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Moxidectin

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of a parasiticide moxidectin (CAS No. 113507-06-5). Negative results were obtained in all of the genotoxicity studies. In addition, no carcinogenicity was identified in combined chronic toxicity/carcinogenicity studies in mice and rats. The results from a reproductive and developmental toxicity study of moxidectin in rats implied its toxicity to human infants due to exposure through breast milk. However, different from rats, P-glycoprotein is expressed in human fetuses from the middle pregnancy period and is present throughout adulthood after birth. Additionally cytochrome P450 3A form, which is an isoform involved in metabolism of moxidectin, is identified in human fetuses from the late pregnancy period as well as after birth. Therefore, FSCJ concluded that the effects of moxidectin on human infants due to exposure through breast milk are not as great as those on rats. A developmental toxicity study in CF-1 mice reported a significant increase in the malformation percentages of cleft palate and others in the offspring, but the no-observed-adverse-effect level (NOAEL) was 1.5 mg/kg body weight/day. Neurotoxic signs such as tremor and hypersensitivity reactions to contact were observed in toxicity studies of moxidectin, but lacked histopathological findings. Further, the recovery from such signs was observed in rats and dogs when the dose was reduced. Considering the differences in the toxicities including neurotoxicity between the structurally similar moxidectin and ivermectin, FSCJ concluded that neurotoxicity of moxidectin is short-lasting and reversible. The effect identified at the lowest dose in the toxicity studies of moxidectin was dose-dependent reductions in body weights and food consumption observed in a 90-day subacute toxicity study in dogs, and NOAEL was 0.3 mg/kg body weight/day. Applying the safety factor of 100 to NOAEL, FSCJ specified the acceptable daily intake (ADI) of moxidectin to be 0.003 mg/kg body weight/day.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of a parasiticide moxidectin (CAS No. 113507-06-5) based on a set of data submitted from the Ministry of Health, Labour and Welfare (MHLW), evaluation documents from Joint FAO/WHO Expert Committee on Food Additives (JECFA) and European Medicines Agency (EMEA), documents from the Australian Government, and others. The data used in the risk assessment are on: pharmacokinetics (rats, cattle, sheep and horses), metabolism (rats, cattle, sheep and *in vitro*), residues (cattle, sheep, deer and horses), genotoxicity and acute toxicity (mice, rats, rabbits and chicken), subacute toxicity (mice, rats and dogs), chronic toxicity (dogs), chronic toxicity and carcinogenicity (mice and rats), reproductive and developmental toxicity (mice, rats, rabbits and dogs), and general pharmacology data. Negative results were obtained in all of the genotoxicity studies and FSCJ concluded that moxidectin has no genotoxicity relevant to human health. In addition, no carcinogenicity was identified in combined chronic toxicity/carcinogenicity studies in mice and rats. Therefore, FSCJ concluded that moxidectin is not a genotoxic carcinogen and its acceptable daily intake (ADI) can be specified. The results from a reproductive and developmental toxicity study of moxidectin in rats implied its toxicity to human infants due to exposure through breast

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milk. However, different from rats, P-glycoprotein is expressed in human fetuses from the middle pregnancy period and is present throughout adulthood after birth. Additionally cytochrome P450 3A form, which is an isoform involved in metabolism of moxidectin, is identified in human fetuses from the late pregnancy period as well as after birth. Therefore, FSCJ concluded that the effects of moxidectin on human infants due to exposure through breast milk are not as great as that on rats. A developmental toxicity study with oral gavage in CF-1 mice reported a significant increase in the malformation percentages of cleft palate and others in the offspring, but the no observed adverse effect level (NOAEL) was 1.5 mg/kg body weight/day. Neurotoxic signs such as tremor and hypersensitivity reactions to contact were observed in toxicity studies of moxidectin, but lacked histopathological findings. Further, the recovery from such signs was observed in rats and dogs when the dose was reduced. Considering the differences in the toxicities including neurotoxicity between the structurally similar moxidectin and ivermectin, FSCJ concluded that neurotoxicity of moxidectin is short-lasting and reversible, and an additional safety factor on the neurotoxicity is not necessary. The effect identified at the lowest dose in the toxicity studies of moxidectin was dose-dependent reductions in body weights and food consumption observed in a 90-day subacute toxicity study with dietary administration in dogs, and NOAEL was 0.3 mg/kg body weight/day. Applying the safety factor of 100 (10 for species difference and 10 for individual difference) to NOAEL, FSCJ specified the ADI of moxidectin to be 0.003 mg/kg body weight/day.