

action. However, there are products that are not naturally occurring, yet they are registered by the Agency as "biochemical-like," insofar as data requirements are concerned. Thus, while 2, 6-DIPN, is synthetic and does not occur naturally in any food or non-food plants, it is structurally similar to three compounds (1-isopropyl- 4,6-dimethylnaphthalene, 1-methyl-7-isopropyl-naphthalene, and 4-isopropyl-1,6-dimethylnaphthalene) that occur naturally in potatoes, and 2,6-DIPN is functionally identical to the naturally occurring plant growth regulator in potatoes.

Comment 2. Mr. Forsythe expressed concern that the Agency had not presented any public documentation demonstrating that the mode of action of 2,6-DIPN is non-toxic.

EPA Response. The new active ingredient, 2,6-DIPN, is a plant growth regulator (PGR) intended to inhibit sprouting in stored potatoes. PGRs may stimulate or retard ripening, maturity of whole plants and/or fruits, enhance growth, yield, enhance or counteract the activities of other PGRs, and/or change plant architecture (amongst other processes). PGRs are not toxic to the target plant, especially at the application rate. Tests conducted during the experimental use permit showed no toxicity to potatoes. None of these actions are directly lethal to the plants upon which they are applied, which supports a determination that 2, 6-DIPN operates through a non-toxic mode of action. Diisopropyl-naphthalene is similar in molecular structure, and functions as three sprout inhibiting compounds naturally occurring in potatoes (1-isopropyl-4,6-dimethylnaphthalene, 1-methyl-7-isopropyl-naphthalene, and 4-isopropyl-1,6-dimethylnaphthalene). The three compounds found in potatoes and 2,6 DIPN are all isopropyl naphthalene, a sprout inhibitor in a manner comparable to natural PGRs found in potato plants (as described above). In addition, acute toxicity studies conducted on animals indicated Toxicity Category IV for all routes of exposure and chronic studies were not triggered following the data requirements for biochemical pesticides as given in 40 CFR 158.690(c). EPA therefore has concluded that its mode of action can be classified as "non-toxic."

Comment 3. Mr. Forsythe expressed concerns regarding dietary intake of 2,6-DIPN, due to: (1) The synthetic nature of the compound; and (2) the lack of toxicity information to support an assessment of dietary exposure to 2,6-DIPN.

EPA Response. As discussed in the previous response, the data support the

classification of 2,6-DIPN as a biochemical, based on its structural similarity to naturally occurring PGRs. In addition, the registrant has conducted a series of toxicity tests according to the requirements listed in 40 CFR 158.690, in support of experimental use permits (EUPs) and for product registration. Dietary exposure estimates were based on the assumption that 100% of the crop will be treated, and other worst-case assumptions were applied to overestimate the typical dietary exposure likely under normal conditions of use.

A 90-day oral toxicity study (MRID 450493-01) demonstrated that rats did not exhibit immune system effects, demonstrated by no changes in spleen or thymus weights and absence of lesions in spleen, thymus, and lymph nodes. The 90-day oral no observable adverse effects level (NOAEL) was 100 milligrams/kilogram/day (mg/kg/day), and the lowest observable adverse effects level (LOAEL) was 200 mg/kg/day, based on decreased body weight gain and food consumption. In a developmental toxicity study (MRID 4500010-01) in rats, the test animals did not exhibit increased fetal susceptibility to 2,6-DIPN when compared to untreated animals. The prenatal developmental toxicity NOAEL was 150 mg/kg/day and the LOAEL was 500 mg/kg/day, based on decreased fetal body weight and a possible treatment-related cartilage anomaly.

The toxicity data on 2,6-DIPN does not indicate extra sensitivity of offspring when compared with that of adult animals, but the data base does not represent a complete assessment of potential age-related sensitivity or acute effects other than lethality. The absence of a developmental toxicity study in a second species, a multigeneration reproduction toxicity study, or a range of doses adequate to induce a full range of toxic responses, especially potential acute effects in any of the available studies, required that the FQPA 10-fold safety factor be retained in defining EPA's level of concern.

Studies submitted to test the potential genotoxicity or mutagenicity of 2,6-DIPN included a reverse mutation (Ames) assay (MRID 446141-11), an unscheduled DNA synthesis assay in rat primary hepatocytes (MRID 446141-10), and a mouse micronucleus assay (MRID 446141-12); all of these were negative. A mouse lymphoma assay (MRID 454388-01) was positive at higher concentrations for mutagenicity, but since 2,6-DIPN was cytotoxic (killed the test cells) at the those concentrations where the positive results occurred (with and without metabolic activation),

the test results are considered as being equivocal, or falsely positive. As a group, these four studies demonstrated that 2,6-DIPN is not a mutagen.

Information supplied by the commenter (Ref. 5) noted that "Di-Isopropyl-naphthalene(s) contained no chemical groups that would be structurally alerting for potential mutagenicity." Additionally, in spite of the equivocal study (MRID 454388-01), "there was no evidence for a mutagenic effect in other *in-vitro* mutagenicity tests or in an adequately performed *in vivo* micronucleus assay in mice. The Committee agreed that no further mutagenicity testing was required."

Based on the absence of effects on the immune system in the 90-day subchronic study, no effects on developing rats at doses below those causing maternal effects, and no genetic toxicity, Tier II and Tier III toxicity data requirements were not triggered. The Agency does not require any additional toxicity studies at this time although a livestock feeding study must be conducted as a condition of registration (see EPA Response to Comment 4).

Comment 4. Mr. Forsythe stated that, in the absence of any chronic toxicity data, "it would be inappropriate to disregard the safety factor" (referring to the FQPA 10-fold margin of safety to account for effects on sensitive populations, such as infants and children), and that "threshold effects cannot be fully determined, and a safety factor would seem appropriate to address this lack of a complete data set regarding dietary exposure and chronic toxicity."

EPA Response. As stated above, the Agency has retained the FQPA safety factor in its assessment of the dietary exposure to 2,6-DIPN.

Comment 5: Mr. Forsythe stated that the Agency should consider non-dietary and non-occupational sources of human exposure to 2,6-DIPN. The commenter submitted an EPA document (Ref. 5), in which 2,6-DIPN is described as an "emerging pollutant" in Lake Michigan. The document also states that polychlorinated biphenyl (PCB) substitute compounds (which include 2,6-DIPN), are "detected in effluent, sediment, and fish in the basin; bioaccumulative and toxic."

Additionally, the commenter provided information that European governments have expressed concerns regarding public exposure to DIPNs via the paper industry. In studies conducted by the United Kingdom Joint Food Safety and Standards Group (JFSSG), it was determined that DIPNs could be present in recycled food packaging and in packaged food (Ref. 5). DIPNs were