

870.3700; 152–23; MRID 450001–01), the maternal toxicity LOAEL is 150 mg/kg/day based on reduced body weight gains and food consumption. The maternal toxicity NOAEL is 50 mg/kg/day. The developmental toxicity LOAEL is 500 mg/kg/day based on reduced fetal body weights and a slightly increased incidence of a skeletal alteration (fusion of cartilaginous bands in the cervical centra). The developmental toxicity NOAEL is 150 mg/kg/day.

A mouse lymphoma gene mutation assay (OPPTS Harmonized Guideline 870.5300; 152–17; MRID 454388–01) showed that 2,6-DIPN might be mutagenic without metabolic activation at doses between 10–30 µg/mL. With metabolic activation, the results were equivocal at doses between 25–90 µg/mL. Cytotoxicity was observed in tests using the aforementioned doses, with and without metabolic activation. No genotoxicity was observed in other acceptable studies including a reverse mutation (Ames) assay (OPPTS 870.5100; 152–17; MRID 446141–11), *in vivo/in vitro* unscheduled DNA synthesis (UDS) assays in rat primary hepatocytes (OPPTS 870.5550; 152–17; MRID 446141–10), and a mouse micronucleus assay (OPPTS 870.5395; 152–17; MRID 446141–12). The collective data from the four-study mutagenicity battery demonstrates that 2,6-DIPN is not likely to be mutagenic.

#### B. Toxicological Endpoints

1. *Acute toxicity.* The acute toxicity studies were acceptable in accordance with the guidelines as discussed in Unit III.A. All studies were performed at a single limit dose with no observable (non-lethal) toxic endpoints.

2. *Short-term and intermediate-term toxicity.* Although the rat developmental toxicity study indicates a lower maternal NOEL (50 mg/kg/day) for similar toxicity than the subchronic toxicity study (reduced body weight, weight gain and food consumption), the maternal LOAEL of 150 mg/kg/day falls between the subchronic NOEL of 104–121 mg/kg/day and the subchronic LOAEL of 208–245 mg/kg/day. The maternal NOEL of 50 mg/kg/day from the developmental toxicity study may be appropriate for use in characterization of risks for the subpopulation of women 13–49 years of (child-bearing) age. However, the 104 mg/kg/day NOEL in the subchronic study was selected as the endpoint for short-term and intermediate-term dietary assessments since the effects observed at the subchronic LOAEL (208–245 mg/kg/day) were more thoroughly defined than the developmental effects observed at the

LOAEL (500 mg/kg/day) in the developmental toxicity study, which were minimal.

A reference dose (RfD) of 1 mg/kg/day is established by dividing the 104 mg/kg/day NOEL by a 100-fold uncertainty factor (10X for interspecies extrapolation and 10X for intraspecies variability). Available developmental toxicity data on 2,6-DIPN does not indicate extra sensitivity of offspring when compared with that of adult animals, but a developmental toxicity study in a second species and a multigeneration reproduction toxicity study are needed to fully determine age-related differences in response. In addition, residues have been detected in treated potatoes under laboratory and field conditions. Therefore, the default safety factor of 10X is retained, and acute and chronic population adjusted doses (aPAD and cPAD) for dietary risk characterizations are established by dividing the RfD by 10X (accounting for age-related sensitivity for the subpopulations of infants and children). Therefore, the aPAD and cPAD are 0.1 mg/kg/day.

3. *Chronic toxicity.* An extra 10-fold uncertainty factor for the absence of chronic toxicity data were not applied to determine a RfD because 2,6-DIPN has been classified as a biochemical pesticide having a non-toxic mode of action with biological activity more specific to plants than animals. Acute toxicity studies on animals indicated Toxicity Category IV for all routes of exposure. Chronic studies are not required to support registration of biochemical pesticides unless all of the following are true:

- i. Has subchronic toxicity.
  - ii. Its use pattern involves a significant rate, frequency or site of application.
  - iii. The frequency and level of human exposure are significant (40 CFR 158.690(c)).
- These criteria were evaluated in the Agency's risk assessment (Refs. 1 and 2) which compared the cPAD to worst-case estimates of dietary exposure. The use pattern and exposure associated with 2,6-DIPN on potatoes in storage does not trigger chronic studies. Since the conservative exposure estimates did not result in risk characterizations exceeding the defined level of concern (exposure >100% of the cPAD).

4. *Carcinogenicity.* Based on the 90-day oral toxicity study and the genotoxicity/mutagenicity studies, there were no results to indicate potential neoplastic changes, and the genetic toxicity studies did not suggest carcinogenic potential in mammalian cells.

#### C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* There is a potential for dietary exposure to 2,6-DIPN, which can occur following its application to stored potatoes. According to the label, the plant growth regulator is to be applied at a rate of 16.6 ppm (weight/weight), and as many as three applications can be used in a storage period with a minimum interval between application and use of the treated potatoes of 30 days.

*Residue profile.* The submitted residue chemistry data for the use of 2,6-DIPN on potatoes is limited, and important factors in this assessment depend on default assumptions or hypothetical calculations having a low level of confidence.

For purposes of this rule, the regulated residue is considered to be 2,6-DIPN, and a potential for some accumulation of 2,6-DIPN residues in body and subcutaneous fat was observed. These results and the possible use of peels with residues from treated potatoes as livestock feed (processed potato wastes are used for this purpose) suggest that residues of 2,6-DIPN may occur in meat and milk; however, this has not been evaluated in a livestock metabolism study.

Limited field and laboratory residue data suggested tolerance levels as high as 0.5 ppm in/on whole potatoes, 3 ppm on potato peels, 1.35 ppm in meat and meat by-products, and 0.7 ppm in milk.

The analytical method for 2,6-DIPN has a level of quantification (LOQ) of 0.02 ppm and field and laboratory studies suggests that 20 ppm is a likely maximum commercial application rate for 2,6-DIPN. Residue levels expressed as 2,6-DIPN were reported at 3 ppm in potato peels and 0.5 ppm in whole potatoes.

In a published report (MRID 451632–01), the investigators noted that DIPNs could accumulate in the fat of treated rats suggesting a potential for secondary residues in meat and milk from livestock fed treated potatoes, but a livestock metabolism study was not submitted. Worst-case estimates of secondary residues were calculated for meat (1.35 ppm) and milk (0.7 ppm) of beef/dairy cattle fed waste from 2,6-DIPN-treated processed potatoes.

Supplementary metabolism information was submitted on 2,6-DIPN in rats from two published articles (MRID 451632–01). In one study, rats were given either a single dose or 30 daily oral doses, at 100 mg 2,6-DIPN per kg body weight. Residues of 2,6-DIPN were detected in all tissues 2 hours after receiving the test dose. With the