FUNCTIONAL, BIOCHEMICAL AND IMMUNOLOGICAL EFFECTS OF NIVALENOL AFTER ORAL ADMINISTRATION FOR 90-DAY IN F344 RATS

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Nivalenol (NIV) is one of trichothecene mycotoxins produced by Fusarium species because of its frequent co-contaminates in wheat and barley with deoxynivalenol in Japan. While deoxynivalenol has been evaluated regarding toxicity profile and established PMTDI by WHO/FAO JECFA, nivalenol has not yet because of its poor information about the toxicity. In the present study, we examined subchronic toxicity of NIV in male and female F344 rats by exposure through diets at doses of 0, 6.25, 25, and 100 ppm for 90 days.

During the experimental period, suppression of body weight gain as well as loose stool was observed at 100 ppm from the 1st week till the end of experiment in both sexes. Suppression of body weight gain was also observed at 25 ppm from week 6 thereafter in males and at week 4 in females. At necropsy, increase of relative testicular weight and decrease of relative thymus weight in females were detected at 100 ppm. Hematologically, decrease of white blood cell counts was found at 100 ppm in males and from 6.25 ppm in females. Histopathologically, treatment-related changes were predominantly observed in the hematopoietic and immune systems in both sexes and female reproductive system at 100 ppm, such as atrophy of the thymus, reduction of hematopoietic cells in the bone marrow, atrophy of uterine corpus, thinning of the vaginal mucosa (diestrus), increase of the ovarian atretic follicles, and increase of castration cells in the anterior pituitary.

Since the immunotoxicity and xenobiotic metabolism are the most concern of NIV, immune function and the activities of the xenobiotic enzymes in microzone and cytozole in liver were also examined using male animals. The results of serum immunoglobulin levels revealed a slight increase of IgM at 100 ppm, while IgM at lower doses and IgG or IgA at any doses did not change. Increases of B-cell population from 25 ppm and decrease of T-cell population in splenic cells were observed by flow cytometric analysis, indicating that the ratio of helper/cytotoxic T lymphocytes increased from 25 ppm. Regarding to the activities of such xenobiotic metabolite enzymes, as cytochrome P450 3A2 and 1A2, and cytosolic glutathione-S-transferase isozymes in the liver, NIV did not induce any dose-related change. Furthermore, de-epoxy NIV could not be detected in the feces or sera of administered animals by GC-MS analyze.

Taken together, NIV targets female reproductive system as well as hematopoietic and immune systems in rats. The effect was apparent at doses from 25 ppm judging from the increase of splenic B-cell population on immunotoxicity, but such toxicities were not accompanied by changes in the liver function for xenobiotic metabolism. Based on the hematology data, the no-observed-effect level of NIV was determined to be less than 6.25 ppm.