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Director

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March 8, 2005

TO: INTERESTED PARTIES

SUBJECT: REQUEST FOR COMMENTS ON ACTIVE INGREDIENTS PRIORITIZED FOR RISK ASSESSMENT INITIATION

The purpose of this notice is to seek public comment on the choice of pesticide active ingredients prioritized for risk assessment initiation.

During the past year, the Department of Pesticide Regulation (DPR) has been implementing a revised process for the selection of active ingredients for risk assessment initiation in order to make the process more consistent, understandable, and transparent. The process was initially discussed with the Pesticide Registration and Evaluation Committee (PREC) in January 2004 and then released for public comment. After considering received comments, a final version, "Process for Human Health Risk Assessment Prioritization and Initiation," dated July 1, 2004, was made available on DPR's Web site. ([www.cdpr.ca.gov/docs/risk/raprocess](http://www.cdpr.ca.gov/docs/risk/raprocess)).

The current document presents the active ingredients that have been prioritized for risk assessment initiation, following the steps set forth in the above process. DPR did not delay the initiation of risk assessments due to this new process. As a result, risk assessments have already been initiated on chloropicrin, sulfuryl fluoride, and methyl iodide, and these active ingredients have been removed from consideration in the prioritization process.

### **Details of the Prioritization Process**

The Risk Assessment Prioritization Work Group (RAPWG) was formed to carry out this process and is made up of senior scientists from DPR's Medical Toxicology, Worker Health and Safety, and Environmental Monitoring Branches, as well as a senior scientist from both the Air Resources Board (ARB) and the Office of Environmental Health Hazard Assessment (OEHHA). A number of factors were considered in the prioritization process. These factors include physical-chemical properties (vapor pressure, environmental persistence, water solubility, soil binding, bioconcentration potential, etc.); toxicological properties (No Observed Effect Level/Lowest Observed Effects Level, NOEL/LOEL), severity of effect, number of effects, number of studies and species showing the effect, dose-response relationship, relevance of mechanism of action to humans, systemic vs. local effects, etc.); and exposure characteristics (types of exposures, amount of use, use patterns, number of crops and sites, locations of use, methods of application, types of formulations, illness surveillance data, availability of exposure data, etc.).



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At the first RAPWG meeting (August 20, 2004), twenty active ingredients were selected for more in-depth review. Primary consideration was given to active ingredients that were placed in the "High Priority" group by the Adverse Effects Advisory Committee (AEAP, many of the same members as the RAPWG); however, all active ingredients were open for consideration. Based upon input from all members of the work group, consensus was reached on the twenty active ingredients:

acrolein	aldicarb	boric acid
cyhalothrin	esfenvalerate	lindane
linuron	methomyl	methyl iodide
oryzalin	oxydemeton methyl	oxyfluorfen
paradichlorobenzene	phosphine-producing chemicals	
phosmet	phorate	propanil
propyzamide	sodium tetrathiocarbonate/carbon disulfide	
vinclozolin		

2,4-D was considered; however, the U.S. Environmental Protection Agency (U.S. EPA) is currently conducting a risk assessment on this compound. This is an in-depth assessment and includes advice and review by their Scientific Advisory Panel (SAP). Considerable scientific resources (that DPR could not match) have been devoted to this assessment and it was felt that DPR resources would be more effectively applied to other active ingredients. As a result, 2,4-D was not included in this initial prioritization process. The progress of U.S. EPA's risk assessment, as well as the potential positive impact of initiating a risk assessment at DPR, will be considered by the RAPWG during the next annual risk assessment prioritization process.

Following the August 20 meeting, information on each active ingredient was collected and distributed to the members of the RAPWG for review. This information included the Medical Toxicology Branch Summary of Toxicological Data for each active ingredient, toxicology fact sheets available from U.S. EPA, data on use, information on the status at U.S. EPA, data on physical-chemical properties, data on illness incidences and exposure characteristics, relevant information available from the Agency for Toxic Substances Disease Registry (ATSDR), and fact sheets from the Extension Toxicology Network (EXTOXNET) or the National Pesticide Information Center (NPIC). EXTOXNET is a cooperative effort of the toxicology extension programs of the land grant universities. NPIC is a cooperative effort of Oregon State University and U.S.EPA.

A second RAPWG meeting was held on October 7, 2004. At this meeting, there was extensive discussion of each of the twenty active ingredients. In addition, there was a consensus that organophosphates not be included in this round of prioritization. This decision was not based on a lack of concern; however, it was felt that the initiation of new risk assessments on additional organophosphates should be delayed until U.S. EPA has completed its assessments on these

materials, including the cumulative risk considerations under the requirements of the Food Quality Protection Act (FQPA). These assessments and the cumulative risk evaluation will likely result in a number of regulatory decisions or proposals by U.S. EPA. These decisions could have a significant impact on the use patterns of the various organophosphates. U.S. EPA is devoting extensive scientific resources to this effort and their decisions should occur in the near term, as required on the schedule established by FQPA. DPR's concentrating on other active ingredients will avoid duplication of effort and will allow DPR to focus on active ingredients that may be receiving less attention from U.S. EPA. As with 2,4-D, the organophosphates will be considered during the next annual risk assessment prioritization discussion, and inclusion will be reconsidered at that time.

In choosing the list of ten active ingredients, the RAPWG followed a consensus approach. As a first step, the group went through the list of twenty candidate active ingredients and identified those that everyone agreed should be on the list of ten. These compounds were methyl iodide, propanil, phosphine generating compounds, and sodium tetrathiocarbonate/carbon disulfide. The group then went through the remaining compounds, discussed each one, and reached consensus on whether it should be added to the list. The result was a list of eleven active ingredients. However, since a risk assessment on methyl iodide had just been initiated, it was removed from the list. As a result, the following active ingredients constituted the list of ten: acrolein, boric acid, esfenvalerate, linuron, methomyl, paradichlorobenzene, phosphine generating compounds, propanil, sodium tetrathiocarbonate/carbon disulfide, and vinclozolin.

Following the meeting, an approximately two-page draft document was prepared for each of the ten chemicals. Each document provides summaries of the toxicology data, physical/chemical and environmental characteristics, use information, and relevant exposure information. In addition, a summary of the RAPWG's rationale for prioritizing the chemical for risk assessment initiation is included. These documents are short summaries and are intended to provide some insight into the selection of the chemicals, as opposed to being comprehensive descriptions of the chemicals. A comprehensive description will be part of the risk assessment. It should also be noted that some of the toxicological conclusions and values (NOEL, LOEL) might change with the more in-depth evaluation that will take place in the risk assessment.

A unique situation arose with vinclozolin, one of the ten chemicals. In the course of preparing the summary, it was determined that use was being phased out federally and that legal use on lettuce was to end on November 30, 2005. Since 80 percent of the total of 22,664 pounds reported used in California in 2002 was on lettuce, a risk assessment on vinclozolin would be a waste of resources. The registrant provided DPR with the Federal Register notice that confirmed this phase out. Since DPR did not want to add another delay to the prioritization process to select another chemical and nine active ingredients would provide a sufficient pool, the RAPWG agreed to move forward with nine active ingredients.

The summaries (see Supporting Documentation at the end of this notice) were circulated to all members of the RAPWG for review, comment, and approval. In addition, the members were asked to confirm the choices for the chemicals to be prioritized for risk assessment prioritization. The members of the RAPWG were also asked to rank the chemicals from one to ten for risk assessment initiation, with one being the highest priority. The numerical rankings for each chemical were averaged to give an overall ranking. The final ranking is as follows:

### **Prioritized List of Candidate Active Ingredients**

1. Sodium tetrathiocarbonate
2. Paradichlorobenzene
3. Methomyl
4. Phosphine and phosphine generating compounds
5. Acrolein
6. Esfenvalerate\*
6. Linuron\*
6. Propanil\*
9. Boric acid

\* Esfenvalerate, linuron and propanil were tied in the overall ranking.

### **Recommendations on Initiation**

The prioritized list was presented to the PREC on January 21, 2005 for their input. DPR branch chiefs and senior scientific staff next considered the availability of resources in light of the risk assessments currently underway ([www.cdpr.ca.gov/docs/risk/riskproc](http://www.cdpr.ca.gov/docs/risk/riskproc)) and recommended the goal of initiating two new risk assessments in the coming year, as existing risk assessments are completed. They also recommended that if two new risk assessments are initiated, they be initiated on sodium tetrathiocarbonate and paradichlorobenzene. DPR management concurred with these recommendations. It is important to note that this is a best estimate for initiating risk assessments. Unforeseen circumstances, such as emergencies or changes to available resources, could affect the risk assessments that are initiated. However, both the risk assessments that DPR hopes to initiate in the coming year, as well as the ranked list of nine active ingredients, indicate DPR's planned risk assessment activity over the next couple of years.

### **Opportunity for Public Comment**

DPR is now seeking public comment on the choice of the nine active ingredients, their ranking, and the choice of the active ingredients on which DPR hopes to initiate risk assessments in the coming year. If you think an active ingredient should not have been included, please include the basis for your conclusions and indicate the active ingredient that should replace it. If you think a different active ingredient should have been included on the list, please indicate the basis for

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your conclusion and indicate the active ingredient that it should replace. The comment period will be open until April 22, 2005. Please send your comments by email to: <risk assessment prioritization@cdpr.ca.gov> or by regular mail to Dr. Jay Schreider, DPR Medical Toxicology Branch, P.O. Box 4015, Sacramento, California 95812-4015. DPR will consider all comments in its final decisions on risk assessment initiation.

Sincerely,

A handwritten signature in black ink that reads "Tobi Jones" with a stylized flourish at the end.

Tobi L. Jones, Ph.D., Assistant Director  
Division of Registration and Health Evaluation  
(916) 445-3984

Attachment

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Information Summaries for Prioritized Active Ingredients

#### Acrolein

CAS # 107-02-8

C<sub>3</sub>H<sub>4</sub>O

CH<sub>2</sub>=CH-CHO

Acrolein is a liquid with a pungent odor that readily dissolves in water. It can be found in soil, water, and air. It evaporates rapidly from water and soil and is reported to breakdown rapidly in air. It is highly volatile with a vapor pressure of 220 mm Hg at 20°C.

Acrolein's pesticidal use is primarily as an herbicide and algaecide, targeting aquatic weeds and algae. The primary use sites are aquatic areas and irrigation systems. Approximately 283,550 lbs. were reported used in California in 2002. Of this total, 22,648 lbs. were reported used in "water areas," 243,119 on "rights of way," and 16,398 in landscape maintenance. There is no agricultural crop use. Use has remained relatively stable over the last several years.

In addition to the pesticidal use, there are a number of other potential sources for exposure to acrolein. Acrolein is an important chemical intermediate used in the production of plastics, paints, etc (through the production of acrylic acid). Acrolein is a byproduct of the combustion of organic material. Thus, it is found in tobacco smoke and automobile exhaust. It is also the breakdown product of other pollutants. It may be found in hazardous waste sites. It is also found in small amounts in some foods (e.g., fried foods, roasted coffees). As a result of its somewhat ubiquitous nature, acrolein is of interest to other California Environmental Protection Agency (Cal/EPA) boards, departments, and offices besides DPR (including the Office of Environmental Health Hazard Assessment (OEHHA); the Air Resources Board (ARB), and the Department of Toxic Substances Control (DTSC). Acrolein is listed as a Toxic Air Contaminant (TAC) due to its identification by the U.S. Environmental Protection Agency (U.S. EPA) as a Hazardous Air Pollutant (HAP).

U.S. EPA is scheduled to complete a Reregistration Eligibility Document (RED) on acrolein in 2006. As part of the Air Toxics Hotspots Program, OEHHA has developed acute (0.19 ug/m<sup>3</sup>) and chronic (0.06 ug/m<sup>3</sup>) Reference Exposure Levels (RELs) for acrolein. The REL is the concentration level at or below which no adverse health effects are anticipated for a specified exposure duration. At the request of DPR, ARB is scheduled to initiate monitoring for acrolein in 2005 as part of the TAC monitoring program.

Acrolein is an acute respiratory and eye irritant. Sufficiently high exposures can result in death (LC<sub>50</sub> ranged from 58 to 300 mg/m<sup>3</sup> or 25 to 130 ppm). OEHHA's 1 hour REL of 0.19 ug/m<sup>3</sup> was based on eye irritation in a study on human volunteers.

More prolonged exposure to acrolein has resulted in nasal and respiratory lesions in animal studies. OEHHA's chronic REL of  $0.06 \text{ ug/m}^3$  was based on histopathological effects in the upper airways of rats exposed to acrolein by whole-body inhalation. A chronic oral study in dogs was reviewed by DPR and judged to have a No Observed Effect Level (NOEL) of  $0.1 \text{ mg/kg}$  for decreased thromboplast time. (A NOEL can be defined as the highest tested dose of a substance that has no observed effect.) A rat oral oncogenicity study was reviewed by DPR and indications of carcinogenicity in that study are under review. Lung lesions were seen in a rat gavage reproduction study; however, the respiratory effects may have been due to aspiration of the gavaged acrolein. Developmental effects were not indicated. Studies reviewed by DPR indicated mutagenic effects. Studies reviewed by DPR did not indicate chromosome effects or DNA damage; however, studies in the open literature did indicate such effects.

Acrolein was prioritized for risk assessment initiation due to its significant pesticidal use, high volatility, high acute toxicity by the inhalation route, and potential nonpesticidal exposures. Both OEHHA and ARB have an interest in these nonpesticidal exposures. It may be appropriate for DPR, OEHHA, and ARB to pursue a collaborative approach to the risk assessment of acrolein. This could result in the most efficient use of resources and a more complete picture of the overall risk.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Boric Acid

CAS # 10043-35-3

H<sub>3</sub>BO<sub>3</sub>

For the purposes of toxicity and risk evaluation, boric acid is grouped with its sodium salts. These salts include sodium tetraborate (Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>, borax) and its hydrates, sodium metaborate (NaBO<sub>2</sub>) and its hydrates, and disodium octaborate (Na<sub>2</sub>B<sub>8</sub>O<sub>13</sub>) and its hydrates.

Boric acid and its salts are registered for use as insecticides, algaecides, fungicides, herbicides, and wood treatments. It is used on a variety of agricultural and nonagricultural (including indoor residential) sites. As an insecticide, it functions as a stomach poison as well as an abrasive on insect exoskeletons. As an herbicide, it functions as a desiccant. Depending on the specific active ingredient and intended use, formulated products may be solids, crystalline rods, powders, dusts, gels, liquids, pastes, baits, and granules. Over 1.4 million pounds of boric acid and its salts were reported sold in California in 2002.

In addition to medicinal uses (primarily as a disinfectant), the nonpesticidal uses of boric acid and its salts are extensive and include use in a variety of industrial processes as well as fire control. In addition, boric acid and its salts are ubiquitous in the environment, due to the ubiquitous nature of boron in the environment. Boron occurs naturally in water, fruits, and vegetables. Boric acid and its salts are solids. Boric acid has a low volatility, is stable in the environment, and highly soluble in water. U.S. EPA completed a RED on boric acid in 1993 and is scheduled to complete a Tolerance Reregistration Eligibility Document (TRED) in 2005.

Boric acid has a relatively low acute toxicity by the oral route, with LD<sub>50</sub>s well over 1000 mg/kg in laboratory animals. However, lethality has occurred in infants after oral ingestion of amounts in the range of 3-6 grams. The dermal toxicity of boric acid is low for intact skin, due to the low dermal absorption. However, absorption in damaged skin occurs much more readily. Earlier uses of boric acid in baby powder resulted in fatalities. The ocular toxicity of boric acid and most of its salts is low; however, sodium tetraborate is highly toxic to the eye.

In laboratory animals, boric acid has been shown to cause reproductive and developmental toxicity. In oral chronic and subchronic toxicity studies in dogs, boric acid caused testicular atrophy and adverse effects on sperm. In rat oral chronic toxicity studies, boric acid and its salts again caused testicular atrophy with NOELs in the range of 350 ppm (in food) in terms of elemental boron. A mouse oncogenicity study indicated a NOEL of 2500 ppm boric acid for testicular atrophy. There were no indications of oncogenic effects and U.S. EPA has classified boric acid as a Group E, evidence of noncarcinogenicity. In a multi-generation rat reproduction study, testicular atrophy, lack of viable sperm, and impaired reproduction were noted. The NOEL was judged to be 150 mg/kg by USEPA in their RED. In a mouse reproduction study, a variety of adverse testicular and reproductive effects were seen with a NOEL of 1000 ppm boric

acid. In a rat developmental toxicity study, boric acid caused developmental effects (increased incidence of wavy ribs, shortened rib, and reduced fetal weight) at a NOEL of 0.075 % boric acid in the diet. A rabbit developmental toxicity study indicated a NOEL of 62.5 mg/kg for a variety of malformations. Likewise, a mouse developmental toxicity study indicated malformations. Genotoxicity studies were generally negative.

Human epidemiology studies of occupationally exposed individuals did not indicate adverse impacts on fertility; however, the studies did have limitations.

Boric acid was originally assigned a moderate priority in the “Prioritization and Status of Active Ingredients for Risk Characterization,” due to the relatively high levels at which adverse effects occurred. However, while the developmental and reproductive effects occurred at relatively high dose levels, the effects were repeatable in a variety of animal species and the same species in different studies. There is use in a variety of settings, including indoor residential use. In addition, boric acid has often been put forward as a “safe” alternative to other pesticides in these same settings, which could lead to less careful use practices, resulting in potentially high exposures. With this in mind, it was judged to be prudent to evaluate the associated risks from these various uses, therefore, boric acid was prioritized for risk assessment initiation.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Esfenvalerate

CAS # 66230-04-4

(S)-alpha-cyano-3-phenoxybenzyl(S)-2-(4-chlorophenyl)-3-methylbutyrate

Esfenvalerate is a synthetic pyrethroid insecticide and has replaced the pesticide fenvalerate, which differs in the proportion of four isomers. Esfenvalerate has a higher percentage of the insecticidally active isomer. The registration of esfenvalerate is supported by toxicity data on fenvalerate and esfenvalerate.

Esfenvalerate is used on a variety of pests and in a variety of sites. The agricultural products are used on a wide variety of crops. Residential/consumer uses include such products as yard sprays, foggers, ant and roach killers, wasp and hornet sprays, multi-purpose insect killers, kennel sprays, etc. Approximately 31,000 pounds were reported used in California in 2002. This total primarily reflects agricultural uses and does not reflect residential/consumer uses. Approximately 43,000 pounds were reported sold in California for the same year, which would include residential/consumer uses. Use has remained relatively stable.

Esfenvalerate is moderately persistent in soil with half-lives ranging from 15 days to 3 months. It binds to soil and is relatively insoluble in water, suggesting a low potential to contaminate groundwater. The pure compound is crystalline and the technical product is a liquid. It has a low vapor pressure.

Esfenvalerate has relatively low toxicity by the dermal route; however, dermal exposure has been associated with skin irritation. Skin lesions have also been seen in some chronic oral studies. An oral LD<sub>50</sub> in rats for esfenvalerate is listed as 458 mg/kg. Esfenvalerate is a Type II pyrethroid and interferes with nerve conduction by interfering with the sodium channels in the nerve membrane. Given this mode of action, it is not surprising that the primary toxic effects seen in animal toxicity studies relate to neurotoxicity. The NOELs for various signs and symptoms of neurotoxicity fall in the same basic range, regardless of whether the studies are acute, subchronic, or chronic.

The lowest acute NOEL is from a recent neurotoxicity Functional Observational Battery (FOB) study in rats, with a value of 1.75 mg/kg for signs including abnormal gait, diarrhea, tremors, etc. While developmental toxicity studies in rats and rabbits did not indicate developmental effects, the NOELs for maternal toxicity added to the database on acute toxicity. Rat and rabbit studies indicated NOELs of 2 mg/kg for symptoms of neurotoxicity, including abnormal gait, jerky movements, tremors, etc.

An oral subchronic rat study had a NOEL of 125 ppm in food (considering the estimated food intake, this is approximately equivalent to 6.25 mg substance/kg bodyweight) for similar signs of neurotoxicity. A subchronic neurotoxicity study in rats had a NOEL of 12.5 mg/kg for nerve

damage. A recently conducted rat oral subchronic neurotoxicity FOB study had a NOEL of 50 ppm (approximately 3.2 mg/kg) for neurotoxicity. Rat reproduction studies indicated a NOEL of 100 ppm (5 mg/kg) for signs of neurotoxicity and a NOEL 75 ppm (3.8 mg/kg) for skin lesions. A chronic oral rat study had a NOEL of 50 ppm (approximately equivalent to 2.5 mg/kg) for symptoms of neurotoxicity including jerky leg movements. A chronic oral dog study did not indicate adverse effects up to and including the high dose of 200 ppm (approximately equivalent to 5 mg/kg). A pilot study for this study indicated neurotoxicity at higher doses; therefore, the high dose of 200 ppm should be considered a NOEL. None of the chronic studies indicated oncogenic effects.

Overexposure of humans has been reported to include such symptoms as dizziness, burning and itching, blurred vision, convulsions, headaches, vomiting, etc.

Esfenvalerate was prioritized for risk assessment initiation due to its low NOELs for neurotoxicity in repeated studies in various animal species, and its use in a wide variety of situations including residential/consumer products.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Linuron

CAS # 330-55-2

3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea

Linuron is an herbicide in the substituted urea class. It is intended to control germinating and newly emerged grasses and broad-leafed weeds. It is registered for agricultural uses with no residential/consumer uses. Of the approximately 62,000 pounds reported used in California in 2002, approximately 52,000 pounds were reported used on carrots, 5,000 on asparagus, and 4,500 on celery. Reported use has gone down slightly over the last several years. U.S. EPA completed a Reregistration Eligibility Document in 1995 and a Tolerance Reassessment in 2002.

The pure compound is an odorless white solid with a low vapor pressure. Linuron is moderately persistent in soils with half-lives reported from 30 to 150 days, depending on the soils and conditions. It is generally immobile in soil, but mobility can increase under certain circumstances. It is slightly to moderately soluble in water and is moderately persistent. Because of its slight to moderate solubility, persistence, and mobility under some circumstances, it has the potential to impact groundwater.

Linuron does not have a high acute toxicity. Oral LD<sub>50</sub>s are reported in the range of 1200 to 2250 mg/kg in rats and rabbits. The dermal LD<sub>50</sub> in rabbits is reported to be greater than 5000 mg/kg. It is a skin sensitizer. The acute toxicity is also low by the inhalation route.

Dietary exposure of rats in a developmental toxicity study indicated a NOEL of 125 ppm (equivalent to approximately 6.25 mg/kg) for maternal effects (decreased weight gain) and developmental effects (slight increases in skeletal abnormalities). A gavage study in rabbits indicated a NOEL of 25 mg/kg for maternal toxicity (decreased weight gain, liver hypertrophy, increased abortions) and limited evidence of skeletal irregularities in the fetuses. While the evidence of developmental effects was limited, the maternal effects indicated increased toxicity with repeated doses, as compared to the acute toxicity. In a multigeneration rat reproduction study, nonreproductive effects (decreased body weight gain and food consumption) were seen with a NOEL of 12.5 ppm (equivalent to approximately 0.63 mg/kg). Various abnormalities of the testes were observed with a NOEL of 100 ppm (equivalent to approximately 5 mg/kg). In addition, increased estradiol and luteinizing hormone levels were seen at the high dose of 625 ppm (31 mg/kg) suggesting endocrine activity. Ocular lesions were seen at the high dose. Pup viability was reduced at 100 ppm. A follow up study supported the endocrine disrupting activity. Another multigeneration rat reproduction study indicated a NOEL of 25 ppm for decreased parental weight gain and a NOEL of 125 ppm for smaller litters and decreased survival of pups. An ancillary study to this latter study maintained some of the animals on treatment for two years and indicated testicular interstitial cell adenomas and hyperplasia at 125 and 625 ppm.

A dog chronic feeding study indicated a NOEL of 25 ppm (equivalent to approximately 0.63 mg/kg) for blood effects (blood cell turnover and destruction). A chronic rat feeding study indicated testicular interstitial cell adenomas and indications of blood cell turnover and destruction, with a NOEL of 50 ppm (2.5 mg/kg). An ancillary study, related to the prior study, also indicated testicular interstitial cell tumors. A mouse oncogenicity study indicated hepatic toxicity in both sexes as well as hepatocellular adenomas in females at 1500 ppm (225 mg/kg). Various studies did not indicate genotoxicity.

Linuron was prioritized for risk assessment initiation due to its relatively low NOELs for toxicity from repeated exposures, reproductive toxicity demonstrated in several studies, testicular adenomas seen in a repeated rat chronic toxicity study, and endocrine disrupting activity.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Methomyl

CAS # 16752-77-5

S-methyl-N-[(methylcarbamoyl)oxy] thioacetimidate

Methomyl is a broad-spectrum carbamate insecticide used on a variety of agricultural crops. Methomyl is a restricted use pesticide. It is also used in a fly-bait formulation for commercial establishments. In 2002, a total of approximately 322,000 pounds were reported used in California. Of this total, approximately 39,000 pounds were reported used on alfalfa, 38,000 on corn, 96,000 on lettuce, and 26,000 on tomatoes. Methomyl is also a degradate of another active ingredient, thiodicarb. However, the reported use of thiodicarb in California in 2002 was 5,000 pounds; making its contribution to the methomyl total insignificant. The reported use of methomyl has been steadily decreasing. U.S. EPA completed a Reregistration Eligibility Document (RED) in 1995.

Methomyl has a reported half-life of 14 days in soil. It is highly soluble in water and does not bind tightly to soil, suggesting the potential to contaminate groundwater. It is moderately persistent in soil, but is broken down by soil microbes. It is a white crystalline solid, has a sulfurous odor, and has a relatively low vapor pressure.

Since methomyl is a carbamate insecticide and inhibits cholinesterase enzymes, it is not surprising that its primary toxic effects involve the nervous system. It is highly acutely toxic by the oral route, with LD<sub>50</sub> values ranging from 10 to 24 mg/kg, depending on the species. Further, the NOELs for oral exposure (short term and long term exposure) are within an order of magnitude of the LD<sub>50</sub> values, indicating a steep dose-response curve. It is moderately toxic by the inhalation route and slightly toxic by the dermal route. As with other cholinesterase inhibitors, symptoms of overexposure may include such signs as weakness, blurred vision, headache, nausea, constriction of pupils, muscle tremors, muscle incoordination, breathing difficulties, loss of reflexes, paralysis, etc.

An acute oral (gavage) neurotoxicity (including functional observational battery, FOB) study in rats indicated a NOEL of 0.25 mg/kg for tremors and significant inhibition of brain cholinesterase. Clinical signs of toxicity disappeared after 24 hours, as might be expected for a carbamate. Another acute gavage neurotoxicity study in rats using a single dose of 1.0 mg/kg also indicated the relatively rapid reversibility of effects (tremors and cholinesterase inhibition). In a dietary subchronic neurotoxicity study in rats, similar signs of toxicity were seen, with a NOEL of 150 ppm (approximately equivalent to 7.5 mg/kg).

Dietary exposure in a rat developmental toxicity study indicated a NOEL of 100 ppm (approximately 5 mg/kg) for maternal toxicity (decreased body weight gain and decreased food consumption). Gavage exposure of rabbits in a developmental toxicity study resulted in a NOEL

of 2 mg/kg for maternal toxicity (various signs of neurotoxicity). Neither study indicated developmental toxicity.

In a multigeneration reproduction study in rats, the NOEL was 75 ppm (approximately 3.5 mg/kg) for decreased maternal food consumption, decreased pup weight, decreases in several maternal RBC parameters, increased weanling spleen weights, and clinical signs of neurotoxicity. A chronic rat feeding study yielded a NOEL of 100 ppm (equivalent to approximately 5 mg/kg) for decreased body weight, mild anemia (reductions in RBC parameters, bone marrow hyperplasia, extramedullary hematopoiesis). Another chronic rat feeding study resulted in a NOEL of 100 ppm for decreases in hemoglobin, extramedullary hematopoiesis, renal tubular dilation, hypertrophy, and vacuolation. A chronic dietary dog study had a NOEL of 100 ppm (approximately equivalent to 2.5 mg/kg) for hematologic changes, extramedullary hematopoiesis, renal tubular swelling and pigmentation, and spleen pigmentation. A mouse oncogenicity study had a NOEL of 75 ppm (approximately 11 mg/kg) for decreased blood parameters. While none of these chronic studies gave indications of oncogenicity, all had signs of indications of hematological problems that were remarkably consistent from study to study.

Methomyl was prioritized for risk assessment initiation due to its widespread agricultural use, its high acute toxicity, the steepness of its acute dose-response curve, its low NOELs for both neurotoxic effects and hematological effects, and the consistency of the hematological effects in different species and study types.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Paradichlorobenzene

CAS # 106-46-7

C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>

Paradichlorobenzene (PDCB) is also called 1,4-dichlorobenzene and goes by several other names. Its pesticidal uses include the control of moths (mothballs, moth crystals, etc.), flea and tick repellants for aviaries, and mildew control. Approximately 800,000 pounds were reported sold in 2002 in California for pesticidal uses. PDCB is also used to make air fresheners as well as toilet/urinal deodorant blocks, and is used industrially as an intermediate for such products as dyes and resins as well as in coating and engraving metal manufacturing.

PDCB is a white solid at room temperature with a strong odor. It slowly sublimates, going directly from a solid to a vapor. It has a vapor pressure of 0.9 mm Hg at 25° C and has an odor threshold of about 0.18 ppm in air and 0.011 ppm in water. It is only slightly soluble in water, but is soluble in acetone, alcohol, and other organic solvents. Depending on environmental conditions, PDCB may bind to soil and is not easily broken down by soil organisms. There is some evidence that it can be absorbed by fish and plants, suggesting the potential for bioaccumulation. It has a reported half-life of about one month in the atmosphere.

PDCB has been found at a number of hazardous waste sites. PDCB is listed as a Toxic Air Contaminant (TAC) due to its identification by U.S. EPA as a HAP. OEHHA has developed a cancer potency factor (1.1 E -03) and a chronic REL (800 ug/m<sup>3</sup>) for PDCB as part of its Air Toxics Hot Spots Program. ARB has proposed regulations to phase-out the use of PDCB in air fresheners and toilet/urinal blocks. The urinal/toilet blocks lead to the presence of PDCB in sewage waters and surface and ground waters. Through evaporation and wastewater treatment, the PDCB is transferred to the air. The blocks also release some PDCB directly to air and the air fresheners release all of the PDCB to air. The insecticidal uses of PDCB are regulated by DPR and will be the specific subject of this risk assessment.

ARB has monitored PDCB in air and has reported the results of other monitoring studies. Measurable levels of PDCB have been found outside of homes and in urban areas where air fresheners are used. ARB reports that the average measured atmospheric concentrations in 1993 in major population centers was 0.87 ug/m<sup>3</sup> (0.142 ppb). Indoor air concentrations are considerably higher and are due primarily to the use of PDCB products (obviously excepting workplace air where PDCB is manufactured or used in manufacturing). In fact, PDCB has been found to be almost ubiquitous in indoor air. In one study, indoor air concentrations averaged 25 ug/m<sup>3</sup> (4.2 ppb) with a maximum concentration of 1,600 mg/m<sup>3</sup> (267 ppb). Other studies produced similar results. PDCB has a relatively long half-life in the body, and body burden studies have indicated almost ubiquitous exposure of the general population.

PDCB is not highly acutely toxic. Oral LD<sub>50</sub> values are generally above 2,500 mg/kg. Inhalation LC<sub>50</sub> values were not available. Vapor exposure can cause eye and nose irritation. Inhalation exposure to extremely high levels can cause nervous system effects. In a rat inhalation developmental toxicity study, the NOEL for maternal toxicity (body weight and food consumption decrements, eyelids partially closed due to tonic muscle contraction) was 50 ppm, while the NOEL for developmental effects (delayed ossification) was 200 ppm. In a rabbit inhalation developmental toxicity study, the NOEL for maternal toxicity (decreased body weight gain) was 300 ppm.

In a rat inhalation multigeneration reproduction study, the maternal NOEL was 50 ppm (increased liver weight), the paternal NOEL was < 50 ppm (hyaline droplet nephropathy), and the reproductive/developmental NOEL was 150 ppm (increased perinatal death, decreased litter size, reduced pup weight). Chronic rat studies (inhalation and oral) demonstrated kidney tumors in males; however, the proposed mechanism is unique to male rat kidneys and may not be relevant to humans. The studies also indicated kidney toxicity with a LOEL of 150 mg/kg. A mouse oncogenicity study demonstrated liver tumors at 600 mg/kg and liver toxicity at 300 mg/kg. This liver toxicity has been seen in other mouse studies. PDCB has been classified as a probable human carcinogen by the National Toxicology Program (NTP) and is listed under Proposition 65 as known to the state to cause cancer. A chronic oral dog study demonstrated liver toxicity with a NOEL of approximately 10 mg/kg. This liver toxicity was also seen in several additional dog studies.

PDCB was prioritized for risk assessment initiation due to its carcinogenicity, its extensive use especially in indoor residential settings, its almost ubiquitous exposure of the general population, and the potential for widespread exposure of children in the home.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Phosphine and Phosphine Generating Compounds

CAS # 7803-51-2

PH<sub>3</sub>

Phosphine, a gas, is a fumigant and may be applied directly as phosphine. It may also be applied in the form of aluminum, magnesium, or zinc phosphide (solids), all of which generate phosphine gas upon exposure to moisture. Phosphine, aluminum phosphide, and magnesium phosphide are used to fumigate a wide variety of agricultural commodities. Aluminum phosphide is also used for vertebrate pest control, while zinc phosphide is used almost exclusively for vertebrate pest control (formulated as a bait). In 2002, approximately 165,000 pounds of aluminum phosphide were reported used in California, and this use level has been increasing. In 2002, approximately 5,000 pounds of magnesium phosphide were reported used in California, and this use level has likewise been increasing. In 2002, approximately 1,000 pounds of zinc phosphide were reported used in California, and this use level has been decreasing. In 2002, approximately 900 pounds of phosphine were reported used in California. All of the following discussion (toxicity, exposure, environmental fate), will pertain to the activity and characteristics of phosphine, the active principle in or resulting from all of the above compounds.

U.S. EPA completed a RED on aluminum and magnesium phosphide in 1998. OEHHA developed a chronic REL of 0.8 ug/m<sup>3</sup> for phosphine in 2002 as part of its Air Toxics Hot Spots Program. Phosphine is listed as a TAC due to its identification by U.S. EPA as a HAP.

Phosphine is a colorless gas at room temperature. Pure phosphine is odorless, but technical grade phosphine has a “fishy” or “garlicky” odor. Phosphine is only slightly soluble in water. Phosphine in soil will rapidly dissipate into the atmosphere. It is subject to photodegradation with a half-life in light of 5 hours. The dark half-life is approximately 28 hours. It is also rapidly broken down in the soil. It has a low potential for contaminating surface or groundwater and does not accumulate in the food chain.

Phosphine is a strong reducing agent and interacts with and inhibits cellular enzymes involved with metabolic processes. It is a strong respiratory irritant and can cause neurotoxicity. Ingestion of aluminum, magnesium, or zinc phosphide leads to the release of phosphine in the gastrointestinal tract and results in the rapid onset of gastrointestinal signs and symptoms. Overexposure of humans may cause headaches, dizziness, numbness, fatigue, nausea, vomiting, breathing difficulties, tachycardia, myocardial damage, pulmonary irritation, pulmonary edema, tremors, liver damage, kidney damage, and convulsions.

A 4-hour LC<sub>50</sub> in rats is reported to be 11 ppm. A 6-hour acute rat inhalation study had a NOEL of 11 ppm (highest dose tested, equivalent to 2.8 ppm for 24 hours based on extrapolating from the 6-hour exposure time of the study). A 3-day rat inhalation study had a Lowest Observed

Effect Level (LOEL) of 10 ppm (equivalent to 2.5 ppm for 24 hours) for lethality, kidney necrosis and pulmonary congestion. A LOEL can be defined as the lowest dose of a substance in a study at which an effect was observed. A 15-day rat inhalation study had a NOEL of 5 ppm (equivalent to 0.89 ppm based on extrapolating from the 6-hour a day, 5 days a week exposure times of the study), which was the highest dose tested. An acute rat inhalation neurotoxicity study had a LOEL of 20 ppm (equivalent to 3.3 ppm) for transient decreased motor activity and decreased body temperature (there was no NOEL). A rat developmental toxicity study had a NOEL of 5 ppm (equivalent to 1.3 ppm) for maternal toxicity for mortality at the next higher dose of 7.5 ppm (equivalent to 1.9 ppm). There were no developmental effects.

A 90-day rat neurotoxicity study had a NOEL of 3 ppm (equivalent to 0.54 ppm, highest dose tested). A 13-week rat inhalation study had a NOEL of 3 ppm (equivalent to 0.54 ppm, highest dose tested). A 13-week mouse inhalation study had a NOEL of 1 ppm (equivalent to 0.18 ppm) for decreased weight gain and an increase in relative organ weights. A 2-year rat chronic inhalation study had a NOEL of 3 ppm (equivalent to 0.54 ppm, highest dose tested). No effects were seen; however, previous studies indicated that higher dose levels would have resulted in lethality. Taken together, the results of the acute and subchronic studies indicate a steep dose-response curve.

Phosphine and phosphine generating compounds were prioritized for risk assessment initiation due to the consistently high acute toxicity, steep dose response curve, the potential for offsite movement from fumigation facilities, and the potential for bystander exposure through inhalation of ambient air.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Propanil

CAS # 709-98-8

3',4'-dichloropropionanilide

Propanil is a broad spectrum, post-emergent herbicide. In California, it is used almost exclusively on rice. It is applied both aerially and by ground boom. It is a California restricted material because it has a history of damage to crops in fields adjacent to the rice fields. Use has expanded significantly since 1997, due, in part, to changes in use regulations. In 2002, approximately 1,470,500 pounds were reported used in California. Of this total, all but about 300 pounds were reported used on rice. U.S. EPA published a risk assessment for propanil in 2002; however, this assessment did not address the risk to bystanders (people living near rice fields) from the offsite movement of propanil.

Propanil technical is a brown crystalline solid with a low vapor pressure ( $9 \times 10^{-7}$  mm Hg). It is rapidly broken down in the soil and water due to microbial activity. It has a field half-life of 1 to 3 days. It is soluble in water and only weakly adsorbs to soil particles, indicating soil mobility. Propanil has been found in surface water in California.

Propanil has relatively low acute toxicity. Reported oral LD<sub>50</sub>s are approximately 1000 mg/kg or higher for rats and dogs. It can cause eye and skin irritation. A reported 4-hour LC<sub>50</sub> in rats is 1.12 mg/L. In a rat developmental toxicity study, the maternal NOEL was 100 mg/kg, the highest dose tested. In a rabbit developmental toxicity study, the maternal NOEL was 20 mg/kg for increased mortality and decreased body weight at 100 mg/kg. The body weight changes were measured after 6 days of exposure; however, there is no way to tell if the effects occurred due to a single or multiple (6) exposures. Similar body weight changes were seen in rat pilot studies after similar timeframes, but with the same caveat regarding a single exposure. There are a number of studies in the open literature reporting the immunotoxicity of propanil after a single dose of propanil in rats and mice.

A 90-day oral study in rats indicated a NOEL of approximately 33 mg/kg for increased relative spleen weights and decreased hemoglobin levels. A 90-day oral study in mice indicated a NOEL of approximately 7 mg/kg for liver toxicity. A multigeneration oral rat reproduction study indicated a parental NOEL of 150 ppm in food (approximately equivalent to 7.5 mg/kg) for decreased body weight, increased spleen weights, increased brain weights, increased testes weights, increased adrenal weights, increased ovary weights, and increased pigmented spleen macrophages at 600 ppm. The reproductive NOEL was 150 ppm for decreased sperm counts. The pup NOEL was 150 ppm for increased liver and testes weights, decreased pup weights, and delayed vaginal perforation and balanopreputial separation. These latter effects, along with the testes and sperm effects, suggest the possibility of neuroendocrine disruption.

A chronic dog feeding study had a LOEL of 200 ppm (approximately equivalent to 5 mg/kg) for several hematological parameters (including methemoglobinemia and hemolysis RBC), decreased body weight gain, and increased hemosiderin pigment in the kidneys. A chronic oral rat study had a NOEL of 200 ppm (10 mg/kg) for non-oncogenic effects including decreased body weight, decreased food consumption, methemoglobinemia, increased spleen weights, congested spleen, various signs of liver toxicity, testicular hyperplasia, absent spermatozoa, prostate atrophy, and hemosiderin pigment in spleen and kidneys. There was also an increased incidence of testicular interstitial cell tumors in males and hepatocellular adenomas in females. An oral mouse oncogenicity study had a NOEL of 500 ppm (approximately equivalent to 75 mg/kg) for methemoglobinemia and increased spleen weights. There was also an increased incidence of malignant lymphoma. Genotoxicity studies were negative.

Propanil was prioritized for risk assessment initiation due to its relatively high use, its demonstrated potential for offsite movement, the potential for bystander exposure, including people living near rice fields, and its demonstrated long-term toxicity. This toxicity included methemoglobinemia and other blood effects, cancer, endocrine effects, and possible immunotoxicity.

## Supporting Documentation to Public Notice on Active Ingredients Prioritized for Risk Assessment Initiation

### Sodium tetrathiocarbonate/ Carbon disulfide

#### Sodium tetrathiocarbonate

CAS # 7345-69-9

Na<sub>2</sub>CS<sub>4</sub>

Sodium tetrathiocarbonate is applied by chemigation to the soil. It converts to carbon disulfide, sodium hydroxide, hydrogen sulfide, and sulfur in the soil. Carbon disulfide is the pesticide active compound and is a soil fumigant. In 2002, approximately 352,000 pounds of sodium tetrathiocarbonate were reported used in California. Of this total, approximately 315,000 pounds were reported used on grapes. This is a decrease from the 800,000 pounds reported used in 1997; however, it is still a relatively high use level.

Sodium tetrathiocarbonate was registered in California in 1994; however, it was not sent to the Adverse Effects Advisory Panel (AEAP) for risk assessment prioritization. It was also not sent to the AEAP in the intervening years. This was recognized in the course of the present process and it is now being prioritized for risk assessment initiation.

Both the parent compound and the conversion products will be addressed in the risk assessment. The toxicology data on file at DPR in support of registration are a mixture of studies on sodium tetrathiocarbonate and carbon disulfide (the pesticide active compound). Sodium tetrathiocarbonate and the other breakdown products are of less toxicological concern, while carbon disulfide and hydrogen sulfide are both of primary toxicological concern. Carbon disulfide and hydrogen sulfide have well-known toxicity profiles. In addition to data on file at DPR or in the open literature, OEHHA has developed both acute and chronic REL documents for both compounds. In addition, the Agency for Toxic Substances and Disease registry (ATSDR) has released detailed health assessments on both compounds. It should be noted that both carbon disulfide and hydrogen sulfide are released, along with Methyl Isothiocyanate (MITC), following the application of metam sodium. Risk assessments on metam sodium and MITC have already been completed by DPR.

#### Hydrogen sulfide

CAS # 7783-06-4

H<sub>2</sub>S

Hydrogen sulfide occurs as a result of numerous natural and anthropogenic processes. It is a gas at room temperature (vapor pressure of 15,000 mm Hg at room temperature) and is soluble in water. When hydrogen sulfide is released as a gas, it remains in the atmosphere for about

18 hours. Hydrogen sulfide exposure is reported to be the most common cause of sudden death in the workplace. Overexposure of people is of greatest concern when the exposure takes place in a confined space. A lethal exposure of people was documented at 600 ppm and concentrations greater than 200 ppm cause irritation of exposed body surfaces and pulmonary edema. In rats, a 4-hour LC<sub>50</sub> was estimated to be 440 ppm. Concentrations above 1000 ppm caused respiratory arrest in dogs after 15-20 minutes. Hydrogen sulfide has a strong and offensive odor and, depending on the study, the odor threshold for people ranged from 0.00007 to 1.4 ppm. Concentrations that significantly exceed the odor threshold can cause nausea, headache, eye, nose, and throat irritation, and signs of neurological effects. In establishing an acute REL (42 ug/m<sup>3</sup>), OEHHA estimated a 1-hour NOEL of ≤ 0.03 ppm in people for headache and nausea. Longer-term exposures of people have resulted in many of these same effects. A 90-day inhalation exposure of rats resulted in decreased body weights with a NOEL of 30.5 ppm (equivalent to an average daily exposure of 5.4 ppm). A 90-day inhalation study in mice resulted in a NOEL of 30.5 ppm (equivalent to an average daily exposure of 5.4 ppm) for decreased body weight and nasal mucosal inflammation. OEHHA has set a chronic REL of 10 ug/m<sup>3</sup>.

### Carbon disulfide

CAS # 75-15-0

CS<sub>2</sub>

Carbon disulfide has a large number of industrial uses, in addition to its uses as a fumigant. It has a vapor pressure of 297 mm Hg at room temperature and is slightly soluble in water. It evaporates rapidly when it is released into the environment. Since it is heavier than air, carbon disulfide may remain close to the ground after release or evaporation. It will break down after about 12 days. While it will rapidly evaporate after release to soil, it also moves rapidly through soil, and can move into groundwater.

A primary toxicological target of carbon disulfide is the nervous system. Toxicity in humans following acute inhalation exposure to very high concentrations of carbon disulfide usually includes symptoms similar to inebriation and a loss of tendon reflexes. Death may occur from respiratory depression. Other symptoms include disorientation, headache, nausea, dizziness, fatigue, heart disturbances, and hallucinations. Longer-term exposures of humans to lower concentrations have resulted in symptoms including polyneuritis, psychoses, gastric disturbances, headaches, impotence, tremors, sleep disturbances, and myopathy. Studies of long-term exposure of workers to low concentrations have identified alterations in nerve conduction. A National Institute of Occupational Safety and Health (NIOSH) study identified a chronic LOEL of 7.6 ppm for decreased nerve conduction. OEHHA has set acute and chronic RELs of 6,200 and 800 ug/m<sup>3</sup>, respectively.

A reported acute 2-hour LC<sub>50</sub> in mice is 3,210 ppm. A 1-hour LC<sub>50</sub> in rats is reported as 15,000 ppm. A 90-day inhalation study in mice had a NOEL of 297 ppm for peripheral nerve degeneration, axonal swelling of the spinal chord, kidney lesions, and reduced brain weight. A 90-day inhalation study in Fisher 344 rats resulted in a NOEL of 50 ppm (equivalent to an average daily exposure of 9 ppm) for ataxia, reduced brain weights, peripheral nerve

degeneration, and axonal swelling of the spinal chord. A 90-day inhalation study in Sprague-Dawley rats resulted in a NOEL of 50 ppm (equivalent to 9 ppm) for nerve degeneration, axonal swelling of the spinal chord, and decreased brain weight. The same laboratory conducted all of these studies. In all three studies, a pathological examination of the brain was not performed; however, such an examination could have resulted in lower NOELs.

Carbon disulfide also causes reproductive toxicity and has been listed under Proposition 65 as reproductive and developmental toxicant. A rat reproductive toxicity study resulted in a NOEL of 250 ppm (equivalent to a daily average of 63 ppm) for difficulty with delivery, increased pup mortality, decreased pup viability, and decreased mean litter size. A rat developmental toxicity study resulted in a NOEL of 200 ppm (equivalent to 50 ppm) for decreased fetal body weight, increased incidence of unossified sternabrae, and a non-statistically significant increase in the incidence for clubfoot. A rabbit developmental toxicity study resulted in a NOEL of 600 ppm (equivalent to a daily average of 150 ppm) for increased resorptions, decreased mean fetal body weight, and increased incidence of skeletal and visceral malformations. A rat multigeneration reproduction study resulted in a LOEL of 30 ppm for central nervous system (CNS) abnormalities and gross malformations including clubfoot and hypognathia. Male rats exposed to 610 ppm 6 hours per day, five days per week (equivalent to a daily average of 109 ppm) for 10 weeks resulted in reduced sperm counts and reduced copulatory behavior. Some studies of workers' occupational exposure to carbon disulfide indicated adverse effects on several reproductive parameters including spermatogenesis, serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH), libido, and incidence of menstrual disturbances.

Sodium tetrathiocarbonate was prioritized for risk assessment initiation due to its relatively high use; the breakdown into hydrogen sulfide and carbon disulfide (the pesticide active compound); the high acute toxicity of hydrogen sulfide; the acute, developmental, reproductive, and neurotoxicity of carbon disulfide; the repeatability of this toxicity in difference studies; the finding of these effects in occupationally exposed people; and the potential for offsite movement of carbon disulfide and hydrogen sulfide resulting in potential ambient air exposures of bystanders and persons living near treatment areas.