5.7 CHLOROTHALONIL (081)

TOXICOLOGY

Chlorothalonil is the ISO approved common name for tetrachloroisophthalonitrile. Chlorothalonil (CAS No. 1897-45-6) is a non-systemic foliar fungicide used to control a wide range of fungal diseases in a variety of crops.

Chlorothalonil was previously evaluated by the JMPR in 1974, 1977, 1978, 1979, 1981, 1983, 1985, 1987, 1990 and 1992. In 1990, an ADI of 0–0.03 mg/kg bw was established based on the NOAEL of 3 mg/kg body weight per day, identified in a 2-year study in dogs, which was evaluated in 1974.

Chlorothalonil was re-evaluated by the present Meeting as part of the periodic review programme of the CCPR. The present Meeting evaluated newly submitted studies, including mechanistic studies in rats into the effects of chlorothalonil on the kidneys and studies on SDS-3701, a metabolite that is found in plants, soil and ruminants. Both the new data and the relevant data from previous studies were considered by the present Meeting.

All critical studies complied with GLP.

Biochemical aspects

In rats given a single oral dose of chlorothalonil at 1.5–50 mg/kg bw, absorption was about 31%, with 17–21% being excreted in the bile and about 8–12% being excreted in the urine. At 200 mg/kg bw, excretion in the bile (8%) and the urine (5%) was lower, suggesting that saturation of absorption was occurring. In females, biliary excretion was lower (–20%) and urinary excretion was higher (about +35%) than in males. Urinary excretion in mice and dogs was about 5–10% and 1.4%, respectively. In rats, the highest tissue concentrations were found in the kidney, probably due to binding to kidney proteins. Chlorothalonil is metabolized via initial glutathione conjugation and subsequent enzymatic processing of the di-and triglutathion substituents via the mercapturic acid and cysteine conjugate β-lyase pathways yielding N-acetyl cysteine, cysteinyl-glycine and S-methyl-derivates.

Toxicological data

The acute oral and dermal toxicity of chlorothalonil is low (oral and dermal LD_{50}, > 5000 mg/kg bw). A study of acute inhalation yielded a LC_{50} of 0.1 mg/L air. Chlorothalonil is a mild skin irritant and is severely irritating to the eye. No valid test for sensitization was available. In EHC 183, it is reported that the results of studies of skin sensitization in guinea-pigs were inconclusive[29].

Studies of toxicity with repeated doses showed that in mice and rats, but not in dogs, the kidney is the prime target organ for systemic toxicity attributable to chlorothalonil. In studies in mice and rats, chlorothalonil also caused local toxicity in the forestomach. In a 90-day study in mice, the NOAEL for systemic effects was 275 ppm, equal to 48 mg/kg bw per day, on the basis of an increased incidence of hyperplasia in the proximal tubules of the kidneys and increased kidney weight at 750 ppm, equal to 124 mg/kg bw per day. In a 13-week study in rats, the NOAEL for systemic effects was 10 mg/kg bw per day on the basis of increased kidney weights and hyperplasia in the kidneys at 40 mg/kg bw per day.

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[29] IPCS (1996) Chlorothalonil. Environmental Health Criteria 183. (http://www.inchem.org/documents/ehc/ehc/ehc183.htm#SectionNumber:8.1)

Studies of acute toxicity in rats have demonstrated that chlorothalonil, given by gavage, induces renal tubular necrosis in the S2 segment of the proximal convoluted tubules (hyper-eosinophilic cells, multi-focal hydropic vacuolation). These effects were observed at doses of 175 mg/kg bw and higher. The overall NOAEL for toxic effects on the kidney in studies of acute toxicity was 60 mg/kg bw per day.

In a 90-day study in dogs, the NOAEL for systemic effects was 15 mg/kg bw per day on the basis of reductions in body-weight gain and changes in clinical chemistry parameters, (not related to kidney toxicity) at 150 mg/kg bw per day. In a 1-year study in dogs, the NOAEL was 150 mg/kg bw per day on the basis of reduced body-weight gain, reduced serum albumin and total protein, and increased relative liver weight and serum cholesterol at 500 mg/kg bw per day.

In a 2-year study of carcinogenicity in mice, the LOAEL was 750 ppm, equal to 119 mg/kg bw per day (the lowest dose tested), on the basis of increased kidney weights, macroscopic changes in the kidney and forestomach, microscopic changes in the kidney, forestomach and oesophagus. In addition, at the LOAEL renal tubular adenomas and carcinomas in males and forestomach tumours, mainly squamous cell carcinomas in males and females were found. In a second 2-year study of carcinogenicity in mice, no pre-neoplastic changes in the forestomach were observed at 10/15 ppm, equal to 1.9 mg/kg bw per day. Increased incidences in hyperplasia and hyperkeratosis of the forestomach were observed at dietary concentrations of 40 ppm and higher, equal to 5.1 mg/kg bw per day. A slightly higher incidence in forestomach tumours was observed at doses of 750 ppm, equal to 98 mg/kg bw per day. In this study, increased incidences in renal tubular hyperplasia and karyomegaly were observed at doses of 175 ppm and higher, equal to 23 mg/kg bw per day. No effects on kidneys were observed at 40 ppm, equal to 5.1 mg/kg bw per day.

Three long-term studies of toxicity in rats were available. In the first study, the LOAEL was 40 mg/kg bw per day (the lowest dose tested) on the basis of macroscopic and histopathological lesions of the kidneys, increased incidence of kidney tumours, changes in urine-analysis parameters, increased kidney weights, histological changes in the oesophagus, forestomach, glandular stomach and duodenum and an increased incidence of forestomach papillomas. In a second study in rats, the NOAEL was 1.8 mg/kg bw per day on the basis of an increased incidence of renal tubular epithelial hyperplasia in females at 3.8 mg/kg bw per day. In a third study in rats, the NOAEL was 2.7 mg/kg bw per day and the LOAEL was 10.6 mg/kg bw per day on the basis of increased kidney weight, changes in kidney macroscopy and histology and haematological changes.

In the long-term studies of toxicity in rats, kidney tumours, predominantly tubular adenomas and carcinomas, were observed at dietary doses equal to 15 mg/kg bw per day in males or higher in males and females. The overall NOAEL for kidney tumours in rats was 3.8 mg/kg bw per day. Also in the three long-term studies of toxicity in rats, forestomach tumours (papillomas and carcinomas) were observed at doses of 3.8 mg/kg bw per day and higher.

Chlorothalonil was tested for genotoxicity in vitro and in vivo in an adequate range of studies. Chlorothalonil was not mutagenic in bacteria or in tests for gene mutation in vitro in the absence or presence of metabolic activation. The results of a test for chromosomal aberration in CHO cells in vitro were positive in the absence of metabolic activation but negative in the presence of metabolic activation. However, the results of numerous tests for clastogenicity in vivo in several species (i.e., mice, rats, Chinese hamsters) given single or repeated doses were negative, except for a few inconclusive or equivocal findings.

Considering all the results of studies of genotoxicity, the Meeting concluded that it is unlikely that chlorothalonil is genotoxic.

Repeated dosing with chlorothalonil resulted in hyperplasia and tumour formation in the forestomach in rats and mice. Oral administration of a mono-glutathione conjugate of chlorothalonil did not cause forestomach toxicity, suggesting that forestomach lesions are a consequence of a direct irritant effect of chlorothalonil. Chlorothalonil did not cause tumours in the oesophagus, which also has squamous epithelium. This indicates that this substance needs to be in prolonged contact with

squamous epithelium in order to induce tumours. The data indicate a process that starts with irritation and cytotoxicity, followed by cell proliferation, ulceration and erosion, regenerative hyperplasia and hyperkeratosis and ultimately resulting in forestomach tumours. Chlorothalonil did not induce tumours in the glandular stomach in rats and mice. Unlike rats and mice, humans and dogs do not have a forestomach. In a 1-year study in dogs, no stomach lesions were observed at doses up to 500 mg/kg bw per day. In a 2-year dietary study in dogs, which was evaluated by JMPR in 1992, moderate to severe gastritis was found irregularly at dietary concentrations of 15000 ppm, equivalent to 375 mg/kg bw per day, and higher. The Meeting considered the forestomach tumours induced by chlorothalonil to be a rodent-specific lesion that is not relevant for humans, because of differences in anatomy and function.

The studies of mode of action of chlorothalonil in kidney toxicity in rats and studies with repeated doses show that chlorothalonil-induced renal tumours occur as a direct consequence of sustained damage to the S2 segment of the proximal tubules of the kidney. The occurrence of tumours is preceded by renal cytotoxicity, which is followed by regenerative cell proliferation/hyperplasia. Renal cytotoxicity and regenerative cell proliferation occur at doses lower or similar to those causing tumours. Cytotoxicity/regenerative proliferation is a well-established mode of action for the formation of kidney tumours, although the cause of the initial cytotoxicity may differ. On the basis of information on other chlorinated compounds, it is possible that the nephrotoxicity caused by chlorothalonil may be due to reactive metabolites formed from the renal β-lyase cleavage of cysteine-S conjugates transported in the renal tubular cells. This mode of action is supported by the finding that when a mono-glutathion conjugate of chlorothalonil is administered orally, similar kidney lesions are observed at a comparable dose. Because human β-lyase activity is lower in human kidney tissue than in that of rodents, rodents would be expected to be more sensitive to this bioactivation pathway. In a 2-year dietary study in dogs, which was evaluated by JMPR in 1992, renal glomerulosclerosis and degenerative renal tubular changes (tubular hypertrophy and dilation) were found at dietary concentrations of 15000 ppm and higher, equivalent to 375 mg/kg bw per day. The kidney toxicity in dogs given high doses of chlorothalonil only is likely be due to species differences in bioactivation (as well as absorption). However, there is insufficient data on chlorothalonil to quantitatively characterize this differential difference in renal-enzyme activity/bioactivation between rodents, dogs, and humans.

The Meeting concluded that the formation of kidney tumours was the result of prolonged renal cytotoxicity and regenerative cell proliferation, and is consistent with a threshold phenomenon.

In a two-generation study of reproductive toxicity with chlorothalonil in rats, the LOAEL for parental toxicity was 500 ppm, equal to 22 mg/kg bw per day, i.e.,the lowest dose tested, on the basis of effects on kidneys and forestomach in males and females observed at all doses. One tubular adenoma and one tubular carcinoma were found the kidneys of males at 145 mg/kg bw per day. The NOAEL for offspring toxicity was 1500 ppm, equal to 68 mg/kg bw per day, on the basis of a decrease in body weight of the F1 pups at the highest dose. The NOAEL for reproductive effects was 3000 ppm, equal to 138 mg/kg bw per day, i.e., the highest dose tested.

In a study of developmental toxicity in rats, the NOAEL for maternal toxicity was 100 mg/kg bw per day on the basis of increased mortality, clinical signs, reduced body weight and food consumption observed at 400 mg/kg bw per day. The NOAEL for fetal toxicity was 100 mg/kg bw per day on the basis of increased post-implantation loss and reduced viable litter size. In a study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of body-weight loss during treatment with chlorothalonil at 20 mg/kg bw per day. The NOAEL for fetal toxicity was 20 mg/kg bw per day, i.e., the highest dose tested.

No data on chlorothalonil in humans were provided. In the published literature it is reported that chlorothalonil may cause dermatitis[30].

Studies on the metabolite SDS-3701

4-Hydroxy-2,5,6-trichloroisophthalonitrile (company code, SDS-3701) is a soil and plant metabolite of chlorothalonil and has also been identified as a metabolite in ruminants. The toxicology of this metabolite had been tested extensively.

Biochemical aspects of the metabolite SDS-3701

After single oral doses of ^{14}C-ring labelled SDS-3701 at 4.3 or 62.4 mg/kg bw in rats, about 65–74% and 7.5–9.7%, was recovered from the faeces and urine, respectively. Radiolabel was found in the blood (5–6.9%), muscle (4.7–7.9%), fat (3.1–3.6%), liver (1–2%) and kidneys (0.4–0.7%). The highest concentrations of radiolabel were found in the liver. The tissue and urine concentrations indicate an oral absorption of at least 26–30% of the administered dose. Biliary excretion was not measured, so actual oral absorption may be higher than indicated.

Toxicological data

SDS-7301 is moderately toxic after acute oral administration (LD_{50}, 242–422 mg/kg bw). Mortality was observed after single oral doses of 150 mg/kg bw or higher.

In a 2-year dietary study with SDS-3701 in mice, in which a limited number of parameters were evaluated, a reduction in body weight and an increase in food consumption were observed at 1500 ppm, equivalent to 225 mg/kg bw per day. Absolute and relative liver weights were increased in females at 750 ppm, equivalent to 113 mg/kg bw per day, and higher. No treatment-related effects on the incidences of non-neoplastic and neoplastic lesions were observed at dietary concentrations of up to and including 1500 ppm, equivalent to 225 mg/kg bw per day (the highest dose tested).

Dietary studies of toxicity in rats given repeated doses (60-day, 2-year) of SDS-3701 show that the haemopoietic system is the prime target organ for toxicity. The overall NOAEL in studies in rats given repeated doses of SDS-3701 was 3 mg/kg bw per day on the basis of increased mortality, clinical signs, reduced body weight gain, changes in haematological and clinical chemistry parameters, hypoplastic bone marrow, increased spleen weight, haemosiderin deposition in liver and bone marrow and degenerative tissue changes observed at 10/15 mg/kg bw per day in a 2-year dietary study. No treatment-related changes in the incidence of neoplastic lesions were observed at doses up to and including 30/20 mg/kg bw per day.

In a 90-day study in dogs, the NOAEL was 100 ppm, equivalent to 2.5 mg/kg bw per day, on the basis of severe toxicity resulting in death observed at 200 ppm, equivalent to 5 mg/kg bw per day. In a 1-year study in dogs, the NOAEL was 30 ppm, equal to 0.83 mg/kg bw per day, on the basis of reductions in body-weight gain and increased serum concentrations of glucose observed at 60 ppm, equal to 1.8 mg/kg bw per day.

SDS-3701 was tested in an adequate range of tests of genotoxicity. Most of the tests showed that SDS-3701 was not mutagenic or clastogenic. A test for chromosomal aberration in vitro in CHO cells gave positive results with and without metabolic activation. However, SDS-3701 gave negative results in vivo in a test for chromosomal aberration in Chinese-hamster bone marrow and in dominant lethal tests in rats and mice. The Meeting concluded that it is unlikely that SDS-3701 will show mutagenic activity in vivo.

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[30] IPCS (1996) Chlorothalonil. Environmental Health Criteria 183. (http://www.inchem.org/documents/ehc/ehc/ehc183.htm#SectionNumber:8.1).

In view of the lack of genotoxicity in vivo and the absence of carcinogenicity in mice and rats, the Meeting concluded that SDS-3701 is unlikely to pose a carcinogenic risk to humans.

In two studies of reproductive toxicity in rats, the overall NOAEL for parental toxicity was 120 ppm, equivalent to 8 mg/kg bw per day, the highest dose tested. The overall NOAEL for offspring toxicity was 30 ppm, equivalent to 2 mg/kg bw per day, on the basis of reduction in body weight at 60 ppm. The NOAEL for reproductive toxicity was 120 ppm, equivalent to 8 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity in rats, the NOAEL for maternal toxicity was 5 mg/kg bw per day on the basis of reductions in body-weight gain and food consumption at 15 mg/kg bw per day. The NOAEL for fetal toxicity was 5 mg/kg bw per day on the basis of an increase in number of early and late resorptions, a decrease in fetal weight at and an increase in the frequency of 14th rudimentary ribs at 15 mg/kg bw per day. In a study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 1 mg/kg bw per day on the basis of a mortality and an abortion observed at 2.5 mg/kg bw per day. It was not reported at which day of treatment the mortality and abortion occurred. The NOAEL for developmental toxicity was 2.5 mg/kg bw per day on the basis of early post-implantation loss at 5 mg/kg bw per day. In these studies, no teratogenic effects were observed with SDS-3701.

The Meeting concluded that the existing database on chlorothalonil and its soil and plant metabolite SDS-3701 was sufficient to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

Chlorothalonil

The Meeting established an ADI for chlorothalonil of 0–0.02 mg/kg bw based on a NOAEL of 1.8 mg/kg bw per day identified on the basis of kidney toxicity observed in long-term studies of toxicity in rats and using a safety factor of 100. This ADI provides a margin of 200 for the induction of renal tumours in rats. This ADI is similar to the one derived by JMPR in 1974 and 1990 from a 2-year study in dogs in which the NOAEL was 3 mg/kg bw per day. Previously the JMPR has based the ADI on data from dogs, arguing that the rat is particularly sensitive to kidney toxicity induced by chlorothalonil. The Meeting concluded that whilst there were some uncertainties it was possible to establish a plausible mode of action for the renal carcinogenesis of chlorothalonil. This comprises initial conjugation with glutathione followed by sequential biotransformation to thiol derivatives in renal proximal tubule cells by β-lyase. The thiol metabolites are cytotoxic, resulting in renal proximal tubule cell necrosis followed by regenerative proliferation. The final step is the appearance of tumours. As there are no fundamental qualitative differences between rodents and in humans in the processes underlying these key events, it was not possible to dismiss human relevance on qualitative grounds. Whilst quantitative differences in some of the metabolic steps, such as the cysteine S-conjugate β-lyase pathway, have been demonstrated between rodents and humans for some other compounds sharing this mode of action, specific information on chlorothalonil was not available. Hence, the Meeting concluded that while it is plausible that humans are less sensitive to the renal effects of chlorothalonil, it was not possible to dismiss relevance to humans on quantitative grounds, nor was it possible to quantify any difference in sensitivity.

Studies of acute toxicity have demonstrated that exposure to chlorothalonil on a single day may induce kidney toxicity in rats. The overall NOAEL for kidney toxicity in studies of acute toxicity was 60 mg/kg bw. Based on this NOAEL, the Meeting established an ARfD of 0.6 mg/kg bw, using a safety factor of 100.

Given the species differences in the β-lyase bioactivation pathway, the ADI and ARfD are likely to be conservative.

SDS-3701 (4-Hydroxy-2,5,6-trichloroisophthalonitrile)

The Meeting established an ADI for SDS-3701 of 0–0.008 mg/kg bw based on a NOAEL of 0.83 mg/kg bw per day identified on the basis of a reduction in body-weight gain in females, a reduction in erythrocytes in males and increased serum concentrations of glucose in males and females in a 1-year study in dogs, and using a safety factor of 100.

In a study of developmental toxicity with SDS-3701 in rabbits, early implantation loss was observed at a dose of 5 mg/kg bw per day. The NOAEL for this effect was 2.5 mg/kg bw per day. On the basis of these findings, the Meeting established an ARfD of 0.03 mg/kg bw using a safety factor of 100. The Meeting considered that the abortions and deaths observed in this study in rabbits at 2.5 and 5 mg/kg bw per day were considered to be unlikely to be induced by a single dose of SDS-3701. In studies of acute oral toxicity in rats, in which LD_{50}s of 242–422 mg/kg bw were identified, deaths were observed at doses of 150 mg/kg bw or higher. In view of information from the LD_{50} studies and the absence of other adequate data on acute toxicity, the ARfD of 0.03 mg/kg bw applies to the general population as well as women of childbearing age.

A toxicological monograph was prepared.

Levels relevant for risk assessment of chlorothalonil

Species	Study	Effect	NOAEL	LOAEL
Rat	Acute toxicity [b]	Toxicity	60 mg/kg bw per day [c]	175 mg/kg bw per day [c]
	Two-year study of toxicity and carcinogenicity [a]	Toxicity	1.8 mg/kg bw per day	3.8 mg/kg bw per day
		Carcinogenicity	3.8 mg/kg bw per day	15 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Parental	— [d]	500 ppm, equal to 21.7 mg/kg bw per day
		Offspring toxicity	1500 ppm, equal to 68 mg/kg bw per day	3000 ppm, equal to 138 mg/kg bw per day
		Reproductive toxicity	3000 ppm, equal to 138 mg/kg bw per day	— [e]
	Developmental toxicity[b]	Maternal toxicity	100 mg/kg bw per day	400 mg/kg bw per day
		Fetotoxicity	100 mg/kg bw per day	400 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	20 mg/kg bw per day
		Fetotoxicity	20 mg/kg bw per day	— [e]
Dog	Two-year study[a,f]	Toxicity	120 ppm, equal to 3 mg/kg bw per day	— [e]

[a] Dietary administration.

[b] Gavage administration.

[c] Overall NOAEL and LOAEL for several studies.

[d] Lowest dose tested.

[e] Highest dose tested.

[f] Evaluated by JMPR in 1974 and 1992.

Levels relevant for risk assessment of SDS-3701

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of carcinogenicity [a]	Carcinogenicity	1500 ppm, equivalent to 225 mg/kg bw per day	— [c]
Rat	Two-year study of toxicity and carcinogenicity [a]	Toxicity	3 mg/kg bw per day	10 mg/kg bw per day
		Carcinogenicity	20 mg/kg bw per day	— [c]
	One-generation study of reproductive toxicity[a]	Parental	120 ppm, equivalent to 8 mg/kg bw per day	— [c]
		Offspring toxicity	30 ppm, equivalent to 2 mg/kg bw per day	60 ppm, equivalent to 4 mg/kg bw per day
		Reproductive toxicity	120 ppm, equivalent to 8 mg/kg bw per day	— [c]
	Developmental toxicity[b]	Maternal toxicity	5 mg/kg bw per day	15 mg/kg bw per day
		Fetotoxicity	5 mg/kg bw per day	15 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	1 mg/kg bw per day	2.5 mg/kg bw per day
		Fetotoxicity	2.5 mg/kg bw per day	5 mg/kg bw per day
Dog	One-year study[a]	Toxicity	0.83 mg/kg bw per day	1.8 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

Estimate of acceptable daily intake for humans

Chlorothalonil 0–0.02 mg/kg bw

SDS-3701[31] 0–0.008 mg/kg bw

Estimate of acute reference dose for:

Chlorothalonil 0.6 mg/kg bw

SDS-3701 0.03 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 exposures in humans

[31] 4-Hydroxy-2,5,6-trichloroisophthalonitrile

Critical end-points for setting guidance values for exposure to chlorothalonil and its metabolite SDS-3701 (4-Hydroxy-2,5,6-trichloroisophthalonitrile)

Absorption, distribution, excretion and metabolism in animals		
	Chlorothalonil	SDS-3701
Rate and extent of absorption	Rapid, incomplete and dose-dependent oral absorption (31% at 1.5–50 mg/kg bw; 13% at 200 mg/kg bw).	Rapid, incomplete oral absorption (26–30% at 4–62 mg/kg bw)
Distribution	Highest concentration in kidney (rat)	Percentage of administered dose in blood (5–6.9%), muscle (4.7–7.9%), fat (3.1–3.6%), liver (1–2%) and kidneys (0.4–0.7%) 4 days after dosing. Highest concentrations of radiolabel were found in liver.
Potential for accumulation	Low (rat)	Moderate, in view of amount in tissue after 4 days (rat)
Rate and extent of excretion	Plasma half lives, 6–7 h at 5–50 mg/kg bw, > 10 h at 200 mg/kg bw (rat)	75–82% in 4 days (rat)
Metabolism in animals	Extensive, metabolized by enzymatic processing of the di-and triglutathion substituents via the mercapturic acid and cysteine conjugate β-lyase pathways yielding N-acetyl cysteine, cysteinyl-glycine and S-methyl-derivates.	No data
Toxicologically significant compounds (in animals, plants and the environment)	Chlorothalonil	SDS-3701
Acute toxicity		
LD_{50}, oral, rat	> 5000 mg/kg bw	242–422 mg/kg bw
LD_{50}, dermal, rat	> 5000 mg/kg bw	No data
LC_{50}, inhalation, rat	0.1 mg/L air	No data
Rat, dermal irritation	Not an irritant	No data
Rabbit, ocular irritation	Severely irritating	No data
Dermal sensitization	Inconclusive	No data
Short-term studies of toxicity		
Target/critical effect	Kidney (rat, rabbit)	Haemopoietic system (rat); body weight (dog)
Lowest relevant oral NOAEL	1.8 mg/kg bw per day (rat)	0.83 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	Systemic: 2.5 mg/kg bw per day (rabbit) Local: 2.5 mg/kg bw per day (rabbit)	No data
Long-term studies of toxicity and carcinogenicity		
Target/critical effect	Kidney: tubular epithelial necrosis/hyperplasia (mouse, rat, dog)	Haemopoietic system (rat)
Lowest relevant	1.8 mg/kg bw per day (rat)	3 mg/kg bw per day (rat)

Absorption, distribution, excretion and metabolism in animals		
	Chlorothalonil	SDS-3701
NOAEL		
Carcinogenicity	Carcinogenic, secondary to renal toxicity (mice, rats)	Not carcinogenic (mice, rats)
Genotoxicity		
	Not genotoxic	Not genotoxic
Reproductive toxicity		
Reproduction target/critical effect	No reproductive effects (rats)	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	3000 ppm, equal to 138 mg/kg bw per day, i.e.,highest dose tested (rats)	120 ppm, equivalent to 8 mg/kg bw per day, i.e.,highest dose tested (rats)
Developmental target	Increased post-implantation loss, observed at maternally toxic doses only (rats)	Increased early and late post-implantation loss, decreased fetal weight, increased frequency of 14th rudimentary rib, observed at maternally toxic doses only (rats)
		Increased early post-implantation loss, observed at maternally toxic doses only (rabbits)
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rats)	5 mg/kg bw per day (rats)
	20 mg/kg bw per day i.e.,highest dose tested (rabbits)	2.5 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity		
Neurotoxicity	No data. No indication of neurotoxic potential	No data. No indication of neurotoxic potential.
Medical data		
	Dermatitis reported in published literature	No data

Summary for chlorothalonil

	Value	**Study**	**Safety factor**
ADI	0–0.02 mg/kg bw	2-year study in rat	100
ARfD	0.6 mg/kg bw	Studies of acute toxicity, rat	100

Summary for SDS-3701

	Value	**Study**	**Safety factor**
ADI	0–0.008 mg/kg bw	1-year study, dog	100
ARfD	0.03 mg/kg bw	Study of developmental toxicity, rabbit	100

DIETARY RISK ASSESSMENT

Deferred to 2010, when residue re-evaluation is scheduled.