FOOD SAFETY

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Risk assessment report

Dexamethasone (Veterinary medicinal products)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of dexamethasone (CAS No. 50-02-2), a synthetic adrenocortical hormone, using mainly the evaluation reports from the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the European Medicines Agency (EMEA). Major adverse effects of dexamethasone were observed in the decrease in white blood cell count (WBC), atrophy of thymus and spleen as well as the decrease in adrenal weights, which were found in various toxicity studies. These effects are attributable to the glucocorticoid action. FSCJ supported the EMEA's judgment "dexamethasone lacks structural similarity with known carcinogens", and concluded that this drug is unlikely to be carcinogenic. Teratogenicity was observed in rats developmental toxicity studies and the no-observed-adverse-effect level (NOAEL) for fetus was 10 μg/kg bw/day. The effect observed at the lowest dose in various toxicological studies was decreased WBC in rats in an endocrinological study. The NOAEL in this study was 1μg/kg bw/day. JECFA and EMEA specified an acceptable daily intake (ADI) based on the pharmacological action, the induction of tyrosine aminotransferase activity (TAT), in rat liver. However FSCJ judged this endpoint is not appropriate to establish an ADI, because the increase of TAT in response to glucocorticoid was a physiological response, and the relationship of changes in TAT with the toxicological findings was obscure. Consequently, FSCJ specified the ADI for dexamethasone at 0.01μg/kg bw/day, based on NOAEL of 1μg/kg bw/day, which was obtained in rats in an endocrinological study, applying a safety factor of 100.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of dexamethasone (CAS No. 50-02-2), a synthetic adrenocortical hormone, using mainly the evaluation reports from the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the European Medicines Agency (EMEA).

The data used in the assessment include on pharmacokinetics (rats, rabbits, dogs, cattle, pigs, horses and humans), residues (cattle, pigs and horses), genotoxicity, acute toxicity (mice, rats and guinea pigs), subacute toxicity (rats and dogs), as well as reproductive and developmental toxicity (mice, rats and rabbits).

No genotoxicity relevant to human health was observed in the various genotoxicity studies of dexamethasone. Therefore, an acceptable daily intake (ADI) is possible to be established for dexamethasone.

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While no carcinogenicity study has been conducted on the drug, genotoxicity studies yielded negative results. Furthermore, no report is available on human carcinogenicity associated with clinical uses of dexamethasone. Therefore, FSCJ supported the EMEA's judgment "dexamethasone

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lacks structural similarity with known carcinogens", and concluded that this drug is unlikely to be carcinogenic. Teratogenicity was observed in rats developmental toxicity studies and the no-observed-adverse-effect level (NOAEL) for fetus was 10 μg/kg bw/day.

The effect observed at the lowest dose in various toxicological studies was decreased WBC in rats in an endocrinological study. The NOAEL in this study was 1μg/kg bw/day.

JECFA and EMEA specified an acceptable daily intake (ADI) based on the pharmacological action, the induction of tyrosine aminotransferase activity (TAT), in rat liver. However FSCJ judged this endpoint is not appropriate to establish an ADI, because the increase of TAT in response to glucocorticoid was a physiological response, and the relationship of changes in TAT with the toxicological findings was obscure.

Consequently, FSCJ specified the ADI for dexamethasone at 0.01μg/kg bw/day, based on NOAEL of 1μg/kg bw/day, which was obtained in rats in an endocrinological study, applying a safety factor of 100.

Table 1. *Levels relevant to toxicological evaluation of dexamethasone*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Mouse	Developmental toxicity study (the 2nd study)	6 (Subcutaneous administration)	-a
Rat	10-day subacute toxicity study	0, 3.8, 11.3, 38 μg/rat/day Dexamethasone (as the phosphate ester) in the drinking water	-b
	30-day subacute toxicity study	0, 38, 188, 750 μg/rat/day Dexamethasone (as the phosphate ester) in the drinking water	-b
	6-week subacute toxicity study	0.05 (Subcutaneous administration)	-a
	13-week subacute toxicity study	0, 0.04, 0.079 (Subcutaneous administration)	-a
	181~185-day subacute toxicity study	0, 0.125, 0.25, 0.4 (Oral administration)	0.125 (LOAEL) Suppressed body weight, increase in relative kidney weights, decreases in absolute/relative pituitary and thymus weights, and increase in the number of neutrophils and decrease in the number of eosinophils in the bone marrow
	Developmental toxicity study (the 1st study)	0, 0.02, 0.04, 0.079 (Subcutaneous administration)	-a
	Developmental toxicity study (the 2nd study)	0, 0.02, 0.2, 1 (Oral administration)	Maternal: 0.02 Suppressed body weight, decreased feed consumption and thymus involution Embryo/fetus: 0.02 (LOAEL) Thymus hypoplasia
	Developmental toxicity study (the 3rd study)	0, 0.04, 0.079 (Subcutaneous administration)	-a
	Developmental toxicity study (the 4th study)	0, 0.02, 0.04, 0.08 (Subcutaneous administration)	-a
	Developmental toxicity study (the 5th study)	0.25, 1, 4 (Sucutaneous administration)	-a
	Developmental toxicity study (the 6th study)	0, 0.01, 0.05, 0.25, 1.25 (Oral administration)	Maternal and Embryo/fetus: 0.01 Maternal: Suppressed body weight and thymus involution Embryo/fetus: Thymus hypoplasia
	Endocrine toxicity study	0, 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1 (Oral administration)	M: 0.003 F: 0.001 M: Suppressed body weight, decreased activity, piloerection, decrease in total and differential leukocyte counts, decreases in adrenal and thymus weights, and decrease in corticosterone level F: Decrease in WBC
	1 or -7-day administration study	0, 0.0005, 0.001, 0.0015, 0.002, 0.004 (Oral administration)	0.0015 (NOEL) Increased TAT activity

Table 1. *Levels relevant to toxicological evaluation of dexamethasone (continued)*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Rabbit	Developmental toxicity study (the 1st study)	0.025 ~ 1 (Intramuscular administration)	-c
	Developmental toxicity study (the 2nd study)	0, 0.02, 0.04, 0.079 (Subcutaneous administration)	-a
	Developmental toxicity study (the 3rd study)	0, 0.04, 0.079 (ubcutaneous administration)	-a
Dog	6-week subacute toxicity study	0, 0.125 (Oral aminstration)	-d
	13-week subacute toxicity study	0, 0.04, 0.079 (Intramuscular administration)	-c
	26-week subacute toxicity study	2, 8 mg/day (Oral aministration)	2 mg/day (LOAEL) Atrophy of lymphoid organs and decrease in adrenal weights
Toxicological ADI (μg/kg bw/day)			0.01 NOAEL: 1 SF: 100
The critical study for setting the ADI			Endocrine toxicity study in rats
ADI (μg/kg bw/day)			0.01

M, Male; F, Female; -, NOAEL was not specified for the following reasons: a, subcutaneous treatment; b, no data on dose levels, small number of animals allocated in each group, and male only; c, intramuscular treatment; d, one dose group only; NOEL, No-observed-effect level; TAT, tyrosine aminotransferase