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Methylprednisolone

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of methylprednisolone (CAS No. 83-43-2), a steroidal anti-inflammatory agent, using the evaluation reports from EMA (EMEA) and other related documents. Although no genotoxicty study *in vivo* was available, all the genotoxicity studies *in vitro* were negative. In addition, prednisolone, a structural analogue of methylprednisolone, is judged to have no genotoxicity relevant to human health. Thus, methylprednisolone is considered to have no genotoxicity relevant to human health. Therefore, FSCJ concluded it possible to specify an acceptable daily intake (ADI) of methylprednisolone. Major adverse effects of methylprednisolone observed are reduced counts of leukocyte, thymic atrophy, decreased weights of spleen, and glycogen accumulation in hepatocyte. FSCJ specified an ADI of 0.0003 mg/kg bw/day for methylprednisolone applying a safety factor of 1,000 to the LOAEL of 0.3 mg/kg bw/day in the 63-day subacute toxicity study in rats.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of methylprednisolone (CAS No. 83-43-2), a steroidal anti-inflammatory agent, using the evaluation reports from EMA (EMEA) and other related documents.

The data used in the assessment include pharmacokinetics (rats, dogs, horses and humans), residues (cattle and horses), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats and dogs), chronic toxicity (rats), reproductive and developmental toxicity (mice, rats and rabbits), and also general pharmacology and pharmacological actions.

Although no genotoxicty study *in vivo* was available, all the genotoxicity studies *in vitro* were negative. In addition, prednisolone, a structural analogue of methylprednisolone, is judged to have no genotoxicity relevant to human health. Thus, methylprednisolone is considered to have no genotoxicity relevant to human health. Therefore, FSCJ concluded it possible to specify an acceptable daily intake (ADI) of methylprednisolone.

Major adverse effects of methylprednisolone observed are reduced counts of leukocyte, thymic atrophy, decreased weights of spleen, and glycogen accumulation in hepatocyte.

Although no carcinogenicity study was available, methylprednisolone contains no alert chemical structure for known carcinogens. In addition, there is no evidence to suggest the carcinogenicity of prednisolone, a structural analogue. Moreover, methylprednisolone-associated cancer has not been reported for more than 50 years of clinical experience. FSCJ judged that methylprednisolone has no carcinogenicity relevant to humans.

The various effects have been observed in developmental toxicity studies after the subcutaneous or intramuscular administration as follows: 1) Cleft palate and delayed eyelid opening in mice, 2) Delayed ossification, ventricular septum

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http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20070115015&fileId=201
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defect and delayed eyelid opening in rats, 3) Hydrocephalus, limb deficiencies and spina bifida in rabbits. Among these studies, the lowest adverse effect was observed at a dose of 0.1 mg/kg bw/day in rabbits after the intramuscular administration. No adverse effect was at 0.02 mg/kg bw/day.

Among the oral studies of methylprednisolone, the lowest low-observed-adverse-effect-level (LOAEL) was 0.3 mg/kg bw/day on decreased weight of spleen in a 63-day subacute toxicity study in rats.

FSCJ judged that it appropriate to apply an additional safety factor ten for an ADI specification of methylprednisolone from the following reasons:

1) Only the LOAEL, but not NOAEL, was obtained,
2) No definitive conclusion is ascribed from the experiment of in the 63-day subacute toxicity study mainly due to the insufficient number of animals examined,
3) No data on the oral chronic toxicity are available.

In conclusion, FSCJ specified an ADI of 0.0003 mg/kg bw/day for methylprednisolone applying a safety factor of 1,000 to the LOAEL of 0.3 mg/kg bw/day in the 63-day subacute toxicity study in rats.