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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ASANA Insecticide 1.9 EC (24.0% ai) - EPA File Symbol 201-URI and Technical ASANA Insecticide (75.0% ai) - EPA File Symbol 201-URO: Response to the Sponsor's Proposal to Raise the NOEL of 50 ppm to 150 ppm in the 13-Week Rat Feeding Study

Tox. Chem. No. 77A

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Under cover letters dated May 23 and July 21, 1986, the Shell Chemical Company has proposed that the no-observed-effect level (NOEL) observed in the 13-week rat feeding study be raised from 50 parts per million (ppm) to 150 ppm. The Shell Chemical Company provided the following rationale as to why the NOEL should be raised.

> "During the course of the study, rat TP3M22 in the 150 ppm dose group was observed to have 'jerky leg movements' on week 11 of the study . . . this incident consisted of a mild prolonged flexion of the hindlimb

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as the animal reentered his cage following examination. The sign was not observed during any subsequent examinations of the animal. Therefore, it was a unit event of a subjective observation which cannot be confirmed due to lack of reoccurrence of longer duration of the clinical sign. In fact, it is not unlikely for such an incident to occur if an animal's leg were to be temporarily caught in the wire floor of a cage. In addition to the fact that this sign is not clinically significant, since it was only observed in one animal at one time point, it is important to considered that pyrethoids have two distinctive actions - a short-term pharmacological effect which results in sparse axonal damage. The clinical signs, jerky leg movements, would be a reversible pharmacological action as opposed to a neurotoxic effect. Therefore, it can be concluded that the 'jerky leg movements,' which were barely detectable in one rat of 40, is not a significant toxicologic event. Based on the above reasoning, the no observable effect level is 150 ppm."

In addition, the Shell Chemical Company enclosed documentation from the veterinary pathologist at the contract laboratory that addresses the significance of the observations of "jerky leg movements" in rats in the study. The pathologist (W.A. Kelly) indicated that by the end of week 1 some of the animals in the 500 ppm group had abnormal forelimb and hindlimb movements and an abnormal gait which was recorded as "jerky leg movements" and "unsteady gait." By week 5 "jerky leg movements" were observed in some of the animals in the 300 ppm group. During week 11, prolonged flexion of the hindlimbs was noted in one rat in the 150 ppm group. This was the only time during the study that the rat in the 150 ppm group exhibited "jerky leg movements." The pathologist's summary was as follows:

"In summary, during weekly clinical examinations performed by the study director, group/treatment related clinical signs characterized by abnormal limb movements were noted for animals fed the 300 and 500 ppm MO 70616 diets. The presence of these signs was based on subjective evaluation and usually required close observation of limb movements during ambulation. The clinical signs were most

severe and observed early in the study in the 500 ppm MO 70616 group animals. Later in the study, some animals fed the 300 ppm MO 70616 diet had similar but milder clinical signs which were usually limited to a prolonged flexion of the hindlimbs observed as the animals entered their cages. On one occasion, prolonged flexion of the hindlimbs was noted for one of the 40 animals in the 150 ppm MO 70616 group. This mild clinical sign was not observed during subsequent weekly examinations of this animal."

The Toxicology Branch (TB) believes that neurological dysfunction as manifested by the "jerky leg movements" can be attributed to administration of the test material. There is a clear dose-response relationship as indicated by an increasing incidence of this pharmacotoxic sign in groups of animals as dosage increased, beginning at the 150 ppm dose level. In addition, the latency period for developing this pharmacotoxic sign was decreased as dosage increased. Also, the severity of the neurological signs observed increased as dosage increased. Although only one animal out of the 40 in the 150 ppm group displayed "jerky leg movements" it is believed that if the number of animals in the group was increased additional animals would probably have exhibited this clinical sign of toxicity. Considering that the one animal in the 150 ppm group exhibited mild clinical signs identical to the type observed in animals in the higher-dose groups, and the low number of animals per group, TB cannot discount the occurrence of the observation of "jerky leg movements" in the one animal even though it was only observed on one occasion.

The Shell Chemical Company also presents the argument that this abnormal clinical sign was a "reversible pharmacological action" and not a "significant toxicologic event." TB disagrees; the distinction between pharmacological and toxicological effects are difficult, if not impossible, to define. Therefore, TB considers the occurrence of "jerky leg movements" to be a pharmacotoxic effect, synonymous in a regulatory sense to an "adverse effect." In conclusion, the NOEL is still considered to be 50 ppm and will not be raised to 150 ppm.

Recommendation

Despite the arguments presented by the Shell Chemical Company concerning raising the NOEL from 50 ppm to 150 ppm, the TB maintains that the NOEL should be 50 ppm. TB cannot discount the observation of "jerky leg movements" in one

animal in the 150 ppm group because the pharmacotoxic sign was observed with increasing frequency in other groups of animals as dosage increased.