loading and application	Use Sites	Application rate range	Timing and frequency of applications	Comments
Emulsifiable Concentrate 6 lb a.i./gal	chemigation equipment	Tomatoes	4 - 6 lb ai/A	1 X / season	pre-emergent herbicide; must be soil-incorporated for efficacy. Post-emergent/after transplant, on tomatoes only, applications must be swept to cover.
	groundboom sprayer	Tomatoes Tobacco Sugar Beets	3 - 10 lb ai/A (10 lb ai/A is tomato only)	1-2 X / season	
	Drop type tractor drawn spreader, specialized truck, soil injection equipment	Tobacco	4 lb ai/A (dry bulk fertilizer application)	1 X / season	
	Specialized equipment	Tobacco, Tomatoes	4-10 lb ai/A (bulk fluid fertilizer application)	1 X / season	

4.3.1 Handler

The Agency has determined that there are potential exposures to mixers, loaders, and applicators when using pebulate. Again, mixer/loaders are the people who prepare spray solutions and applicators are the workers who drive the tractors with sprayers during application. Based on the labels and crop-specific use information, the following kinds of exposures were associated with the use of pebulate:

- mixing/loading emulsifiable concentrates for chemigation, soil injection, and groundboom application;
- mixing/loading emulsifiable concentrates for impregnation on dry bulk fertilizer;
- mixing loading emulsifiable concentrate for combination with fluid fertilizer;
- applying with a groundboom sprayer;
- applying liquid by soil injection; and

- applying dry and liquid fertilizers, treated with pebulate.

These 6 exposures scenarios were further sub-divided into 20 exposure sub-scenarios with varying application rates and crops for risk assessment purposes. A scenario is a way to describe how exposures occur in a specific setting. For example, pebulate scenarios include considering exposures to an applicator using a groundboom sprayer tomatoes in the western region of the United States.

The Agency classifies these as short-term exposures (one-week or less) and intermediate-term exposures (seven days to several months). Although pebulate is applied mostly once per season, some applicators may apply pebulate over a period significantly exceeding one week because they need to cover large acreage or they may be custom or professional applicators. Typically the Agency conducts separate assessments for exposures less than one week, and greater than one week, for pesticides with the use patterns previously described. However, the toxicity studies for pebulate indicate that effects are similar for these periods, so they will be considered together. The toxicity information for pebulate also indicates that the Agency needs to separately consider exposures to the skin and exposures via inhalation because it causes different effects when it gets on your skin compared to being inhaled.

Generally, the Agency prefers to use chemical- and scenario-specific data to assess occupational exposures. In the absence of these data, the Agency uses monitoring data from similar exposure scenarios that have been collected and incorporated into a system known as the Pesticide Handlers Exposure Database (PHED).

In the case of pebulate, the registrant submitted an exposure study of a handler using groundboom application for the compound cycloate, which is similar to pebulate (i.e., mixer, loaders and applicators were the same person in some of the data). This study used biological monitoring (urine collection) to assess exposures to people during application to sugar beets. It was submitted to the Agency to support the reregistration of several herbicides, known as the thiocarbamates, including pebulate. The Agency reviewed this study and found it inadequate for risk assessment purposes because of the way the study was designed and conducted. It was very difficult to interpret. For example, seventeen people were monitored in the study and each individual applied the pesticide in a slightly different manner using different levels of protective equipment and at varying rates (from 1.7 to 3.2 lb ai per acre). However, the study was used by the Agency to provide a frame of reference (i.e., referred to in the risk assessment process as risk characterization) because it indicates that workers are exposed during use and, to some extent, it shows the level of the exposure of workers using pebulate.

PHED, a library of actual exposure monitoring data that can be used to analyze specific types of exposures for those individuals involved in the application of pesticides (e.g., mixer/loaders, applicators), was used for all of the quantitative risk assessments that were completed for pebulate. This system has been in use worldwide since 1992 and was developed by a task force that includes the EPA, Health Canada, the California Department of Pesticide Regulation, and

the pesticide industry. The scientific basis for PHED has long been accepted by these groups. PHED forms the backbone of the vast majority of handler risk assessments completed by the Agency. The system now contains data from approximately 1700 exposures which were monitored when individuals were making actual pesticide applications in a variety of settings.

The basis of PHED is that individual handler exposures are related to how an application is made and not the specific pesticide being applied. The aspects of an application that are thought to affect exposures include: the kinds of equipment involved in application; the nature of the product being used (e.g., formulation and packaging); the application parameters such as application rate and total pounds of active ingredient applied; and the devices used by an individual to protect themselves during an application (e.g., additional clothing, chemical-resistant gloves, and closed tractor cabs).

The values that are calculated using PHED are called unit exposures and are generally presented as milligrams (or 1/1000th of a gram) exposure of active ingredient per pound active ingredient applied. For example, if one makes similar groundboom applications of 10 pounds of pesticide A or B, the unit exposures (1/10th of the exposure from applying 10 pounds of active ingredient A or B) would be proportional to the total amount applied and not whether pesticide A or B was in the spray tank. Separate unit exposures are typically calculated for the different equipment types that can be used in applications (e.g., open-cab groundboom and airblast applications would have different unit exposures). Separate unit exposures are also calculated for varying protective measures used during application with the same equipment. For example, there are specific unit exposures for groundboom applications for individuals wearing normal work clothing, wearing normal work clothing under coveralls and with gloves, and for making applications using a closed cab tractor. In cases where data are not complete, the Agency uses available data and standard measures of protection to estimate exposure levels. For example, the agency believes that the use of a coverall or a pair of chemical-resistant gloves provide a certain amount of protection when worn. These levels of protection and similar exposure data are used to calculate exposures where directly applicable data are not complete.

Along with the exposure values considered in the risk assessment (obtained from PHED), other information is needed to calculate the risk. Values needed are application rates, number of acres treated per day, body weight, and frequency of application. Amount of active ingredient handled per day is based on the number of acres treated and the application rate. These values are coupled with the unit exposures to calculate the daily exposure to the worker.

Initially the Agency calculates the risk using the least amount of protective measures, which is called the baseline assessment. For those involved in applications this usually represents an individual's normal work clothing, i.e. long sleeve shirts, long pants, no gloves, and no respirator. If there is a concern at this level, the Agency would require the use of devices to lower the risk. The first kinds of devices we would require are refereed to as personal protective equipment (PPE). PPE can include an extra layer of clothing, chemical-resistant gloves, and respirators. If concerns persist, then the Agency would require additional protective measures often described

as engineering controls. Common examples of engineering controls include enclosed tractor cabs, closed loading systems, and gel packs. This approach is commonly referred to as a tiered approach, and is well established in the area of risk assessment.

Product labels generally specify a certain level of PPE. However because the labels for older products are generally not based on a risk assessment, the Agency must begin its assessment assuming baseline measures and increase those measures until an acceptable level is obtained. Therefore any proposed label modifications will be based on this risk assessment instead of standard label recommendations.

Toxicology tests are required for all pesticides in order to define numerical endpoints that can be used in the risk assessment process. The kinds of tests that are completed are based on how chemicals enter the body (e.g., orally, through the skin, or by breathing), how long one is exposed, and the levels of exposures one might expect. The findings of these tests define the kinds of exposure and risk assessments that are completed. These endpoints are then compared to the exposures that reflect what workers do to calculate risks (i.e., referred to as MOEs or Margins of Exposure). The higher the MOE, the less the concern over the use. Typically, for workers, the Agency has concerns for MOEs that are less than 100 (i.e., anything less than 100 represents a level of concern). The 100 accounts for differences between the animals used for the toxicity tests and people (inter-species) as well as the differences that canoccur among peopleintra-species). The available toxicity data indicate that pebulate can cause different effects when it gets on the skin and when it is inhaled. Likewise, workers are thought to be exposed because they use pebulate on single, isolated days i.e., referred to as short-term exposures, representing 1 to 7 days) and for several days in a row, typically in the intense planting season (i.e., referred to as intermediate-term exposures, for pebulate this represents 1 week to 25 days of use). hese use patterns are similar to what the Agency would anticipate for all agricultural use herbicides. ased on the toxicity studies, both short term and intermediate term exposures create similar responses and are assessed together. Differences occur in responses seen for the different types of exposure, therefore, two types of assessments were completed for pebulate to represent dermal exposure and inhalation exposure (1) both single day and intense planting season exposures to the skin, and (2) both single day and intense planting season exposures from inhalation.

The results of the risk assessment indicate that, at a baseline mitigation level, risks to applicators will not exceed the Agency's level of concern for any scenario with the exception of dry bulk fertilizer applications to tobacco; this scenario requires that an organic vapor respirator be worn by the applicator. Mixer and loader scenario results indicate that pebulate can be mixed and loaded with the use of PPE (long sleeved shirt, long pants, plus coveralls, chemical resistant gloves and an organic vapor respirator). A detailed summary of results is presented in Table 7. **Note that the risk assessments are identical for short-term and intermediate-term exposure durations.**

Table 7. Summary of Short-Term and Intermediate-Term Risks: MOEs for Dermal and Inhalation Scenarios.

Exposure Scenario (Scen. #)	Crop Type/Use	Acres Treated or Amount Handled per Day	Application Rate (lb ai/A)		*Baseline MOE		*PPE MOE		*Engineering Controls MOE	
					Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation
Mixer Loader Exposures										
Mixing/Loading Emulsifiable Concentrate for Chemigation (1a)	Tomatoes	350 acres	6 lb ai/acre		1	25	**200**	**250**	NA	NA
			4 lb ai/acre		2	37	**290**	**370**	NA	NA
Mixing/Loading Emulsifiable Concentrate for Soil Injection and Groundboom Application (1b)	Tomatoes (Western Region)	80 acres	10 lb ai/acre		3	65	**510**	**640**	NA	NA
	Sugar Beets, Tomatoes, Tobacco		6 lb ai/acre		5	**110**	**860**	NA	NA	NA
			4 lb ai/acre		8	**160**	**1300**	NA	NA	NA
	Tobacco		3 lb ai/acre		10	**220**	**1700**	NA	NA	NA
Mixing/Loading Emulsifiable Concentrate for Impregnation on Dry Bulk Fertilizer (Closed System) (1c)	Dry Bulk Fertilizer (assuming 40 ten ton trucks loaded per day)	3,200 lb ai/day	4 lb ai/acre	1,000 lb fertilizer/acre	NA	NA	NA	NA	**250**	**230**
		1,600 lb ai/day	4 lb ai/acre	2,000 lb fertilizer/acre	NA	NA	NA	NA	**510**	**470**
Mixing/Loading Fluid Formulation for Combination with Liquid Fertilizer (1d)[a]	Fluid Fertilizer	No Data	10 lb ai/acre	10 gallons fertilizer/acre	No Data	No Data	No Data	No Data	No Data	No Data
		No Data	10 lb ai/acre	20 gallons fertilizer/acre	No Data	No Data	No Data	No Data	No Data	No Data
		No Data	10 lb ai/acre	40 gallons fertilizer/acre	No Data	No Data	No Data	No Data	No Data	No Data

Exposure Scenario (Scen. #)	Crop Type/Use	Acres Treated or Amount Handled per Day	Application Rate (lb ai/A)	*Baseline MOE		*PPE MOE		*Engineering Controls MOE	
				Dermal	Inhalation	Dermal	Inhalation	Dermal	Inhalation
Applicator Exposures									
Applying with a Groundboom Sprayer (2)	Tomatoes (Western Region)	80 acres	10 lb ai/acre	**630**	**110**	NA	NA	NA	NA
	Sugar Beets, Tomatoes, Tobacco		6 lb ai/acre	**1000**	**180**	NA	NA	NA	NA
			4 lb ai/acre	**1600**	**260**	NA	NA	NA	NA
	Tobacco		3 lb ai/acre	**2100**	**350**	NA	NA	NA	NA
	Fluid Fertilizer		10 lb ai/acre	**630**	**110**	NA	NA	NA	NA
Applying Dry Bulk Fertilizer with a Drop Type Tractor Drawn Spreader (3)	Dry Bulk Fertilizer	80 acres	4 lb ai/acre	**2200**	**160**	NA	NA	NA	NA
Applying Bulk Fertilizer with a Specialized Truck (4)	Dry Bulk Fertilizer	500 acres/day	4 lb ai/acre	**350**	26	NA	**260**	NA	NA
Applying Fluid Fertilizer with Specialized Equipment (5)[b]	Bulk Fluid Fertilizer	No Data	10 lb ai/acre	No Data	No Data	No Data	No Data	No Data	No Data
Soil Injection (6)[b]	Dry Bulk Fertilizer	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data

* NOTE: For occupational risk,MOEs greater than 100 are considered above the Agency's level of concern

a No data exists in PHED for mixer/loader combining pebulate with a liquid fertilizer. Therefore, no MOEs could be calculated.

b No data exists in PHED for applicators using specialized equipment for the application of a combination of pebulate and fluid fertilizer and for application by soil injection. Therefore, no MOEs could be calculated

The results of the risk assessment indicate that concerns over exposure from inhaling pebulate can be addressed for all exposures considered through the use of protective measures such as organic vapor respirators or closed systems. No respiratory protection is required for many workers using pebulate. MOEs for these people range from 110 to 350. Organic vapor respirators are required for workers who use chemigation to treat large acreage and those who prepare spray solutions for applications to tomatoes at very high rates in the western region of the United States. MOEs for workers wearing respirators range from 250 to 640. The preparation of large quantities of dry bulk fertilizer coated with pebulate requires the use of a closed loading system. This label modification is thought to be very practical considering the nature of how pebulate is used in these settings and the equipment that is typically required for preparation of bulk quantities of fertilizer. MOEs for these workers range from 230 to 470.

For dermal exposures, the results of this risk assessment indicate that concerns for worker exposure can be addressed in all of the worker scenarios. All pebulate loading scenarios for groundboom equipment do not exceed the Agency's level of concern with the use of PPE (i.e., long pants, long sleeved shirt, chemical resistant gloves, coveralls). The MOEs for the mixer/loaders using PPE range from 200 to 1700. The MOEs for the pebulate applicator exposures are greater than 100 at baseline (range is 350 to 2200). The remaining scenario, mixing and loading emulsifiable concentrate for impregnation of dry bulk fertilizer with a closed mixing system, has an MOEs greater than 100 (range is 250 to 510). .

Occupational Handler Characterization

Information used in this risk assessment was obtained from the pebulate product label, from PHED and other Agency offices. Maximum application rates stated on the label were used along with more typical use rates to help characterize the range of worker exposures. The range of application rates used in the risk assessment correspond directly with the 1990 through 1996 quantitative use analysis for pebulate for pebulate conducted by the Biological and Economic Analysis Division of OPP. PHED values are characterized as central tendency, and so do not represent the worst or best case of worker exposure. Further, the PHED unit exposure values for many of the scenarios was graded as AB grade, i.e., the unit exposure values were generated using high quality analytical techniques. Most of the scenarios used from PHED also had many replicates, which increases the confidence in the data and better represents the worker exposure. One mixer/loader and two applicator scenarios did not have corresponding exposure unit values in PHED or any study data. These scenarios were not evaluated in this risk assessment (mixing/loading for combination with fluid fertilizer and applying bulk fertilizer combination with specialized equipment and soil injection applications). Based on the calculations for the other scenarios, the mixing and loading of large quantities (≥800 lb ai) and the application of high rates (10 lb ai/A) would likely achieve a level of concern for worker exposure. When the biomonitoring study data from the cycloate study is used to calculate the MOE for worker exposure, the average unit exposure value results in an MOE of 580 and the geometric average unit value results in an MOE of 1500; these reflect total exposure as reflected by biomonitoring compared to the dermal endpoint, which was the most sensitive endpoint. The similarities in the

MOEs help to further characterize this risk assessment representing worker exposure. Considering the quality of the values used and the information on actual use rates, this risk assessment is thought to well represent worker exposure to pebulate.

4.3.2 Post-Application Exposure

The Agency generally completes risk assessments for those individuals who can be exposed from entering previously treated areas to work (i.e., referred to as post-application exposures). The most common examples of these kinds of exposures are farmworker activities such as picking grapes or citrus. When these kinds of assessments are completed by the Agency, the cultural practices of the crop and the reason for using the chemical are considered. Pebulate is a pre-plant/pre-emergent herbicide that is applied only to sugar beets, tobacco, and tomatoes. The Agency does not believe that there are any post-application exposure concerns over the use of pebulate on sugar beets. Likewise, the Agency did not complete a risk assessment on tomatoes and tobacco because there are no major activities that contribute to post-application exposure. According to the label, workers can re-enter a pebulate treated field 12 hours after application. Any worker entering the field before that time must wear personal protective equipment if coming in contact with treated soil (i.e., hoeing tomatoes or plug planting into treated soil). Current pebulate labels address this issue with the following language:

> "... mechanical transplanting only. DO NOT apply Tillam 6-E prior to hand transplanting."

However, there are some types of tomato and tobacco transplanting that may involve human contact with freshly treated soil even though the process is described as being mechanical in nature. Label changes to eliminate this possible exposure by requiring direct seeding instead of mechanical transplanting would be considered by the Agency. If the label is not modified, Zeneca (the registrant) must provide additional information on how transplanting in tobacco and tomatoes occurs in relation to pebulate use.

4.4 RESIDENTIAL EXPOSURE

There are no products containing pebulate that may be used in a residential setting. Therefore, no exposure and risk assessment is necessary for residential scenarios. The Agency recognizes there are many issues related to the use of agricultural chemicals and exposures in the general population. For example, the issues of spray drift and exposures to farmworker children are often raised. We note, however, that application methods do not include aerial or airblast; as a result, drift is expected to be minimized. The Agency is in the process of developing guidance and procedures for characterizing these kinds of exposures. They are not addressed in this document. This guidance will be included in our upcoming revised SOPs for Residential Exposure Assessment anticipated in 1999.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Risk

Acute aggregate risk estimates do not exceed HED's level of concern (aPAD of 0.5 or 0.05 mg/kg/day, depending on the population subgroup). The aggregate acute dietary risk estimates include exposure to pebulate residues in food and water. Anticipated residues derived from field trial data, percent-crop-treated data, and a probabilistic assessment were used to refine acute dietary risk (food only). Acute dietary risk to all population subgroups was calculated to be <1% of the aPAD. Although the most conservative assumptions (tolerance level residues and 100% crop treated) resulted in risk below the Agency's level of concern, refinements were made to permit a more realistic calculation of DWLOCs and in anticipation of a cumulative risk assessment. Estimated peak concentrations of pebulate residues in both surface water and ground water were well below the calculated DWLOCs for all population subgroups. Thus, pebulate is not expected to pose an acute risk of concern to any population.

5.2 Chronic (Noncancer) Aggregate Risk

Chronic (noncancer) aggregate risk may exceed the Agency's level of concern (cPAD of 0.007 or 0.0007 mg/kg/day, depending on the population subgroup) if the conservative assumptions to derive the pebulate sulfoxide estimated environmental concentrations in groundwater prove to be close to reality. There is no residential component to the aggregate risk because use of pebulate in residential settings is not expected. Risk contributed by the consumption of food is quite small: <1% of the cPAD for all population subgroups using anticipated residue and percent-crop-treated data. Although sufficient monitoring data are not available to permit quantitative inclusion of drinking water residues in the aggregate risk, very conservative modeled estimates of ground water concentrations of pebulate + pebulate sulfoxide suggest that infants, children, and women (13-50 yr) may be exposed to residues in water that exceed the Agency's level of concern. Ground water estimates may be refined if additional environmental fate properties of pebulate sulfoxide were available.

6.0 ENDOCRINE DISRUPTOR EFFECTS

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority-setting scheme to implement this program. When the program is implemented, EPA may require further testing of pebulate for endocrine effects.

7.0 CUMULATIVE EXPOSURE AND RISK

EPA does not have, at this time, available data to determine whether pebulate has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance reassessment, therefore, EPA has not assumed that pebulate has a common mechanism of toxicity with other substances.

8.0 DATA NEEDS

The following additional data requirements have been identified:

Toxicology

870.6300	Developmental Neurotoxicity in Rats

Product and Residue Chemistry

830.6313	Stability to Metals
830.7050	UV/Visible Absorption Spectra
860.1200	Directions for Use: 1. Increase tomato PHI from 8 days to 30 days. 2. Propose a 4-month plantback interval for all rotational crops.

Occupational and Residential Exposure

875.----	1. Provide information on occupational exposure during transplanting tomatoes and tobacco: The registrant must provide the Agency with exposure data or cultural practices information concerning pebulate use and planting techniques for tomatoes and tobacco. 2. Organic vapor respirators are required for people who use chemigation to treat large acreage and those who prepare spray solutions for applications to tomatoes at very high rates in the western region of the United States. The preparation of large quantities of dry bulk fertilizer coated with pebulate requires the use of a closed loading system.
.*	The registrant must provide information to permit refinement of the ground water exposure estimates, particularly of pebulate sulfoxide, so that assumptions regarding the environmental fate properties need not be used. This is to be jointly reviewed by HED and EFED.