5.5 CADUSAFOS (174)

TOXICOLOGY

Cadusafos is the ISO approved common name for S,S-di-sec-butyl O-ethyl phosphorodithioate (IUPAC) or O-ethyl S,S-bis(1-methylpropyl) phosphorodithioate (CAS) and has the CAS No. 95465-99-9. Cadusafos is an organothiophosphate insecticide.

The toxicity of cadusafos was first evaluated by the 1991 JMPR, when an ADI of 0–0.0003 mg/kg bw per day was established on the basis of a NOAEL of 0.03 mg/kg bw per day for the inhibition of cholinesterase activity in plasma and erythrocytes in a multigeneration study in rats and with a safety factor of 100. Cadusafos was reviewed by the present Meeting within the periodic review programme of the CCPR.

In addition to the studies evaluated in 1991, the present Meeting evaluated four new studies, a study of acute neurotoxicity and a short-term study of neurotoxicity in rats, a short-term study of dermal toxicity in rats and an assay for reverse mutation assay.

Biochemical aspects

Studies in male and female rats given [butyl-^{14}C]cadusafos at a dose of 1 mg/kg bw showed that the radiolabel was absorbed (highest blood concentrations being reached at about 4–8 h) and rapidly excreted (> 80% of the administered dose within 24 h). Of the recovered radiolabel, 70–80% was excreted in the urine, 4–14% in the faeces and 12–18% as CO_2. The results of a study with intravenous application of radiolabelled cadusafos suggested that approximately 5% of faecal excretion is attributable to biliary excretion. Oral absorption in males is therefore estimated to be close to 100% and > 90% in females. Cadusafos was widely distributed among the organs, a peak of 1.2% of the administered dose being found in the body at 7 days after dosing. Highest concentrations were observed in the liver, fat, kidney and lungs. There was no evidence for accumulation of cadusafos in the body. Cadusafos is extensively metabolized in rats. Metabolism starts by cleavage of one of the thio-butyl groups to give butyl-mercaptan and O-ethyl-S-(2-butyl) phosphorothioic acid, which can then be cleaved to S-(2-butyl) phosphorothioic acid or O-ethyl phosphorothioic acid. Butyl-mercaptan is biotransformed to methyl sec-butyl sulfide and sulfoxide and sulfone and finally to hydroxysulfones. Alternatively, butyl mercaptan can be oxidized to butyl sulfonic acid, then ethyl and methyl sulfonic acid. The results suggested that there are no significant differences between males and females in the toxicokinetic parameters and the metabolic profile observed with cadusafos a dose of 1 mg/kg bw.

Toxicological data

Cadusafos was of high to moderate toxicity by the oral route, with an LD_{50} of 30–131 mg/kg bw in rats and 68–82 mg/kg bw in mice. By the dermal route, the LD_{50} was 12–42 mg/kg bw in rabbits. By inhalation, the LC_{50} was 0.04 mg/L air in rats. In rabbits, cadusafos was not irritating to the eye or the skin. In a Buehler test, no evidence for delayed contact hypersensitivity was observed.

In studies with repeated doses, the main effect was the inhibition of cholinesterase activity in plasma, erythrocytes and brains of treated animals and related clinical and behavioural signs of intoxication.

In a 4-week feeding study in mice, the only effect was the inhibition of erythrocyte cholinesterase activity at 10 ppm and of brain cholinesterase activity at 33 ppm. The NOAEL was 3 ppm, equal to 0.83 mg/kg bw per day, on the basis of inhibition of erythrocyte cholinesterase activity at 10 ppm.

In a 4-week feeding study in rats, a NOAEL could not be identified because marked inhibition of cholinesterase activity and concomitant clinical signs were observed at the lowest dietary concentration tested, 50 ppm, equal to 4.7 mg/kg bw per day. In a 13-week feeding study in rats, very high mortality was observed at 800 ppm and one female died at the next lower dietary concentration of 5 ppm. At 800 ppm, typical clinical signs of cholinesterase inhibition were identified. Inhibition of erythrocyte cholinesterase activity was seen in males and females at 5 ppm towards the end of the study and in males and females at 800 ppm at all time-points. Brain cholinesterase activity was inhibited in females at 5 and 800 ppm and in males at 800 ppm. The NOAEL for rats was 1 ppm, equal to 0.067 mg/kg bw per day, on the basis of reduced erythrocyte and brain cholinesterase activity at 5 ppm.

In a 2-week study in dogs given capsules containing cadusafos, no treatment-related effects were observed up to 0.02 mg/kg bw per day, the highest dose tested. In a 13-week study in dogs given capsules, no effects on erythrocyte and brain cholinesterase activity was observed up to 0.09 mg/kg bw per day, the highest dose tested. The only effect was a decrease in mean testes weights at 0.03 mg/kg bw per day and above. Therefore, the NOAEL was 0.01 mg/kg bw per day. In a second 13-week study in dogs given a newer batch of cadusafos, the effect on testes weights was no longer observed up to 0.1 mg/kg bw per day, the highest dose tested. In a 1-year study in dogs fed capsules, no treatment-related clinical effects were observed and erythrocyte and brain cholinesterase activity were not inhibited at up to 0.02 mg/kg bw per day, the highest dose tested. The only finding was inhibition of plasma cholinesterase activity in females at 0.005 and 0.02 mg/kg bw per day. The Meeting considered that this effect was not toxicologically relevant, and the NOAEL was thus 0.02 mg/kg bw per day, the highest dose tested. The overall NOAEL for 13-week and 1-year studies in dogs was 0.09 mg/kg bw per day on the basis of the absence of any toxicologically relevant effects at the highest dose tested in the 13-week study.

Cadusafos was tested for genotoxicity in an adequate range of studies. In the submitted studies, there was no evidence for genotoxicity in vitro or in vivo.

The Meeting concluded that cadusafos was unlikely to be genotoxic.

In a 94–97 week feeding study in mice, plasma and erythrocyte cholinesterase activity was reduced in males and females and brain cholinesterase activity in males at the highest dietary concentration of 5 ppm, equal to 0.705 mg/kg bw per day. The incidence of non-neoplastic lesions such as cortical atrophy and hypertrophy/hyperplasia in the adrenals were increased in rats at 5 ppm when compared with controls, but there was no consistent dose–response relationship. Duodenal epithelial hyperplasia was increased in females at 5 ppm, and necrotizing arteritis of the kidneys was increased in males at 1 ppm and 5 ppm. Non-dose-related increases in the incidences of lung and liver tumours in males were not considered to be treatment-related. In males, an increase in the incidence of lymphoreticular tumours was observed (8 out of 49 and 11 out of 50 at 1 and 5 ppm, respectively, versus 6 out 49 in the controls) that was also greater than the incidence observed in one contemporary historical-control group. As the increase was not statistically significant and lymphoreticular tumours are common in aging mice, the effect was not considered to be treatment-related. The NOAEL was 0.5 ppm, equal to 0.072 mg/kg bw per day, on the basis of histological changes in the kidneys of male mice at 1 ppm. The Meeting concluded that cadusafos is not carcinogenic in mice.

In a 100–104 week feeding study in rats, females receiving the highest dietary concentration of 5 ppm showed decreased locomotion activity. Additionally, slightly more males showed lacrimation at this dietary concentration than did all other groups. Although brain cholinesterase activity was not inhibited at 12 months or at study termination in any group, plasma and erythrocyte acetylcholinesterase activity was inhibited (mostly statistically significantly) throughout the whole dosing period in males and females at 5 ppm. No increase in the frequency of any non-neoplastic or neoplastic changes was observed. The NOAEL was 1 ppm, equal to 0.045 mg/kg bw per day, on the basis of inhibition of erythrocyte acetylcholinesterase activity and depressed locomotor activity at 5 ppm. The Meeting concluded that cadusafos is not carcinogenic in rats.

In the absence of genotoxic and carcinogenic potential, the Meeting concluded that cadusafos is unlikely to pose a carcinogenic risk to humans.

The reproductive toxicity of cadusafos has been investigated in a two-generation study in rats. No treatment-related clinical signs were observed in any parental group. A slight and not dose-related decrease in the body weights of lactating F_1 females was observed at all doses. The Meeting considered this effect to be of questionable toxicological relevance. In F_1 males, a mild decrease in absolute liver and brain weights was observed without any histological correlates at 5 ppm, equal to 0.262 mg/kg bw per day. At 5 ppm, male and female F_0 and F_1 rats had statistically significantly lowered plasma and erythrocyte acetylcholinesterase activity in the pre-mating phase and at weaning. Reproductive performance, litter data and postnatal development were not affected by treatment. The NOAEL for parental toxicity was 0.5 ppm, equal to 0.026 mg/kg bw per day, on the basis of erythrocyte cholinesterase inhibition at 5 ppm. The NOAEL for reproductive and developmental toxicity was 5 ppm, the highest dose tested.

The developmental toxicity of cadusafos has been investigated in rats and rabbits. In the study in rats, maternal body weights and food intake were decreased at the highest dose of 18 mg/kg bw per day. One rat in the group at 6 mg/kg bw per day and all rats at the highest dose showed severe signs of intoxication starting on day 7 of gestation. Litter data were not affected by treatment in any group. Body weights of male and female pups at the highest dose were reduced by 8% and 6%, respectively. The incidence of fetuses with absent sternebrae and partially ossified supraoccipital bone, sternebrae and absent metcarpals was increased at 18 mg/kg bw per day, and there were more fetuses with absent xiphoid at 6 and 18 mg/kg bw per day. A non-statistically significant increase in the incidence of dilated ureters in litters and fetuses was found at 18 mg/kg bw per day. The NOAEL for maternal toxicity was 2 mg/kg bw per day on the basis of clinical signs in dams at 6 mg/kg bw. The NOAEL for developmental toxicity was 2 mg/kg bw on the basis of absent xiphoids in fetuses at 6 mg/kg bw.

In a range-finding study of developmental toxicity in rabbits, an increase in mortality (one death at study day 8 and another one at day 20) was observed at 1.0 mg/kg bw per day and above and the surviving rabbits showed lower body-weight gain compared with the controls. In the main study in rabbits, one rabbit died on day 15 at 0.3 mg/kg bw per day, two rabbits at 0.9 mg/kg bw per day aborted on day 27, one rabbit delivered on day 28 and two rabbits died (one on day 20 and the other on day 23). Additionally, an increased incidence of several other clinical signs of neurotoxicity induced by cholinesterase inhibition were observed at doses of 0.3 mg/kg bw per day and above, starting on day 15. At a dose of 0.2 mg/kg bw per day, there was marked inhibition of erythrocyte acetylcholinesterase activity in the range-finding study. At 0.3 and 0.9 mg/kg bw per day, the frequency of early resorptions was increased while the frequency of late resorptions decreased. The Meeting did not consider this finding to be treatment-related, because the total number of resorptions was only minimally increased and because the ratio of early to late resorptions is highly variable. No treatment-related effects were observed on fertility, the number of corpora lutea, the implantation sites, litter size, sex ratio, viability, fetal body weight, skeletal or visceral development. The NOAEL for maternal toxicity was 0.1 mg/kg bw per day on the basis of clinical signs at 0.3 mg/kg bw per day. The NOAEL for developmental toxicity was 0.9 mg/kg bw per day, the highest dose tested. The Meeting concluded that cadusafos was not teratogenic at doses that were not toxic to dams.

The Meeting concluded that the existing database on cadusafos was adequate to characterize the potential hazard to fetuses, infants and children.

In a study of delayed neurotoxicity in hens, one out of ten hens given cadusafos at a dose of 8 mg/kg bw (a potentially lethal dose) showed axonal degeneration in the spinal cord, but not in the peripheral nervous system. In view of the fact that clinical signs of delayed neuropathy were not observed and that axonal lesions in the spinal cord were observed occasionally in hens in the control group, the Meeting concluded that cadusafos is unlikely to cause delayed neuropathy at lethal doses.

In a study of acute neurotoxicity in rats, two females at 40 mg/kg bw group died on treatment days 2 and 3, respectively. Treatment-related clinical signs were noted in rats at 25 or 40 mg/kg bw.

These signs resolved within 5 days. Females at 40 mg/kg bw were soiled by body fluids on day 0 and were limp when handled, showed abnormal posture, tremors, staggered gait, splayed hindlimbs and reduced motor activity in the open field, reduced hindlimb grip strength and a significant increase in tail-flicking latency. At day 7 and 14, no FOB effects were observed in any group. At study termination, no gross lesions or microscopic changes in nervous tissues were observed. At 25 and 40 mg/kg bw, plasma and erythrocyte cholinesterase activity was inhibited. Brain cholinesterase activity was not statistically significantly inhibited at any dose, but individual data showed an increase in the incidence of rats with low brain cholinesterase activity at 25 and 40 mg/kg bw. The NOAEL was 0.02 mg/kg bw on the basis of inhibition of erythrocyte and brain cholinesterase activity, FOB effects and clinical signs at 25 mg/kg bw. The Meeting noted the large dose spacing in the study of acute neurotoxicity. In a 13-week feeding study of neurotoxicity in rats, females at 300 ppm showed increased hypersensitivity and males displayed a reduction in the landing foot-splay parameter and forelimb grip strength was reduced. No other FOB effects were observed and motor activity was not affected at any dose and no treatment-related gross lesions or histological changes in the nervous system were seen. In the groups at 300 ppm at study termination, plasma, erythrocyte and brain cholinesterase activity was reduced statistically significantly in males and females (erythrocyte cholinesterase activity was not statistically significantly reduced in females). The NOAEL was 0.5 ppm, equal to 0.031 mg/kg bw per day, on the basis of clinical signs, reduced body weights and reduced erythrocyte and brain cholinesterase activity at 300 ppm. The Meeting considered that cadusafos is neurotoxic.

No reports on health effects in personnel exposured to cadusafos were submitted.

Toxicological evaluation

The Meeting established an ADI of 0–0.0005 mg/kg bw based on a NOAEL of 1 ppm, equal to 0.045 mg/kg bw per day, identified on the basis of inhibition of erythrocyte cholinesterase activity at 5 ppm, equal to 0.222 mg/kg bw per day, in the long-term study in rats. A safety factor of 100 was applied.

The Meeting established an ARfD of 0.001 mg/kg bw based on a NOAEL of 0.1 mg/kg bw per day identified on the basis of clinical effects in dams at 0.3 mg/kg bw per day in the study of developmental toxicity in rabbits. A safety factor of 100 was applied. The large dose spacing between the LOAEL and the NOAEL in the study of acute neurotoxicity made this study unsuitable for the derivation of an ARfD. The Meeting also noted that the ARfD established might be conservative because it was derived using clinical signs that occurred only after administration of several doses.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	0.5 ppm, equal to 0.072 mg/kg bw per day	1 ppm, equal to 0.141 mg/kg bw per day
		Carcinogenicity	5 ppm, equal to 0.705 mg/kg bw per day[d]	—
Rat	Two-year study of toxicity and carcinogenicity[a]	Toxicity	1 ppm, equal to 0.045 mg/kg bw per day	5 ppm, equal to 0.222 mg/kg bw per day
		Carcinogenicity	5 ppm, equal to 0.222 mg/kg bw per day[d]	—
	Two-generation study of	Reproductive	5 ppm, equal to	—

	reproductive toxicity[a]	toxicity	0.262 mg/kg bw per day[d]	
		Parental toxicity	0.5 ppm, equal to 0.0262 mg/kg bw per day	5 ppm, equal to 0.262 mg/kg bw per day
		Offspring toxicity	5 ppm, equal to 0.262 mg/kg bw per day[d]	—
	Developmental toxicity[b]	Maternal toxicity	2 mg/kg bw per day	6 mg/kg bw per day
		Embryo/fetotoxicity	2 mg/kg bw per day	6 mg/kg bw per day
	Acute neurotoxicity[b]	Toxicity	0.02 mg/kg bw	25 mg/kg bw
Rabbit	Developmental toxicity[b]	Maternal toxicity	0.1 mg/kg bw per day	0.3 mg/kg bw per day
		Embryo/fetotoxicity	0.9 mg/kg bw per day[d]	—
Dog	Combined from a 13-week and a one-year studies[c]	Toxicity	0.09 mg/kg bw per day[d]	—

[a] Dietary administration.

[b] Gavage administration.

[c] Capsule administration.

[d] Highest dose tested.

[e] Lowest dose tested.

Estimate of acceptable daily intake for humans

0–0.0005 mg/kg bw

Estimate of acute reference dose

0.001 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to cadusafos

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, 90–100%
Distribution	Extensive, highest levels in liver, fat, kidney and the lungs
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid, nearly complete within 48 h, mainly via urine
Metabolism in animals	Extensive, primarily via oxidation and cleavage
Toxicologically significant compounds (animals, plants and the environment)	Cadusafos

Acute toxicity	
Rat, LD_{50}, oral	30 mg/kg bw
Rabbit, LD_{50}, dermal	12 mg/kg bw
Rat, LC_{50}, inhalation	0.04 mg/L air
Rabbit, dermal irritation	Not an irritant
Rabbit, ocular irritation	Not an irritant
Guinea-pig, dermal sensitization (test method used)	Not a sensitizer (Buehler)
Short-term studies of toxicity	
Target/critical effect	Erythrocyte cholinesterase inhibition (rat)
Lowest relevant oral NOAEL	0.067 mg/kg bw per day (rat)
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Erythrocyte cholinesterase inhibition and decreased locomotor activity (rat)
Lowest relevant NOAEL	1 ppm, equal to 0.045 mg/kg bw per day (rat)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects
Lowest relevant reproductive NOAEL	5 ppm, equal to 0.262 mg/kg bw per day, highest dose tested (rat)
Developmental target/critical effect	Skeletal findings at overtly maternally toxic doses (rat)
Lowest relevant developmental NOAEL	2 mg/kg bw per day (rat)
Neurotoxicity/delayed neurotoxicity	
	Organothiophosphorous compound, neurotoxic. No evidence of delayed neuropathy

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.0005 mg/kg bw	Long-term study; rat	100
ARfD	0.001 mg/kg bw	Study of development toxicity; rabbit	100

DIETARY RISK ASSESSMENT

Deferred to 2010, when residue re-evaluation is scheduled

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