Outer Continental Shelf Oil and Gas Lease Sale 181 (December 2001), Gulf of Mexico, Offshore Marine Environment and Coastal Counties/ Parishes of LA, MI, AL and northwestern FL, Due: August 13, 2001, Contact: Archie Melancon (703) 787–1547.

EIS No. 010248, Draft EIS, USN, HI, Programmatic EIS—Ford Island Development Program, Proposed Consolidation of Selected Operation at Pearl Harbor by Locating and Relocating Certain Activities Ford Island, HI, Due: August 27, 2001, Contact: Stanley Uehara (808) 471–9338.

EIS No. 010249, Draft EIS, COE, CA, Pine Flat Dam Fish and Wildlife Habitat Restoration Investigation, Propose to Restore and Protect the Ecosystem for Fish and Wildlife Resource, King River Basin, Fresno County, CA, Due: August 27, 2001, Contact: David Tedrick (916) 557–7087.

EIS No. 010250, Draft EIS, FRC, MA, CT, Phase III/Hubline Project, Construction and Operation a Natural Gas Pipeline, Maritimes and Northeast Pipeline (Docket No. CPO1–4–000), Algonquin Gas Transmission (Docket No. CP01–5–000) and Texas Eastern Transmission (Docket No. CP01–8–000), MA and CT, Due: September 03, 2001, Contact: Berne Mosley (202) 208–0004.

EIS No. 010251, Final EIS, FTA, CA, Mid-Coast Corridor Mass Transit Improvement Project, Funding, San Diego County, CA , Due: August 13, 2001, Contact: Tim Pennington (415) 744–3116.

Dated: July 10, 2001.

B. Katherine Biggs,

Associate Director, NEPA Compliance Division, Office of Federal Activities.

[FR Doc. 01–17627 Filed 7–12–01; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[ER–FRL–6619–9]

Environmental Impact Statements and Regulations; Availability of EPA Comments

Availability of EPA comments prepared June 04, 2001 through June 08, 2001 pursuant to the Environmental Review Process (ERP), under Section 309 of the Clean Air Act and Section 102(2)(c) of the National Environmental Policy Act as amended. Requests for copies of EPA comments can be directed to the Office of Federal Activities at (202) 564–7167. An explanation of the ratings assigned to draft environmental impact statements (EISs) was published in FR dated April 14, 2000 (65 FR 20157).

Draft EISs

ERP No. D–AFS–J65337–MT Rating EC2, Cave Gulch Post-Fire Salvage Sale, Harvesting Dead or Dying Trees, Implementation, Helena National Forest, Big Belts Mountain, Lewis and Clark Counties, MT.

Summary: EPA expressed concerns about adverse effects of timber harvest on water quality. EPA indicated that harvest methods and mitigation measures should avoid and minimize further adverse impacts to fire stressed water bodies and recommended additional mitigation, and monitoring to detect effects on water quality.

ERP No. D–AFS–L65232–OR Rating EC2, Deep Vegetation Management Project, Implementation, Ochoco National Forest, Paulina Ranger District, Crook and Wheeler Counties, OR.

Summary: EPA expressed concerns about possible impacts to air and water quality, the limited information on cumulative impacts, and the limited range of alternatives. EPA requests that the final EIS discuss these potential impacts in greater detail.

ERP No. D–AFS–L65369–00 Rating EC2, Boise National Forest, Payette National Forest and Sawtooth National Forest, Forest Plan Revision, Implementation, Southwest Idaho Ecogroup, several counties, ID, Malhaur County, OR and Box Elder County, UT.

Summary: EPA expressed environmental concerns regarding air and water quality impacts and with the discussion regarding alternatives and cumulative impacts.

ERP No. D–BOP–K81025–CA Rating LO, Fresno Federal Correctional Facility Development, Orange Cove, Fresno County, CA.

Summary: EPA had no objections to the project.

ERP No. DS–DOE–A06181–00 Rating EC2, Geologic Repository for the Disposal of Spent Nuclear Fuel and High-Level Radioactive Waste, Construction, Operation, Monitoring and Eventually Closing a Geologic Repository at Yucca Mountain, Updated and Additional Information, Nye County, NV.

Summary: The Supplement updates information about the repository design, but because of its limited scope, the Supplement does not address most of the comments EPA had on the draft EIS. EPA therefore continues to have environmental concerns with the project. EPA also requests additional information to clarify information presented in the Supplement.

ERP No. D1–AFS–J65250–CO Rating LO, Forest Development Trail (FDT) 1135 (Arapaho Ridge Trail), Forest Development Road (FDR) 711.1 and FDR 711.1A Motorized or Non-Motorized Determination and Trailhead Parking Areas Creation at both ends of the Trail, Routt National Forest, Jackson County, CO.

Summary: EPA expressed a lack of objections with the preferred alternative.

Final EISs

ERP No. F–AFS–J65322–MT, Spar and Lake Subunits Forest Health Project, Improvements, Kootenai National Forest, Three Rivers Ranger District, Lincoln County, MT.

Summary: EPA expressed environmental concerns about the lack of information on aquatics monitoring and weed control chemicals to be used in the project area.

ERP No. F–RUS–E39053–KY, Jackson County Lake Project, Implementation, To Provide Adequate Water Supplies for the Projected Residential, Commercial and Industrial Needs, Funding and Possible COE Section 10 and 404 Permits, Jackson County, KY.

Summary: EPA's original environmental concerns remain, especially since other water supply options can address purpose/need goals with lesser adverse (long-term) water quality impacts.

Dated: July 10, 2001.

B. Katherine Biggs,

Associate Director, NEPA Compliance Division, Office of Federal Activities.

[FR Doc. 01–17628 Filed 7–12–01; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[PF–1028; FRL–6785–8]

Notice of Filing a Pesticide Petition to Establish a Tolerance fora Certain Pesticide Chemical in or on Food

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice announces the initial filing of a pesticide petition proposing the establishment of regulations for residues of a certain pesticide chemical in or on various food commodities.

DATES: Comments, identified by docket control number PF–1028, must be received on or before August 13, 2001.

ADDRESSES: Comments may be submitted by mail, electronically, or in person. Please follow the detailed instructions for each method as provided in Unit I.C. of the **SUPPLEMENTARY INFORMATION.** To ensure proper receipt by EPA, it is imperative that you identify docket control number PF–1028 in the subject line on the first page of your response.

FOR FURTHER INFORMATION CONTACT: By mail: Mary L. Waller, Registration Division (7505C), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460; telephone number: (703) 308–9354; e-mail address: waller.mary@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be affected by this action if you are an agricultural producer, food manufacturer or pesticide manufacturer. Potentially affected categories and entities may include, but are not limited to:

Categories	NAICS codes	Examples of potentially affected entities
Industry	111 112 311 32532	Crop production Animal production Food manufacturing Pesticide manufacturing

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in the table could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether or not this action might apply to certain entities. If you have questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Additional Information, Including Copies of this Document and Other Related Documents?

1. *Electronically*. You may obtain electronic copies of this document, and certain other related documents that might be available electronically, from the EPA Internet Home Page at http://www.epa.gov/. To access this document, on the Home Page select ''Laws and Regulations,'' ''Regulations and Proposed Rules,'' and then look up the entry for this document under the ''**Federal Register**—Environmental Documents.'' You can also go directly to the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

2. *In person*. The Agency has established an official record for this action under docket control number PF–1028. The official record consists of the documents specifically referenced in this action, any public comments received during an applicable comment period, and other information related to this action, including any information claimed as confidential business information (CBI). This official record includes the documents that are physically located in the docket, as well as the documents that are referenced in those documents. The public version of the official record does not include any information claimed as CBI. The public version of the official record, which includes printed, paper versions of any electronic comments submitted during an applicable comment period, is available for inspection in the Public Information and Records Integrity Branch (PIRIB), Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA, from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

C. How and to Whom Do I Submit Comments?

You may submit comments through the mail, in person, or electronically. To ensure proper receipt by EPA, it is imperative that you identify docket control number PF–1028 in the subject line on the first page of your response.

1. *By mail*. Submit your comments to: Public Information and Records Integrity Branch (PIRIB), Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460.

2. *In person or by courier*. Deliver your comments to: Public Information and Records Integrity Branch (PIRIB), Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), Environmental Protection Agency, Rm. 119, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA. The PIRIB is open from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The PIRIB telephone number is (703) 305–5805.

3. *Electronically*. You may submit your comments electronically by e-mail to: opp-docket@epa.gov, or you can submit a computer disk as described above. Do not submit any information electronically that you consider to be CBI. Avoid the use of special characters and any form of encryption. Electronic submissions will be accepted in Wordperfect 6.1/8.0 or ASCII file format. All comments in electronic form must be identified by docket control number PF–1028. Electronic comments may also be filed online at many Federal Depository Libraries.

D. How Should I Handle CBI That I Want to Submit to the Agency?

Do not submit any information electronically that you consider to be CBI. You may claim information that you submit to EPA in response to this document as CBI by marking any part or all of that information as CBI. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. In addition to one complete version of the comment that includes any information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public version of the official record. Information not marked confidential will be included in the public version of the official record without prior notice. If you have any questions about CBI or the procedures for claiming CBI, please consult the person identified under **FOR FURTHER INFORMATION CONTACT**.

E. What Should I Consider as I Prepare My Comments for EPA?

You may find the following suggestions helpful for preparing your comments:

1. Explain your views as clearly as possible.

2. Describe any assumptions that you used.

3. Provide copies of any technical information and/or data you used that support your views.

4. If you estimate potential burden or costs, explain how you arrived at the estimate that you provide.

5. Provide specific examples to illustrate your concerns.

6. Make sure to submit your comments by the deadline in this notice.

7. To ensure proper receipt by EPA, be sure to identify the docket control number assigned to this action in the subject line on the first page of your response. You may also provide the name, date, and **Federal Register** citation.

II. What Action is the Agency Taking?

EPA has received a pesticide petition as follows proposing the establishment and/or amendment of regulations for

residues of a certain pesticide chemical in or on various food commodities under section 408 of the Federal Food, Drug, and Comestic Act (FFDCA), 21 U.S.C. 346a. EPA has determined that this petition contains data or information regarding the elements set forth in section 408(d)(2); however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data support granting of the petition. Additional data may be needed before EPA rules on the petition.

List of Subjects

Environmental protection, Agricultural commodities, Feed additives, Food additives, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: June 20, 2001.

Peter Caulkins,

Acting Director, Registration Division, Office of Pesticide Programs.

Summary of Petition

The petitioner summary of the pesticide petition is printed below as required by section 408(d)(3) of the FFDCA. The summary of the petition was prepared by the petitioner and represents the view of the petitioners. EPA is publishing the petition summary verbatim without editing it in any way. The petition summary announces the availability of a description of the analytical methods available to EPA for the detection and measurement of the pesticide chemical residues or an explanation of why no such method is needed.

Aventis CropScience

PP 4F4281 and PP 0F6126

EPA has received pesticide petitions (PP 4F4281 and PP 0F6126) from Aventis CropScience, P.O. Box 12014, 2 T.W. Alexander Drive, Research Triangle Park, NC 27709 proposing, pursuant to section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), to amend 40 CFR part 180 by establishing a tolerance for residues of iprodione, 3-(3,5-dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide, its isomer, 3-(1- methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidaxolidinecarboxamide and its metabolite,3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidine carboxamide in or on the raw agricultural commodity rapeseed (canola) at 1.0 part per million (ppm)(4F4281) and increasing the tolerance in or on the commodity almond hulls to 5.0 ppm (0F6126). EPA has determined that the petition contains data or information regarding the elements set forth in section 408(d)(2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1. *Plant metabolism*. The metabolism of iprodione in plants is well understood. EPA concluded that the residues of concern in plants are the parent, its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide.

2. *Analytical method*. An adequate analytical method, gas liquid chromatography using an electron-capture detector, is available in the Pesticide Analytical Manual, Vol. II, for enforcement purposes.

3. *Magnitude of residues —i. Canola*. a. *Foliar application*. Residue data were reported for 11 field trials conducted in the major canola production areas of Canada. Most of the trial locations also represent major canola production areas of the United States. Residues ranged from 0.05 ppm to 0.62 ppm.

b. *Seed treatment*. Residue data were reported for 8 field trials conducted in EPA Regions II, V, VII, and XI. The seed were treated with iprodione and planted with equipment customarily used for canola seed. Mature canola seed generated from the treated seed was collected at normal commercial harvest and analyzed. Iprodione residues were non-detectable in all samples. The LOD was estimated to be 0.005 ppm.

c. *Processing*. A canola processing study was found to be adequate by the Agency to support a tolerance on canola. Combined residues do not concentrate in canola meal, crude oil, or refined oil. Food or feed additive tolerances are not necessary.

ii. *Almonds*. A residue study was conducted at five field trial locations in California, the only state with commercial almond production. The product was applied four times as airblast applications using equipment customarily used to apply pesticides to almonds at a nominal rate of 1.0 lb ai/A per application. This represents a rate increase compared to thecurrent label rate of 0.5 lb ai/A per application. All resulting iprodione residues in/on almond nutmeat samples were below the current tolerance of 0.3 ppm. Residues in almond hull samples ranged from 1.6 ppm to 3.9 ppm.

B. Toxicological Profile

1. *Acute toxicity*. A complete battery of acute toxicity studies for iprodione was completed. Iprodione has low acute toxicity. The acute oral toxicity study in the rat resulted in LD_{50} of 3,629 milligrams/kilograms and 4,468 mg/kg for females and the combined sexes, respectively. The acute dermal LD_{50} in both rats and rabbits is > 2,000 mg/kg. The acute inhalation LC_{50} for a four hour exposure to rats is > 5.16 mg/L. No skin or eye irritation or dermal sensitization is produced by iprodione. Based on the results of this study iprodione was placed in toxicity category III.

2. *Genotoxicty*. Mutagenicity studies completed include*Salmonella typhimurium* and *Escherichia coli* reverse mutation (all negative), induction tests with *Escherichia coli*, (all negative), DNA repair test in *Escherichia coli* (negative), DNA damage in *Bacillus subtilis* (positive), Rec assay in *Bacillus subtilis* (negative), mutagenicity in *Saccharomyces cerevisiae* D7 (negative), forward mutation in CHO/HGPRT assay (negative), chromosome aberrations in CHO cells (negative), sister chromatid exchange in CHO cells (negative), *in vivo* micronucleus test (negative), *in vivo* host mediated assay with *Salmonella typhimurium* G46 (negative) and dominant lethal test in male mice (negative). Based on these data, the weight of evidence indicates that iprodione does not pose a mutagenic hazard to humans.

3. *Reproductive and developmental toxicity*. The embryo/fetal toxicity and teratogenicity of iprodione were evaluated in Sprague-Dawley rats at oral (gavage) dose levels of 0, 40, 90 or 200 mg/kg/day by gavage from day 6 through 15 of gestation. Iprodione showed no embryotoxicity or teratogenicity at any of the dose levels examined. Although no maternal effects were detected at any treatment level in the definitive study, dose selection was justified from the pilot study in which maternal toxicity was noted at 120 and 240 mg/kg/day. In addition, an increase in the average number of late resorptions per litter was observed at 240 mg/kg/day. A clear and conservative developmental and maternal NOAEL was observed at 90 mg/kg/day.

The potential effects of iprodione on pregnancy and on parameters of sex differentiation have been investigated in the rat. Iprodione was administered by gavage at dose levels of 0, 20, 120 or 250 mg/kg/day to pregnant female Sprague –Dawley rats on days 6 to 19 of

gestation. Iprodione induced severe maternal toxicity, including mortality, at 250 mg/kg/day. Maternal body weight gain was reduced during the treatment period at 120 and 250 mg/kg/day. Mean fetal bodyweight was reduced at 250 mg/kg/day in both sexes. In the final report of the FQPA Safety Factor Committee, April 14, 1998, EPA concluded that for developmental toxicity, the NOAEL was 20 mg/kg/day and the LOAEL was 120 mg/kg/day based on decreased anogenital distance in the male pups. Aventis CropScience disagrees with EPA's evaluation of the study findings. The effects observed on AGD at 120 mg/kg/day are marginal (4.5% decrease) and of extremely doubtful biological significance considering the presence of substantial maternal toxicity (28% decrease in maternal body weight gain on GD 16–20). Nevertheless, it should be noted that since the completion of the FQPA Safety Factor Committee, April 14, 1998, EPA Dr. Earl Gray published in the January-March 1999 issue of Toxicology and Industrial Health An International Journal, findings from a sex differentiation study conducted with iprodione. Dr. Gray reports no decrease in AGD in male rats when iprodione is administered at 100 mg/kg/day from gestational day 14 to postnatal day 3. EPA's findings support a change in the NOAEL to 100 mg/kg/day. Additionally, EPA has relied and used the data generated by Dr. Gray to regulate the product, vinclozolin. The Agency should handle iprodione in a similar fashion and use the data generated by Dr. Gray at the 100 mg/kg/day dose level to regulate iprodione concerning this endpoint.

The embryo/fetal toxicity and teratogenicity of iprodione were evaluated in rabbits dosed by gavage at levels of 0, 20, 60 or 200 mg/kg/day No treatment-related embryotoxicity or teratogenicity was noted at doses of 20 or 60 mg/kg/day. Even though iprodione at 200 mg/kg/day was too maternally toxic for a complete teratologic evaluation, no malformations were observed in the fetuses examined from this group. The developmental NOAEL was 60 mg/kg/day and the maternal NOAEL was 20 mg/kg/day based on decreases in maternal body weight gain.

In a multi-generation study, iprodione was administered to male and female Sprague–Dawley rats via dietary admixture at dose levels of 0, 300, 1,000 or 2,000/3,000 ppm (for males 18.5, 61.4 and 154.8 mg/kg/day and for females 22.49, 76.2 and 201.2 mg/kg/day, respectively). It was necessary to reduce the high dose from 3,000 to 2,000 ppm following the first mating period of the F1 parents owing to excessive toxicity. No effects on reproductive performance were observed at any of the treatment levels. Parental toxicity, as evidenced by reduced bodyweight, body weight gain and food consumption was observed at dietary levels of 1,000 ppm and higher. Effects on pup viability and pup weight were noted at 2,000/3,000 ppm. The NOAELs for parental and offspring toxicity were 300 ppm and 1,000 ppm, respectively. Based on these data, it is concluded that Iprodione is not a reproductive toxicant.

4. *Subchronic toxicity*. In a dermal toxicity study, rabbits were administered iprodione on the skin at dose levels of 0, 100, 500, and 1,000 mg/kg/day for 21 days. There were no deaths or clinical signs of toxicity and no adverse effects were observed on body weight, food consumption, the skin, liver or kidneys. The NOAEL was 1,000 mg/kg/day, the highest dose tested (HDT).

In a 90–day subchronic feeding study, rats were administered iprodione in the diet at doses of 0, 1,000, 2,000, 3,000, and 5,000 ppm (0, 78, 151, 252, and 355 mg/kg/day for males and 0, 89, 189, 266, and 408 mg/kg/day for females). The NOAEL in this study was 1,000 ppm (78 mg/kg/day for males and 89 mg/kg/day for females). The LOAEL was 2,000 ppm (151 mg/kg/day for males and 189 mg/kg/day for females), based on decreased body weight gain, decreased food consumption and food utilization, organ weight effects, and microscopic lesions in the sex organs.

5. *Chronic toxicity and carcinogenicity*– i. *Non–rodent dog*. In a first chronic feeding study, 6 Beagle dogs/sex/group were administered iprodione in the diet at dose levels of 0, 100, 600 and 3,600 ppm (equivalent to 0, 4.2, 26.6, and 148.9 mg/kg/day) for 12 months. There were no teatment–related for body weight, food consumption, or clinical signs observed in either male or female dogs. In the 3,600 ppm dose group, increases in alkaline phoshatase, SGOT, SGTP, and LDH levels were observed in both male and female dogs. Increases in absolute and relative liver and adrenal weights were observed in both male and female in the 3,600 ppm dose level. Increased erthrocytes with Heinz bodies were observed in the male dogs at both the 600 and 3,600 ppm dose groups. Additionally decreased prostate weights were seen in these same male dogs. A clear NOAEL was established at 100 ppm (4.2 mg/kg/day). The LOAEL was set at 600 ppm based on equivocal effects such as decreased prostate weight and an increased incidence of Heinz bodies in erythrocytes in males.

A second chronic feeding study designed to complement the above study in dogs was conducted at dose levels of 0, 200, 300, 400 and 600 ppm. In this study no clear indications of any toxicological effects were noted with the exception of minor effects seen at the 600 ppm dose group, which consisted of decreased red blood cell parameters. From the results of the two complementary studies, a conservative NOAEL of 400 ppm (17.5 mg/kg/day in males and 18.4 mg/kg/day in females) and a LOAEL of 600 ppm (24.6 mg/kg/day in males and 26.4 mg/kg/day in females) based on depressed blood cell parameters were established.

ii. *Rodent —Rat*. a. *Study A*. In the initial chronic/carcinogenicity study, Charles River outbred CD albino rats were fed diets containing 125, 250 or 1,000 ppm (6.25, 12.5 and 50 mg/kg/day) of Iprodione technical for 24 months. In this study, no treatment-related effects were observed for parameters measured (i.e., body weight, clinical signs, and etc.) No treatment–related tumors were observed in this study. The NOAEL of iprodione in rats was observed to be greater than 1,000 ppm (i.e. >50 mg/kg/day), the HDT. Therefore, the rat chronic/carcinogenicity study discussed below was repeated to comply with EPA guidelines as in the initial study a MTD was not attained.

b. *Study B*. In the second study, Sprague Dawley rats were administered 150, 300, or 1,600 ppm iprodione technical in the diet for 24 months. The NOAEL for chronic toxicity was set at 150 ppm (mean intake of males and females was 7.25 mg/kg/day) and the LEL was 300 ppm (12.4 mg/kg/day for males and 16.5 mg/kg/day for females). The NOEL for carcinogenicity in males in this study was 300 ppm (12.4 mg/kg/day) and the LEL was 1,600 ppm (69 mg/kg/day). There was no indication of carcinogenicity in females at any dose levels.

The following summarizes the findings at the mid and high dose levels in this study:

In the high dose group mean body weight gains were reduced from 13.7% to 16.4% between weeks 0 to 12, 12 to 22, and 0 to 104 of the study in high dose males.

Terminal sacrifice: Increased relative liver weight was noted in males receiving 300 or 1,600 ppm, significantly increased testes weight were recorded at 1,600 ppm and slight increases in relative adrenal and thyroid weights in males were recorded at 1,600 ppm.

Interim sacrifice: An increased incidence of centrilobular hepatocyte

enlargement was seen in males at 300 and 1,600 ppm and an increased incidence of extramedullary haemopoiesis and haemosiderosis was observed in female rats receiving 1,600 ppm. In the adrenals, generalized and/or focal enlargement of cells of the zona glomerulosa was observed in numerous male and female rats treated at 1,600 ppm. A high proportion of rats in this group revealed generalized rarefaction and fine vacuolation of zona fasciculata; only one female in the 300 ppm group showed this latter change. A high proportion of male rats also showed a generalized fine vacuolation of zona reticularis.

Terminal sacrifice: In the testes, interstitial cell hyperplasia was observed at 300 and 1,600 ppm and an increased incidence of atrophy of seminiferous tubules was noted in rats treated with 1,600 ppm. In the epididymides, reduced spermatozoa were noted at 300 and 1,600 ppm and an increased incidence of spermatozoa absent was noted in males treated with 1,600 ppm. An increased atrophy of the prostate was noted at 1,600 ppm. In seminal vesicles, secretory colloid was absent/empty in rats treated with 1600 ppm and reduced secretion was also observed at 300 ppm. In the spleen, the incidence of minimal haemosiderosis was increased amongst female rats treated with 300 or 1,600 ppm. In the adrenals, an increased incidence of either generalized or focal enlargement of cells of zona glomerulosa for males and females treated with 1600 ppm, often with generalized vacuolation of zona fasciculata and zona reticularis for males treated with 1,600 ppm were noted. Generalized vacuolation of zona reticularis was also observed in male rats treated at 300 ppm.

No increase in tumor incidence was noted at interim sacrifice.

Macroscopic examination of animals found dead or sacrificed in extremis did not show an increased incidence of any tumor type. In the high dose group there was an increase in the incidence of both unilateral and bilateral benign interstitial cell tumors in the testes of males. No treatment–related neoplastic lesions were observed in the 150 or 300 ppm dose levels.

iii. *Rodent —Mouse*. a. *Study A*. In the initial study, Carworth CF–1 outbred albino mice were fed diets containing 200, 500, 1,250 ppm (28.6, 71.4 and 178.6 mg/kg/day) of iprodione technical for 18 months. In this study, no treatment–related effects were observed for parameters measured (i.e., body weight, clinical signs, and etc.). No treatment–related tumors were observed in this study. In this study, the NOAEL of Iprodione in mice was greater than 1,250 ppm (i.e. > 178.6 mg/kg/day). Therefore, the mouse life–time feeding study discussed below was repeated to comply with EPA guidelines as in the initial study a MTD was not attained.

b. *Study B*. In the second study (MRID 42825002), iprodione technical was administered at dietary concentrations of 160, 800 or 4,000 ppm to CD–1 mice for 99 weeks. The NOAEL for chronic toxicity was set at 160 ppm (23 mg/kg/day for males and 27 mg/kg/day for the females) and the LEL at 800 ppm (115 mg/kg/day for males and 138 mg/kg/day for females). The NOAEL for oncogenicity in this study was 800 ppm (115 mg/kg/day in males and 138 mg/kg/day in females) and the LEL was 4,000 ppm (604 mg/kg/day in males and 793 mg/kg/day in females).

The following summarizes the findings at the mid and high dose levels in this study:

Over the duration of the study, weight gain was reduced 14% and 11% in high dose males and females respectively. During weeks 18 to 45, weight gain was reduced 44% and 47%, respectively.

Biochemistry investigations at week 52 revealed significant increases in GOT and GPT values in both sexes at 4,000 ppm.

At interim sacrifice, Significantly higher liver weights and slightly higher adrenal weights were noted in animals of both sexes at 4,000 ppm. A decrease in uterine and ovarian weights was also observed at 4,000 ppm although they were not statistically significantly reduced in comparison with the controls. At terminal sacrifice the following organ weight changes were noted at 4,000 ppm: Significant increases in liver weights in both sexes, marginal increases in thyroid weights in both sexes and significantly decreased uterus weights in females. A decrease in ovarian weights was also noted at 4,000 ppm, although the reduction was not statistically significant.

At interim sacrifice, non-neoplastic findings were only observed in mice treated with 4,000 ppm. In the livers of both sexes an increase in the incidence and degree of centrilobular hepatocyte enlargement was observed with increased incidence of centrilobular hepatocyte vacuolation in females. In the adrenals, an increased incidence of hypertrophy of the cells of the zona fasciculata was observed in females. In the testes, generalized vacuolation and hypertrophy of the interstitial cells was observed in most males. In the ovaries, luteinisation of the interstitial cells and absence of corpora lutea were observed.

At terminal sacrifice, the following non-neoplastic lesions were noted: In the liver, single and multiple areas of eosinophilic hepatocytes, focal fat containing hepatocytes and centrilobular hepatocyte enlargement were present more frequently in both sexes treated at 4,000 ppm with minimal centrilobular hepatocyte enlargement in female mice treated with 800 ppm. In male mice receiving 4,000 ppm, pigmented macrophages were more frequently observed. In the testes, an increased incidence of generalized vacuolation and hypertrophy of interstitial cells of the testes were noted in male mice treated with 800 and 4,000 ppm. In the ovaries, luteinisation of the interstitial cells, absence of corpora lutea, arrest of follicular development were more frequently noted in female mice treated with 4,000 ppm. In the stomach, an increased incidence of hyperkeratosis of the non-glandular stomach was noted in male mice treated with 800 and 4,000 ppm. In the spleen, haemosiderosis was more frequent in females treated with 4,000 ppm. In the kidneys amyloidosis/amyloid deposits and cortical scarring were noted in female mice treated with 4,000 ppm.

Microscopic examination of animals found dead, sacrificed in extremis, or killed at termination after 99 weeks revealed an increased incidence of benign and malignant liver cell tumors in both sexes. A slight increase in the incidence of luteomas in the ovaries of females was also noted at 4,000 ppm.

No increased incidence of any other tumor type was recorded.

No treatment–related neoplastic lesions were observed in the 160 or 800 ppm treatment groups.

c. *Conclusion*. The chronic reference dose (RfD) for iprodione should be 0.0725 mg/kg/day based on the NOEL of 7.25 mg/kg/day determined from the rat combined chronic toxicity and carcinogenicity study. Aventis CropScience believes that using an uncertainty factor of 100 to account for inter- and intra-species variations is adequate to protect all population subgroups.

Aventis CropScience have developed a complete and reliable database which demonstrates that pre-and/or postnatal exposure to iprodione does not result in an increased susceptibility to the developing organism in comparison to the adult.

Iprodione has no teratogenic potential, even at maternally toxic dose levels. In addition the results of a recently completed study have confirmed that iprodione has no effects on sex differentiation. An acceptable two generation rat reproduction study indicated that iprodione has no adverse effects on reproductive performance,

fertility, fecundity, sex ratio or ano-genital distance. Effects on pup weight and viability were only noted in the presence of severe parental toxicity.

These studies constitute a very stringent test of developmental and reproductive toxicity because of the types of dosing regimens employed (e.g. MTD throughout the sensitive period of organogenesis), the large numbers of animals examined, and the multiplicity of parameters measured.

The Agency Hazard Identification Review Committee (HIARC) concluded ''based on the weight-of-the-evidence of all available studies, the HIARC concluded that there is no increased susceptibility to rat and rabbit fetuses following *in utero* and/or post natal exposure to iprodione. Additionally, HED also stated that the special prenatal study in rats ...''demonstrated no indication of increased susceptibility. Therefore, based on these statements and available data base for iprodione, a standard 100–fold UF (10–fold for inter–species extrapolation and 10–fold for intra–species variability) is sufficient to assure protection for all population sub–groups, including females of child-bearing age, infants and children, to dietary, residential or occupational exposure to iprodione residues.

iv. *Supplementary information and discussion.* A number of mechanistic studies have been conducted in order to elucidate the mechanism of testicular toxicity and carcinogenicity in the rat and hepatic toxicity and carcinogenicity in the mouse.

a. *Background and introduction.* The HED Carcinogenicity Peer Review Committee (CPRC) met in 1994 and determined that iprodione should be classified a group B2 carcinogen. The CPRC recommended that a low dose quantitative risk assessment for iprodione be estimated from the benign rat interstitial cell tumors of the testes, and also from the mouse male and female liver tumors separately.

In November 1997, HED's Cancer Assessment Review Committee re-affirmed its position for the risk characterization of iprodione on the basis that a definitive mode of action for the formation of either tumor type had not yet been provided.

Aventis CropScience has since produced significant new data to address all the Agency's outstanding issues relative to the induction of rat Leydig cell tumors by iprodione. These data provide a definitive mode of action for the induction of rat Leydig cell tumors and support a move to a MOE (i.e. non–linear) approach for cancer risk assessment for this tumor type. Work has also been conducted on the mechanism of hepatic toxicity and carcinogenicity in the mouse.

b. *Mechanism of Leydig cell toxicity in the rat.* Aventis CropScience contends that a complete evaluation of the carcinogenicity issue indicates that Iprodione is a threshold carcinogen acting through a non-genotoxic mechanism of toxicity. The application of a low dose quantitative risk assessment for Iprodione is inappropriate. These conclusions are based on the available data from the following areas:

(1) *Genetic toxicity of iprodione.* The genotoxicity of iprodione has been assessed in a large number of assays conducted using bacteria, yeast and mammalian cells and whole animals. A single positive result was observed in an outdated and deficient assay designed to assess DNA damage using *Bacillus subtilis.* All other genotoxicity assays, including those conducted *in vivo*, were found to be negative. This considerable body of data indicates that iprodione does not pose a mutagenic hazard to humans. A hormonally-mediated mechanism of carcinogenesis has therefore been investigated. *In vivo* mechanistic studies: Iprodione has recently been shown to decrease plasma testosterone levels significantly in rats in a dose–dependent manner at dose levels analogous to those at which tumors were induced in the rat bioassay (approx. 70 mg/kg/day). Following a single gavage administration of iprodione, plasma testosterone levels were reduced 2 and 4 hours post dosing. Thereafter plasma testosterone levels returned to baseline, presumably as a consequence of the compensatory increase in plasma LH which was significantly increased 2 and 4 hours post dosing (MRID 44729201). This profile of transient hormonal changes mirrors that of the classic testosterone biosynthesis inhibitor ketoconazole.

In previous *in vivo* studies in the rat, detectable hormonal changes have been limited to increases in LH and FSH levels following 14/15 days of iprodione treatment and alterations in the secretion pattern of LH and testosterone following 30–days of treatment (MRID 43535002, 44171903). The rapid reversibility of the hormonal changes observed in the recent study (MRID 44729201) helps to explain the absence of detectable decreases in testosterone levels *in vivo*in previous studies. In the 15–day gavage study, blood sampling was performed 12–14 hours following the final gavage (MRID 43535002). In the 14–day feeding study, blood samples were not taken until mid- to late morning i.e. several hours following the conclusion of the animals' anticipated nocturnal feeding (MRID 44171903). Since, in the recent study, plasma testosterone levels were observed to return to normal approximately 6 hours post dosing (MRID 44729201) it is probable that no significant decreases in circulating testosteronelevels were demonstrated in earlier experiments due to inappropriate sampling times following iprodione administration.

(2) *Combined chronic toxicity/carcinogenicity studies.* Pathologic evidence of a chronic perturbation of steroidogenesis and/or compromised testosterone availability was observed in the rat bioassay. An increased incidence of Leydig cell hyperplasia was observed both at the interim and terminal sacrifices. Other indicators of testosterone deficiency noted at terminal sacrifice included reductions in epididymal spermatozoa, reduced secretion in the seminal vesicles, and decreased weight of seminal vesicles.

Similar effects on steroid hormone producing organs such as the adrenal cortex, testis and ovary have been observed in other subchronic and chronic studies conducted with iprodione in rodents and dogs. Hypertrophy and intracellular accumulation of lipid, most likely due to an interference with cholesterol utilization in steroidogenesis, was observed in the interstitial cells of the mouse ovary and in the zonal fasciculata of the adrenal cortex in rodents and dogs.

(3) *In vitro mechanistic studies.* No clear evidence of competitive binding to the androgen receptor was found for iprodione or its major metabolites.

Iprodione and certain metabolites (RP36112 and RP36115) have been shown to rapidly and reversibly inhibit testosterone secretion from cultures of porcine Leydig cells. Inhibition was found to occur at media concentration of 1–10 ug/ml. No inhibitory effects on testosterone secretion were noted at media concentrations of iprodione or its active metabolites below 1 ug/ml demonstrating a threshold for this effect. Iprodione has also been shown to inhibit testosterone secretion from rat testicular sections *in vitro* at similar media concentration.

The mode of action whereby iprodione and its metabolites (RP36112 and RP36115) modulates steroidogenesis in Leydig cells has been identified using porcine Leydig cell cultures. Iprodione and RP36112 interfere with the active transport of cholesterol substrate into mitochondria while another metabolite RP36115 appears to inhibit steroidogenic enzymes.

(4) *Toxicokinetic study*. Groups of male Sprague Dawley rats received a single oral administration of ^{14}C-iprodione at the nominal rate of 70 mg/kg. Levels of iprodione and its metabolites RP36112 and RP36115 were estimated in the testes and plasma 0.5, 1, 2, 4, 6, 10, 24, and 48 hours post dose.

The results of this study indicate that the changes previously observed in plasma testosterone and LH levels at 70 mg/kg were most likely induced by the presence of RP36112, RP36115, and/or iprodione, which were present in the testes as early as 0.5 hours post dosing. At 2 hours post dosing, when maximal changes in plasma testosterone levels were observed to have occurred, the concentrations of RP36115 and iprodione were already at, or near, peak values in the plasma and testes. These levels were maintained for at least 8 hours, after which the levels rapidly declined to very low concentrations by 24 hours post dosing. It is also noteworthy that the range of concentrations of iprodione and RP36115 achieved in the testes samples by 2 hours post dosing were of the order of 5.6–6.8 ug/g which fall within the range of concentrations known to provide inhibition of testosterone secretion *in vitro* (1–10 ug/ml).

c. *Hepatotoxicity and carcinogenicity in male and female mice*. The development of hepatocellular tumors in mice appeared secondary to hepatic toxicity at a dose level at which body weight gain was severely reduced indicating that the MTD was probably exceeded (over the duration of the study, weight gain was reduced 14% and 11% in high dose males and females respectively. During weeks 18 to 45, weight gain was reduced 44% and 47%, respectively. This severity of the weight gain decrement is compounded by the fact that the livers in these animals weighed more than double their respective controls, i.e., the weight gain decrement is even more serious than the body weights alone would indicate). The animals at the highest dose level, and to a lesser extent, the mid-dose group, exhibited signs of liver toxicity, including increased liver weights, hepatocytic hypertrophy, enlarged eosinophilic hepatocytes, pigmented macrophages, centrilobular necrosis, amyloid deposits and statistically significant increases in levels of the liver enzymes GPT and GOT. Clear NOAELs exist for these effects. In a 14–day toxicity study in male mice, dose levels similar to those at which tumors were observed in the mouse carcinogenicity study induced a number of hepatic changes including the induction of Cytochrome P450 isoenzymes CYP 2B and CYP 3A and cellular proliferation in a similar manner to the well established liver promotor phenobarbital (MRID 44171902). This mechanism is not relevant to humans based on the pharmaceutical use of phenobarbital in humans for over 50 years.

d. *Conclusion*. As demonstrated above, the administration of iprodione to the Sprague Dawley rat results in transient hormonal imbalances *in vivo* (decreased plasma testosterone and increased plasma LH). It is well established that the chronic administration of a number of xenobiotic chemicals which cause similar changes to the hypothalamic-pituitary-gonodal axis result in the development of Leydig cell tumors in highly sensitive species, such as the rat. The dose–response for this type of hormonally–mediated effect is expected to be non–linear

The biochemical basis for this hormonal imbalance is an inhibition of testosterone biosynthesis by iprodione and its active metabolites(s). Testicular concentrations of iprodione, and at least one of its active metabolites, attained *in vivo* are within the range of those demonstrated to inhibit testosterone biosynthesis in Leydig cells *in vitro*. The mode of action whereby iprodione modulates Leydig cell steroidogenesis is *via* a reversible interference with the active transport of cholesterol into the mitochondria of Leydig cells as opposed to vinclozolin and procymidone which interact directly with the androgen receptor. As shown with vinclozolin and procymidone, direct interaction with the androgen receptor leads to marked effects on reproduction systems. However, iprodione does not lead to such marked reproductive effects. In fact, iprodione has no effects on reproductive parameters, sex differentiation, and other parameters measured in these study types.

For iprodione, the male interstitial cell tumors seen only at the high dose in the lifetime rat study was due to mode of action with a clear threshold. This conclusion is based on the following rationale: (i) The tumors were benign and only observed at a dose level at or above the MTD, (ii) the mechanistic toxicological research designed to elucidate the biochemical mode of action described above and (iii) the consensus of scientific experts that benign Leydig cell tumors in the rat are not valid predictors of human disease as will be discussed below.

Furthermore, concerning the testicular tumors (Leydig cell tumors) and as stated in the recent **Federal Register** notice for Vinclozolin April 21, 2000 (65 FR 21427),(FRL–6555–6) ''the relevance of Leydig cell tumors to men should be seen in the light that this is a very rare human tumor and that the precursor change (i.e. Leydig cell hyperplasia) has not been observed in patients treated with flutamide. In addition, the toxicology of cimitidine, an H2-receptor antagonist with anti-androgenic properties results in a size reduction and atrophy of the prostate and seminal vesicles in chronic rat studies. Moreover, an increase in benign Leydig cell tumors, and a decrease in pituitary and mammary tumor incidence were noted; hence a toxicity potential not unlike that of vinclozolin is evident. Despite the fact that over 30 million patients have been treated with cimitidine, this therapeutic agent has been demonstrated to be extremely safe, clearly indicating that the rat Leydig cell tumors have very little relevance for humans.'' A similar conclusion is drawn by other investigators ''Leydig cell tumors of the rat have limited significance because of the fundamental differences in testicular control mechanisms.'' It is therefore concluded that the observed neoplastic changes do not pose a relevant hazard to humans. EPA in the September 1996, Cancer Peer Review Document for vinclozolin, came to the same basic conclusion that the Leydig cell tumors are a very uncommon tumor type in humans which implies the threshold dose for humans would be greater than for rats. EPA based this conclusion on the work performed by Dr. Charles C. Capen (Professor Charles C. Capen, Leydig Cell Tumors: Pathology, Physiology, and Mechanistic Considerations in Rats, The Toxicology Forum, 1994 Annual Summer Meeting, p. 110). Consistent with the data and the advice of the OPP Scientific Advisory Panel and using its Guidelines for Carcinogen Risk Assessment published September 24, 1986 (51 FR 33992), EPA has classified the potent anti- androgen, vinclozolin, as a Group C chemical–possible human carcinogen. The Agency Cancer Peer Review Committee (CPRC) chose an–linear approach margin (MOE) to regulate vinclozolin. More recently, the Agency in its recent **Federal Register** notice of May 26, 2000 (65 FR 34179),(FRL–6588–6) stated the following, ''Vinclozolin is classified as a Group C carcinogen based on Leydig (interstitial testicular) cell tumors in a perinatal rat developmental toxicity study. A nonlinear (MOE) approach was determined to be appropriate based on the weight of the evidence conclusion that tumor induction is via an anti-androgenic effect mechanism.'' The

Agency should handle iprodione in a similar fashion and regulate iprodione via the MOE Approach.

Supporting this position, Aventis CropScience notes, that the joint meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues and the World Health Organization (WHO) Expert Group on Pesticide Residues determined in 1995 that a risk assessment utilizing a margin of safety approach with an uncertainty factor of 100 applied to the no oberserved adverse effect level (NOAEL) from the chronic rat study was appropriate to provide adequate dietary safety for Iprodione.

Again, Aventis CropScience contends that a complete evaluation of the carcinogenicity issue indicates that iprodione is a threshold carcinogen acting through a non–genotoxic mechanism of toxicity. The application of a low dose quantitative risk assessment for Iprodione is inappropriate.

6. *Animal metabolism*. A general metabolic pathway for iprodione in the rat indicates that biotransformation results in hydroxylation of the aromatic ring, degradation of the isopropylcarbamoyl chain and rearrangement followed by cleavage of the hydantoin moiety. Additionally, structural isomers of iprodione resulting from molecular rearrangement, as well as intermediates in the pathway, were detected.

7. *Metabolite toxicology*. The residues of concern in plants for tolerance setting purposes are the parent, its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1- imidazolidinecarboxamide, and its metabolite 3-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide. In animal commodities, tolerances are established on the parent, its isomer 3-(1-methylethyl)-N-(3,5-dichlorophenyl)-2,4-dioxo-1-imidazolidinecarboxamide, its metabolite 3-(3,5-dichlorophenyl)-2,4- dioxo-1-imidazolidinecarboxamide, and an additional metabolite N-(3,5-dichloro-4-hydroxyphenyl)-ureidocarboxamide.

8. *Endocrine disruption*. In the carcinogenicity studies conducted for iprodione, the primary lesion at the level of the target organs (testes, ovaries & adrenals) is likely to be related to an inhibition of steroid/androgen biosynthesis. The resulting endocrine toxic effect due to iprodione is fairly moderate compared to that produced by potent endocrine disruptors such as Flutamide, Vinclozolin (and other structural analogs) and is insufficiently potent to produce effects on reproduction or development.

The increased incidence in tumors in both rats and mice was only observed when animals were treated at or above the MTD. For all three tumor sites (testis, liver, ovary) tumors only develop on pre–existing non–neoplastic lesions (cell hypertrophy/vacuolation, hyperplasia) and Aventis CropScience concludes that a clear threshold level exist for both non–neoplastic lesions and tumors. Those thresholds are far in excess of those levels of iprodione that the general public would be exposed to. Iprodione is not expected to induce any adverse effects related to endocrine disruption in members of the general population via the consumption of food containing residues of this compound.

C. Aggregate Exposure

1. *Dietary exposure*. Aventis CropScience expects that potential residues resulting from the proposed use of iprodione on canola and the increased application rate on almonds will not significantly affect EPA's exposure and risk assessments for currently registered uses of iprodione.

i. *Food*. Dietary exposures for iprodione were reevaluated by EPA as part of the reregistration process (1998). The lifetime cancer risk from potential iprodione residues in foods with existing tolerances and drinking water was estimated to be 1.8×10^{-6}. This cancer risk corresponds to a dietary exposure of 0.000041 mg/kg/day or 0.2% of the reference dose (RfD). A chronic dietary exposure analysis for iprodione residues in canola only was conducted for the overall population and 0 26 population subgroups, including infants and children, to determine the incremental risk resulting from the proposed use on canola. Chronic exposure estimates from residues in canola only were less than 0.1% of the RfD for all population subgroups examined. The corresponding lifetime cancer risk was estimated to be 9.44×10^{-9} or less for all lifetime population groups. Chronic exposure estimates from residues in almonds only were also less than 0.1% of the RfD for all population subgroups examined. The corresponding lifetime cancer risk was estimated to be 2.23×10^{-8} 8 or less for all lifetime population groups. Thus, the incremental chronic dietary risk resulting from the proposed use on canola and the increased application rate on almonds does not increase the cancer risk to an unacceptable level.

Acute dietary exposure was estimated for the population subgroup of concern, women 13 years of age and older. Utilizing the Tier 3 methodology (Monte Carlo) for acute exposure, margins of exposure (MOEs) up to the 99.9th percentile of exposure for this population subgroup were at least 351 for currently registered crops. Adding residues in canola and residues in almonds that reflect the revised application rate resulted in MOEs of 351 and 366, respectively, at the 99.9th percentile of exposure. The EPA has determined that a MOE of at least 300 is acceptable for iprodione.

ii. *Drinking water*. Iprodione, applied according to labeled use and good agricultural management practices, is predicted and demonstrated to present no significant, if any, concentrations in drinking water sources. Iprodione's physical-chemical properties and actual measured environmental concentrations in field dissipation/monitoring studies provide support for this conclusion.

Five conservative aggregate exposure and risk assessments were conducted by EPA for the Iprodione RED. These risk assessments include combined exposures to iprodione through food and water in the diet: (a) Acute dietary; (b) chronic dietary; (c) cancer; (d) short-term; and (e) intermediate-term risk. EPA concludes in the RED document that residues of iprodione are not expected to exceed the Agency's drinking water level of concern for either acute or chronic exposure. EPA also concluded with reasonable certainty that residues of iprodione in drinking water (when considered along with exposure from food) would not result in unacceptable short-term and intermediate term aggregate human health risk estimates at this time.

Since the completion of the RED, EPA recently issued a Data Call–In requiring the submission of 3,5-dichloroaniline (3,5-DCA)-targeted surface and ground water monitoring studies relating to golf course use of iprodione products. Aventis has since submitted to the Agency an aerobic soil metabolism study and a soil adsorption/desorption study conducted with 3,5-DCA. Risk analyses using these recent data and EPA's standard operating procedures confirm that there is no concern for contamination of drinking water resulting from the use of iprodione products on golf courses.

Aventis CropScience expects that potential residues resulting from the proposed use of iprodione on canola and the proposed application rate increase on almonds will not significantly affect EPA's exposure and risk assessments for drinking water. Most of the use on canola will occur in the states of North Dakota and Minnesota. The amount of product that

will be used on canola is expected to be minimal compared to that used on currently registered crops. The total amount of product used on almonds is not expected to increase significantly.

2. *Non–dietary exposure*. This assessment is not applicable since all residential uses of iprodione products have been cancelled.

D. Cumulative Effects

The Agency has previously noted both structural and toxicological similarities between iprodione, procymidone and vinclozolin. There are clear differences in both the type and magnitude of effects observed after exposure to iprodione in contrast to vinclozolin and procymidone. Vinclozolin and procymidone are known to exert their identical endocrine effects via a blockage of the androgen receptor. By contrast, iprodione has poor binding affinity to the androgen receptor and the primary lesion appears to be a blockage of testosterone biosynthesis and secretion. Subsequently, iprodione only appears to induce transient changes in plasma hormone levels until compensatory mechanisms take effect. Consequently, Aventis CropScience concludes that consideration of a common mechanism of toxicity is not appropriate at this time since there is no reliable data to indicate that the toxic effects caused by Iprodione would be cumulative with those of any other compound.

E. Safety Determination

1. *U.S. population*. Dietary exposures for iprodione were reevaluated by EPA as part of the reregistration process (1998). The lifetime cancer risk from potential iprodione residues in foods with existing tolerances and drinking water is estimated to be 1.8×10^{-6}. This cancer risk corresponds to a dietary exposure of 0.000041 mg/kg/day or 0.2% of the reference dose (RfD). Chronic dietary exposure to iprodione residues in/on canola only was estimated to be less than 0.1% of the RfD for the general U.S. population and 26 population subgroups. The lifetime cancer risk from potential iprodione residues in canola only was estimated to be 8.27×10^{-9} for the overall U.S. population. For the most highly exposed population subgroup, nonhispanics other than black or white, the cancer risk was estimated to be 9.44×10^{-9}. Chronic dietary exposure to iprodione residues in/on almonds only was also estimated to be less than 0.1% of the RfD for the general U.S. population and 26 population subgroups. The lifetime cancer risk from potential iprodione residues in almonds treated at the increased application rate was estimated to be 1.36×10^{-8} for the overall U.S. population. For the most highly exposed population subgroup, those living in the Pacific region of the U.S., the cancer risk was estimated to be 2.23×10^{-8}. The cancer risk estimates for currently registered crops, drinking water, almonds treated at the proposed increased application rate, and the proposed use on canola are within the range the Agency generally considers negligible for excess life-time cancer risk.

For crops with existing tolerances, acute dietary exposure at the 99.9th percentile for women 13 years of age and older resulted in a MOE of 351. Separate acute exposure analyses conducted for (i) all registered crops including almonds treated at the increased application rate and (ii) all registered crops and canola, resulted in MOEs of 351 and 366, respectively, for this subgroup. Iprodione uses are not expected to impact ground water. Upper bound estimates of iprodione in surface waters from conservative screening models indicate concentrations of a few parts per billion.

Both the chronic and acute dietary exposure assessments clearly demonstrate a reasonable certainty that no harm will result from the use of iprodione on currently registered crops, including almonds treated at the increased application rate, and canola.

2. *Infants and children*. In assessing the potential for additional sensitivity of infants and children to residues of iprodione the available teratology and reproductive toxicity studies and the potential for endocrine modulation by iprodione were considered.

Developmental studies in two species indicate that iprodione has no teratogenic potential, even at maternally toxic dose levels. Maternal and developmental NOAELs and LOAELs were generally comparable indicating no increased susceptibility of developing organisms. In addition the results of a recently completed study have confirmed that Iprodione has no effects on sex differentiation. Multigeneration rodent reproduction studies indicated that Iprodione has no adverse effects on reproductive performance, fertility, fecundity or sex ratio. Effects on pup weight and viability were only noted in the presence of severe parental toxicity.

The mechanism of endocrine modulation associated with iprodione (inhibition of testosterone biosynthesis) appears to be distinct from that of anti-androgens acting at the level of the androgen receptor and may help to explain the lack of adverse effects on reproductive function observed with Iprodione.

Therefore, based upon the completeness and reliability of the toxicity data and the conservative exposure assessment, there is a reasonable certainty that no harm will result to infants and children from exposure to residues of iprodione and no additional uncertainty factor is warranted.

The EPA Health Effects Division (HED) determined that the developmental NOAEL for iprodione was relevant only to women of childbearing age and concluded that the developmental NOAEL is not relevant to acute dietary exposures to infants and children. Because no non-developmental acute effects have been identified, there is no acute toxicological endpoint to assess acute dietary risk to infants and children.

Based on the chronic exposure assessment conducted by EPA for uses currently registered, aggregate exposure to iprodione from food utilizes 1.6% of the RfD for non-nursing infants less than 1 year old and less than 1% for all other population subgroups. Chronic dietary exposure to iprodione residues in/on canola only was estimated to be less than 0.1% of the RfD. Chronic dietary exposure to iprodione residues in/on almonds only (treated at the increased application rate) was also estimated to be less than 0.1% of the RfD. EPA generally has no concern for exposures below 100% of the RfD. Since the potential for exposure to iprodione in drinking water is low and there is no risk from non–dietary, non-occupational exposure, the aggregate exposure is expected to be well below 100% of the RfD when accounting for the proposed use on canola and for the increased application rate on almonds. Thus, there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to iprodione residues.

F. International Tolerances

A Codex MRL for iprodione on rape seed is established at 0.5ppm. In Canada, PMRA supports the establishment of a MRL of 1.0 ppm for iprodione on canola and a temporary registration was granted. A Codex MRL for iprodione on almonds is established at 0.2 ppm.

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