

Chlorothalonil

MAK Value Documentation, supplement – Translation of the German version from 2021

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Keywords

chlorothalonil; larynx; lung; respiratory tract; irritation; maximum workplace concentration; MAK value; metaplasia; necrosis

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has reviewed an unpublished inhalation study of chlorothalonil [1897-45-6] to evaluate whether its findings can be used to derive a maximum concentration at the workplace (MAK value). As described in the 2018 supplement, chlorothalonil is corrosive to the eyes of rabbits. Workers reported irritation of the eyes, nose and throat at exposure concentrations of 0.3 to 1.2 mg/m³. An unpublished 2-week inhalation study with exposure of rats to chlorothalonil aerosol concentrations of 0, 1.1, 2.9, 9.6 or 14.3 mg/m³ has been made available to the MAK Commission. Squamous metaplasia and necrosis in the U-shaped cartilage of the larynx were observed in all 10 exposed animals at the low concentration of 1.1 mg/m³ and above; higher concentrations induced additional effects in the larynx, lungs and respiratory tract. It is still not possible to derive a MAK value and chlorothalonil remains assigned to Section IIb of the List of MAK and BAT Values. No other end points were re-evaluated.

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MAK value	not yet established, see Section II b of the List of MAK and BAT Values
Peak limitation	–
Absorption through the skin	–
Sensitization (1992)	Sh
Carcinogenicity	–
Prenatal toxicity	–
Germ cell mutagenicity	–
BAT value	–

For chlorothalonil, the following publications are available: documentation from 1992 (Henschler 1993), a supplement from 2000 giving a detailed presentation of the data for skin sensitization (Greim 2000, available in German only), and a supplement from 2018 for all end points (Hartwig and MAK Commission 2019). An inhalation study in rats, which has recently become available, has been reviewed to evaluate whether its findings can be used to derive a MAK value. No other end points were re-evaluated.

Effects in Humans

In the concentration range of 0.3 to 1.2 mg/m³, chlorothalonil was irritating to the eyes, nose and throat and induced coughing, chest tightness and shortness of breath in occupationally exposed persons (Hartwig and MAK Commission 2019; Huang et al. 1995).

Animal Experiments and in vitro Studies

Acute and subacute toxicity

Inhalation

Until recently, there were no studies available with repeated inhalation exposure, but a previously unpublished subacute study with an acute range-finding study has now been made available to the Commission.

In the acute range-finding study, 5 male Sprague Dawley rats were exposed nose-only to a chlorothalonil concentration of 14.6 mg/m³ for 6 hours; this led to “slightly” decreased body weight gains. No other findings were observed (Charles River Laboratories 2013).

Groups of 10 male Sprague Dawley rats were exposed nose-only to liquid aerosols of a formulation containing chlorothalonil concentrations of 0, 1.1, 2.9, 9.6 or 14.3 mg/m³ for 6 hours daily, on 5 days per week for 2 weeks. A control group was exposed only to air. After a recovery period of 2, 7 or 14 days, the animals were examined. Exposure was to an undiluted commercial formulation containing 53.7% w/v chlorothalonil, and the concentrations were determined gravimetrically. The mass median aerodynamic diameters (MMAD) of the aerosols were in the range of 2.13 µm (geometric standard deviation (GSD) 1.73) to 3.91 µm (GSD 1.59). Chlorothalonil was not measured in the vapour phase. Histopathological examination included the larynx, lungs, nasal cavities, pharynx, trachea, and bronchial and cervical lymph nodes; all other organs were examined only macroscopically. The body weight gains were reduced in all

exposed animals in a concentration-dependent manner (Table 1); during the recovery period, these animals consumed more food. Even at the lowest concentration of 1.1 mg/m³, necrosis of the U-shaped cartilage and squamous metaplasia occurred in all 10 animals in the larynx and degeneration with inflammation in the nasal cavity in 9 of 10 animals. Higher concentrations induced additional effects in the larynx, lungs and respiratory tract. These and other findings are listed in Table 2 (Charles River Laboratories 2013). Therefore, a NOAEC (no observed adverse effect concentration) was not obtained from this study.

Tab. 1 Effects of chlorothalonil after acute and subacute inhalation exposure (Charles River Laboratories 2013)

Species, strain, number per group	Exposure	Findings
rat, Sprague Dawley, 5 ♂	1 day , 0, 14.6 mg/m ³ , aerosol, nose-only, 6 hours, MMAD 3.39 µm (GSD 2.48), examined the same day	14.6 mg/m³ : body weight gains “slightly” decreased
rat, Sprague Dawley, 10 or 5 ♂	2 weeks , 0 (air), 0 (formulation without chlorothalonil); 1.1, 2.9, 9.6, 14.3 mg chlorothalonil/m ³ , aerosol, formulation with 53.7% chlorothalonil by weight, nose-only, 6 hours/day, 5 days/week, MMAD per chlorothalonil concentration group: 2.13 µm (GSD 3.24)–3.92 µm (GSD 2.44); 2.17 µm (GSD 2.78)–3.47 µm (GSD 2.34); 2.17 µm (GSD 2.54)–2.52 µm (GSD 2.47); 2.21 µm (GSD 2.95)–3.13 µm (GSD 2.10); examinations carried out 2 (10 animals per concentration), 7 and 14 days (5 animals per concentration) after termination of exposure	1.1 mg/m³ and above : salivation (during the final days of exposure also in the animals exposed to formulation without chlorothalonil), findings in larynx, nose, trachea (see Table 2); 1.1 mg/m³ : body weight gains about 10% ↓ (not significant); 2.9 mg/m³ and above : food intake ↓; 2.9 mg/m³ : body weight gains about 20% ↓; 9.6 mg/m³ and above : discoloration on snout; 9.6 mg/m³ : body weight gains about 37% ↓; 14.3 mg/m³ : breathing noises in 2 animals, body weight ↓ (between days 1 and 5), on day 12 body weight gains in total about 53% ↓; no findings in ophthalmological examination; during recovery period : slightly increased food consumption in exposed animals, findings in larynx and nasal cavity (see Table 2)

GSD: geometric standard deviation; MMAD: mass median aerodynamic diameter

Tab. 2 Effects of chlorothalonil in the respiratory tract of male rats (Charles River Laboratories 2013)

	Exposure concentration (mg/m ³)					
	0 (A)	0 (F)	1.1	2.9	9.6	14.3
after inhalation exposure for 2 weeks (5 days/week) and a 2-day recovery period						
rats / group	10	10	10	10	10	10
larynx						
necrosis, U-shaped cartilage	0	0	10	10	10	10
squamous metaplasia, ventrolateral	0	0	10	10	10	10
squamous metaplasia, ary cartilage (stellate cartilage)	0	0	0	4	10	10
exudation	0	0	0	0	0	1
infiltration of inflammatory cells, lamina propria, diffuse	0	0	6	8	10	10
infiltration of inflammatory cells, lamina propria, ventral	0	1	4	2	0	0
lungs						
degeneration, bronchial	0	0	1	1	4	6
infiltration of inflammatory cells, peribronchial/peribronchiolar	0	0	4	4	3	6

Tab. 2 (continued)

	Exposure concentration (mg/m ³)					
	0 (A)	0 (F)	1.1	2.9	9.6	14.3
nasal cavity						
section level 1						
squamous hyperplasia	0	0	0	0	1	8
focal squamous hyperplasia	0	0	0	1	0	0
degeneration with inflammation	0	0	0	0	1	2
minimal inflammatory cell infiltrations	0	0	0	0	2	6
ulcer	0	0	0	0	0	2
exudation	0	0	0	0	0	3
section level 2						
degeneration with inflammation	0	0	0	0	0	1
ventral degeneration with inflammation	0	0	9	10	10	9
ventral degeneration	0	0	1	0	0	0
infiltration of inflammatory cells	0	0	0	0	1	0
ulcer	0	0	0	0	0	2
exudation	0	0	1	1	3	3
section level 3						
ventral degeneration with inflammation	0	0	6	8	10	10
ventral infiltration of inflammatory cells	0	0	2	2	0	0
exudation	0	0	0	0	1	2
section level 4						
ventral degeneration with inflammation	0	0	5	4	7	9
ventral degeneration	0	0	2	1	3	1
ventral infiltration of inflammatory cells	0	0	0	1	0	0
section level 5						
ventral degeneration	0	0	0	2	7	7
section level 6						
goblet cell hyperplasia, laryngeal passage	0	0	0	0	0	2
trachea						
degeneration, carina	0	0	0	5	4	5
infiltration of inflammatory cells, carina	0	0	0	0	0	1
findings at the end of the 7-day recovery period						
rats / group	5	5	5	5	5	5
larynx						
necrosis, U-shaped cartilage	0	0	5	5	4	5
squamous metaplasia, ventrolateral	0	0	3	5	5	5
squamous metaplasia, ary cartilage (stellate cartilage)	0	0	0	0	0	1
infiltration of inflammatory cells, lamina propria, diffuse	0	0	0	1	0	2
infiltration of inflammatory cells, lamina propria, ventral	0	0	1	2	2	3

Tab. 2 (continued)

	Exposure concentration (mg/m ³)					
	0 (A)	0 (F)	1.1	2.9	9.6	14.3
nasal cavity						
section level 1						
squamous hyperplasia	0	0	0	0	0	1
section level 2						
diffuse degeneration with inflammation	0	0	0	0	0	1
ventral degeneration with inflammation	0	0	0	2	0	0
ventral degeneration	0	0	4	2	5	2
tumour	0	0	0	0	0	1
exudation	0	0	0	0	0	1
section level 3						
diffuse degeneration with inflammation	0	0	0	0	0	1
ventral degeneration	0	0	0	2	3	0
section level 4						
ventral degeneration with inflammation	0	0	0	1	0	0
ventral degeneration	0	0	0	0	4	1
section level 5						
ventral degeneration	0	0	0	1	1	2
findings at the end of the 14-day recovery period						
rats / group	5	5	5	5	5	5
larynx						
necrosis, U-shaped cartilage	0	0	4	5	5	5
squamous metaplasia, ventrolateral	0	0	1	4	5	5
infiltration of inflammatory cells, lamina propria, ventral	0	0	1	0	0	1
nasal cavity						
section level 2						
ventral degeneration with inflammation	0	0	1	1	1	2
ventral degeneration	0	0	2	1	1	0
ventral infiltration of inflammatory cells	0	0	0	0	1	1
section level 3						
ventral degeneration with inflammation	0	0	0	0	0	1
ventral degeneration	0	0	1	0	0	1
section level 4						
ventral infiltration of inflammatory cells	0	0	0	0	0	2

A: control animals exposed to air only; F: control animals exposed to formulation only

Manifesto (MAK value/classification)

The critical effect of chlorothalonil is its strong local effect in the respiratory tract of humans and animals.

MAK value and peak limitation. In the concentration range of 0.3 to 1.2 mg/m³, chlorothalonil is irritating to the eyes, nose and throat and induced coughing, chest tightness and shortness of breath in occupationally exposed persons (Huang et al. 1995). No new data in humans are available. In the 2-week inhalation study in male rats now available, the lowest concentration studied was 1.1 mg/m³, at which necrosis of the U-shaped laryngeal cartilage was observed in 10 of 10 animals and squamous metaplasia of the larynx in 10 of 10 animals. Inflammatory cells and degeneration in the lungs and nasal cavity occurred with lower incidence. All these findings were still observed at a lower incidence at the end of the 14-day recovery period. The effects in the larynx, trachea, lungs and nasal cavity increased with increasing concentration (Charles River Laboratories 2013). A NOAEC could not be obtained from this study.

Human data indicate that a NOAEC for local effects would have to be below 0.3 mg/m³. As squamous metaplasia and necrosis of the U-shaped laryngeal cartilage occurred in all exposed animals even at the lowest concentration tested of 1.1 mg/m³, extrapolation to a concentration with no effect cannot be carried out and thus a MAK value cannot be established. Therefore, chlorothalonil remains assigned to Section IIb of the List of MAK and BAT Values and peak limitation is still not applicable.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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