TOX REV 276 OK

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Glyphosate - Tolerances for the herbicide N-phosphonomethyglycine and its metabolite aminomethylphosphonic acid.

Toxicology Branch

File of petitions: 4G1444, 5G1523, 5F1536, 6G1679/6H5106, 6F1733/6H5116, 6G1734/6H5118, 6G1757, 6F1758/6H5126, 6F1798, 6G1809, 6G1826/6H5140, 6H5144, 6F1861, 6G1862, 7G1893/7H5158

The no effect level reported for the three generation rat reproduction study in 4G1444, as greater than 300 ppm is incorrect. The text of the reviewers evaluation of the data cite reduced mating, fertility and pregnancy indices for both of the F2a and F3a litters fed the 300 ppm level. There were no differences with reproductive indices between controls and the test groups fed 30 or 100 ppm level. The no-effect level for the three generation rat reproduction study is 100 ppm.

The need for additional subacute studies on the metabolite aminomethylphosphonic acid has been raised with a review of 6F1758/6H5126 by Dr. Quaife. With reference to PP No. 4G1444, Chemistry Branch memo of June 3, 1974 indicates that "significant degradation of the parent compound occurs upon incorporation into the plant followed by formation of natural products within the plant. In this memo CB defers to TB as "to whether any further identification of the unextractables is needed for permanent proposals". TB memo of June 4, 1974 concluded that "the residue on human food crop are negligible and the fraction that is non-extractable would be sufficiently low to be toxicologically insignificant. Forages are not human foods and TB does not consider further identification of the unextractable portion of the residue necessary, since they are probably natural plant constituents.

Considering the similarity in the eliminations (principally in feces) of both the parent compound and its metabolite in the rat it is doubtful if a subacute feeding study on the metabolite would contribute any additional data that would alter the acceptance of the presently established tolerances.

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Toxicology Branch
Registration Division

Hank,
Reproduction
study should
have tolerated
at 100 ppm
Bill D.
my mistake

[illegible] tissues were taken and examined microscopically from 10 male and [illegible] female mice from all three groups: esophagus, stomach, small intestine, caecum, tongue, colon, liver, kidneys, spleen, pancreas, urinary bladder, adrenal gland, testes, seminal vesicles, ovary, bone marrow, thyroid gland, salivary gland, prostate gland, heart, aorta, lung, lymph node, skeletal muscle, peripheral nerve, bone, spinal cord, uterus, trachea, eye, optic nerve, skin and brain.

Results: The number of control animals that died during the experimental period was 36/50 for the males and 29/50 female animals. At the 100 ppm level 35/50 mice died in each group of male and female mice during the 18 month feeding. At the 300 ppm 32/50 mice died in each group of males and females during the experimental period. Gross and microscopic pathologic examination revealed no correlation between the ingestion of the technical material and any neoplastic lesions observed in the test mice. The test material did not induce a carcinogenic response in this test system. The incidence or pattern of mortalities were not affected by the exposure to this material.

Conclusion: Glyphosate is neither tumorigenic nor carcinogenic when fed at dietary levels up to 300 ppm to mice for 18 months.

5/13/74

Original Received

3 Generation Reproduction Study - Rats

Method: Eight males and 16 female rats were fed dietary levels of 0, 30, 100 and 300 ppm for the F_0 parental generation and each of the succeeding F_{1b} and F_{2b} generations. The study was terminated following the weaning of the F_{3b}. Animals in all groups were maintained on their respective diets without interruption until their sacrifice, which followed the weaning of the second litters. Mating trials were initiated when the parental animals were 100 days old. The first litters (F_{1a}, F_{2a} and F_{3a}) obtained were weaned at 21 days post-partum. The parental females were given a 10 day rest period and again mated to obtain the second litter. All females were observed for fertility, length of gestation and lactation performance. All pups were examined for physical abnormalities at birth and the number of viable and still born were recorded. The weight of the liver, kidneys, spleen, gonads, heart, and brain were recorded, along with the final body weight of each rat. Statistical analyses were conducted on absolute organ and upon the organ to body weight and organ to brain weight ratios. The following tissues were examined microscopically from five males and five females from each level tested: heart, trachea, lung, liver, pancreas, stomach, small intestine, caecum, colon, spleen, lymph node, kidney, urinary bladder, testis, ovary, prostate, uterus, pituitary gland, adrenal gland, salivary gland, thyroid gland, parathyroid gland, skeletal muscle, bone marrow, peripheral nerve, brain, seminal vesicles, esophagus, spinal cord.

Results: Ingestion of the test material had no adverse effect upon parental body weight or body weight gains. There were no deaths during the investigation which could be attributed to the test material. No untoward behavioral reactions were noted among test or control animals. Organ weights, organ to body weight and organ to brain weight ratios revealed no consistent intergroup differences. All lesions noted during histopathologic evaluation revealed no relationship to the ingestion of the test material. Parameters of reproductive ability were similar for test and control animals during the first (F_{1a} and F_{1b} litters generation. Animals fed 300 ppm exhibited reduced mating, fertility and pregnancy indices during the first litters of both the second and third generation (F_{2a} and F_{3a} litters). These parameters were comparable to those of the control group during the second litters (F_{2b} and F_{3b}) breedir periods; the reduced parameters of reproductive ability which were observe during the "a" litters then compared favorably with the control group valu There were no intergroup differences with respect to reproductive parameto with either the control or groups fed the 30 or 100 ppm level. No differe between test and control pups which could be attributable to the test material with the number delivered, survival indices, behavioral reactions external anomalies, growth patterns or gross and histopathologic examinati

Conclusion: The reproductive no-effect level for rats fed glyphosate for three generations is greater than 300 ppm.

Metabolism Studies - Rabbit

Methods: Single oral doses of ^{14}C labeled phosphonomethyl were administered in two replicate experiments to three male rabbits receiving the test material labeled in the methylene position and two each received the test material labeled in either the carboxyl or the alpha carbon posit of the glycine moiety. The doses ranged from 5.7 to 8.8 mg/kg. After dos each animal was housed in an individual metabolism unit for 120 hours. Excreta and carbon dioxide samples were collected at 12, 24, 48, 72, 96 and 120 hours post administration. At the termination of the study blood samples were drawn and the following tissues were taken: liver, kidney, muscle, fat, gut, spleen, heart and testes.

Results: More than 90% of the ^{14}C activity cleared within 5 days with 80% in the feces and 7-11% in the urine. Less than 1% was expi as carbon dioxide. Within the first 12-24 hours 25-52% of the dose was cleared from the body. Methylene and carboxyl labeled materials required 120 hours before more than 90% of the dose was voided from the body. At 120 hours approximately 76-93% of the ^{14}C activity could be accounted for by the gut and its contents. In the rabbit tissue, exclusive of the gut, there was 1.2%, 0.7% and 0.1% of the dose administered of alpha carbon, carboxyl or methylene labeled material, respectively, as compared to 0.7% 0.3% and 0.1% for the corresponding labels in the rat. Only the glycine moiety appears as tissue residues with the carbon-2 of the glycine most likely to appear in the tissues. The ranking of tissue concentration of carboxyl label moiety was liver > kidney > spleen > heart, muscle and gonads. Only the alpha carbon moiety was incorporated into the fat in a measurable quantity. The rabbit requires 4 to 5 days to clear a single dose as compared to 95-98% clearance in 48 hours for the rat.