FOOD SAFETY

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Metronidazole

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of metronidazole (CAS No. 443–48-1), an antiprotozoan agents, based on evaluation documents from Joint FAO/WHO Expert Committee on Food Additives (JECFA) and European Medical Agency (EMEA), and others. Metronidazole showed both positive and negative results on the *in vivo* and *in vitro* genotoxicity studies. Metronidazole is reduced in bacteria, and the hydroxylamine produced during the reduction exerts genotoxicity after reacting directly with DNA. Since enzymes that reduce nitro compounds are present also in mammals including humans, the nitro group of metronidazole is possible to be reduced by such enzymes to exert the genotoxicity in humans. Although the reduction of metronidazole *in vivo* seems less likely to occur in mammals than in bacteria, DNA damage occurred after a single application of the therapeutic dose of metronidazole in humans. The genotoxic potential of metronidazole is not thus excluded in humans. In carcinogenicity studies in mice and rats, metronidazole was demonstrated to be carcinogenic. Epidemiological studies in human have suggested an association between metronidazole and tumor occurrence. International Agency for Research on Cancer (IARC) categolized metronidazole into a group of substances which are possibly carcinogenic to humans (group 2B). FSCJ could not exclude the potential of metronidazole to be a genotoxic carcinogen. Therefore FSCJ concluded that it is not appropriate to specify an acceptable daily intake (ADI) for metronidazole.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of metronidazole (CAS No. 443–48-1), an antiprotozoan agents, based on evaluation documents from Joint FAO/WHO Expert Committee on Food Additives (JECFA) and European Medical Agency (EMEA), and others.

The data used in the assessment include pharmacokinetics and metabolism (mice, rats, dogs and human), genotoxicity, acute toxicity (mice, rats and dogs), subacute toxicity (rats, dogs and monkeys), chronic toxicity (mice and rats), and reproductive and developmental toxicity (mice, rats and pigs).

The *in vivo* and *in vitro* studies showed both positive and negative results on the genotoxicity of metronidazole. Metronidazole is reduced in bacteria, and the hydroxylamine produced during the reduction exerts genotoxicity through reacting directly with DNA. Since enzymes that reduce nitro compounds are present in mammals including humans, the nitro group of metronidazole is possible to be reduced by such enzymes to exert the genotoxicity in humans. In addition, the reduction of metronidazole *in vivo*, however, seems less likely to occur in mammals than in bacteria. Reduced metabolites of metronidazole are not produced in germ-free rats, but seem to be produced by intestinal bacterial flora in mammals *in vivo*. It remains unclear on the production of the reduced metabolites of metronidazole in human intestinal

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bacterial flora. DNA damage is detectable even after a single application of the therapeutic dose of metronidazole in humans. Therefore, the genotoxic potential of metronidazole is not excluded in humans.

In carcinogenicity studies in mice and rats, metronidazole was demonstrated to be carcinogenic. Epidemiological studies in human have suggested an association between metronidazole and tumor occurrence. International Agency for Research on Cancer (IARC) categolized metronidazole into a group of substances which are possibly carcinogenic to humans (group 2B). FSCJ could not exclude the potential of metronidazole to be a genotoxic carcinogen.

Therefore FSCJ concluded that it is not appropriate to specify an acceptable daily intake (ADI) for metronidazole.