

2. *Genotoxicity.* Penoxsulam was negative for genotoxicity when tested in *in vitro* and *in vivo* systems.

3. *Reproductive and developmental toxicity.* Penoxsulam did not have any effect on reproductive parameters at dose levels that induced treatment-related effects in parental rats. At the highest dosage tested (HDT) (300 mg/kg/day), body weights and weight gains in both males and females were depressed, liver and/or kidney weights were increased, and histologic changes were noted in the liver (males) and kidneys (females). At 100 mg/kg/day, increased liver weights were recorded in males, with no histologic correlate, and histologic changes noted in the kidneys of females. Transient decreases in pup body weights were seen at the HDT, but dietary concentrations were targeted for adults and consumption of treated diets by the pups resulted in dose levels to the pups approximately 3-fold higher than in adults. A teratogenic potential was not demonstrated for penoxsulam in either rats or rabbits.

4. *Subchronic toxicity.* Dietary exposure to penoxsulam identified the liver and/or urinary tract (kidneys and bladder) as target organs in rats, mice, and dogs following a 4-week and 13-week administration. Effects on the liver were reflected in increased liver weights and hepatocellular hypertrophy, but these effects were not associated with increases in mixed function oxidase (MFO) enzyme activity. Effects noted in the kidneys included crystal deposition, most likely from precipitation of penoxsulam from the urine, with resultant irritation, inflammation, and hyperplasia of renal pelvic transitional epithelium. Other than the crystal deposition in the kidneys, all effects following subchronic exposure to rats appeared to be reversible. Very high doses were associated with significant decreases in body weight, weight gain, and feed consumption.

5. *Chronic toxicity.* Chronic exposure in the dog indicated that the renal effects were not exacerbated with long-term exposure. Following long-term exposure in rats, the kidneys and urinary bladder were the primary target organs. Histologic changes seen at the end of 2 years of exposure consisted of inflammation and hyperplasia of the renal pelvic transitional epithelium, crystal deposition in the kidneys and urinary bladder, and hyperplasia of the mucosa of the urinary bladder. In the mouse, the liver was the primary target organ, and histologic changes consisted of hepatocellular hypertrophy. There were no treatment-related increases in tumors in either rats or mice. The incidence of mononuclear cell leukemia

(Fischer rat leukemia) was increased in all groups of treated male rats compared to the concurrent controls. However, the incidences in the treated groups were identical across a 50-fold increase in dosage, and well within the range of control values reported in the literature.

Using the Guidelines for Carcinogen Risk Assessment published September 24, 1986 (51 FR 33992), it is proposed that penoxsulam be classified as Group E for carcinogenicity (no evidence of carcinogenicity) based on the results of carcinogenicity studies in two species. Dow AgroSciences LLC believes there was no evidence of carcinogenicity in an 18-month mouse feeding study and a 24-month rat feeding study at all dosages tested.

6. *Animal metabolism.* Orally administered penoxsulam is rapidly absorbed, excreted and extensively metabolized in both male and female rats, thus, indicating that penoxsulam is not expected to accumulate in biological systems. The majority of the residue was associated with the parent, penoxsulam. Several metabolites were also observed but the vast majority were <1% of the administered dose. The major route of metabolism involves O-demethylation, producing the OH-Penoxsulam metabolite followed by conjugation.

7. *Metabolite toxicology.* A metabolism study with penoxsulam in rice revealed the presence of the parent, a desmethylation metabolite (5-OH-penoxsulam), and two other polar metabolites, which may represent conjugates of the desmethylated metabolite. The 5-OH-penoxsulam metabolite and its glucuronide and glutathione conjugates have also been identified in the plasma and liver of rats; therefore, plant metabolites are considered of little toxicological concern.

8. *Neurotoxicity.* Penoxsulam has been shown to have no neurotoxicologic potential based on acute and subchronic studies.

9. *Endocrine disruption.* Penoxsulam did not have any effects on endocrine organs or tissues in mice, rats or dogs in any of the studies conducted. There were no indications of effects on fetal development in either rats or rabbits, or on reproductive performance in rats. Based on the lack of any effects on the endocrine system, penoxsulam is not considered an endocrine disrupter.

C. Aggregate Exposure

Dietary exposure. Based on the rapid degradation of penoxsulam, no surface water or ground water contamination is expected. This agrees with EPA Tier I modeling carried out on penoxsulam. Therefore, drinking water will not be a

significant route of exposure. Dietary exposure is very low as previously mentioned. In addition, a rotational crop study showed no carryover of penoxsulam related residues in any representative test crop. There are no residential uses for this compound. As a result, the only potential for exposure is dietary, which is acceptable. Therefore, aggregation of exposures is not necessary.

D. Cumulative Effects

Currently, no methodologies are available to resolve the complex scientific issues concerning common mechanism of toxicity and cumulative exposure and risk. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. Thus, Dow AgroSciences LLC believes it is appropriate to consider only the potential risks of penoxsulam in its exposure assessment.

E. Safety Determination

1. *U.S. population.* Using the conservative exposure assumptions described above, and based on the completeness and reliability of the toxicity data, the aggregate exposure to penoxsulam, as determined under the guidance of the FQPA, will utilize no more than 0.1% of the RfD from the dietary exposure for all subgroups of the U.S. population. Generally and under the Food Quality Protection Act (FQPA), EPA has no concern for exposures below 100% of the reference dose (RfD) because the RfD represents the level at or below which daily dietary exposure over a lifetime will not pose appreciable risks to human health. Additionally, the calculated drinking water levels of concern (DWLOC) was substantially higher than the potential penoxsulam concentration in water. Therefore, there is a reasonable certainty that no harm will result to the general U.S. population from aggregate exposure to penoxsulam residues from proposed use.

2. *Infants and children.* In assessing the potential for additional sensitivity of infants and children to residues of penoxsulam, data from developmental toxicity studies in rats and rabbits and a multi-generation reproduction study in the rat are considered. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development. Reproduction studies provide information relating to effects from exposure of both parents to the pesticide on the reproductive capability and potential systemic toxicity of