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# Lindane – Addendum for re-evaluation of the BAT value

## Assessment Values in Biological Material – Translation of the German version from 2019

B. Brinkmann[1]
H. Drexler[2,*]
A. Hartwig[3,*]
MAK Commission[4,*]

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1 *Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Chair of the Working Group "Setting of Threshold Limit Values in Biological Material", Deutsche Forschungsgemeinschaft, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Henkestr. 9–11, 91054 Erlangen, Germany*

3 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

4 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *E-Mail: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

## Abstract

In 2018, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated lindane [58-89-9]. The critical toxic effects of lindane are immunotoxic and immunomodulating effects. After inhalation exposure, a NOAEC of 0.6 mg/m³ (rat) and 1 mg/m³ (mouse) for histological changes of the spleen, thymus and bone marrow and a NOAEL of 0.45 mg/kg body weight for rats and 2 mg/kg body weight for mice for immunological effects can be derived. Exposure to the MAK value of 0.1 mg/m³ results in a daily intake of 0.014 mg/kg body weight (100% inhalation absorption, 70 kg body weight and 10 m³ respiratory volume) for humans excluding skin contact. In this low concentration range, an inhibition of immunological responses is not likely. So the MAK value of 0.1 mg/m³ was confirmed. No data are available to correlate the concentration of lindane in the air with its concentration in serum. There are no indications that immunotoxic effects occur at a serum concentration of 25 µg lindane/l. Therefore, the BAT value of 25 µg lindane/l is confirmed. The NOAEL for developmental toxicity after oral application is 10 mg/kg body weight per day and corresponds to 900 µg/l serum concentration. The difference to the NOAEL for developmental toxicity relating to the serum concentrations in rats is 40 times the BAT value. Therefore, lindane is assigned to Pregnancy Risk Group C.

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|---|---|
| **BAT value (2000)** | **25 µg/l serum** |
| **MAK value (1998)** | **0.1 mg/m³ E** |
| Peak limitation (2002) | Category II, excursion factor 8 |
| Absorption through the skin (1966) | H |
| Sensitization | – |
| Carcinogenicity (1998) | Category 4 |
| Prenatal toxicity (1998) | Pregnancy Risk Group C |
| Germ cell mutagenicity | – |

## Re-evaluation

Since the last BAT Value Documentation in 2000 (translated in Angerer 2016), new data on several toxicological end points have been published (Hartwig and MAK Commission 2019), which require a re-evaluation of the BAT value.

Lindane (γ-hexachlorocyclohexane) has been used as an insecticide since 1942. It has also been used worldwide for the treatment of parasitic skin infections, especially in patients infested with itch mites and lice, and as an additive in wood preservatives. Production and application peaked in the late 1960s, after which production declined. Under Regulation (EC) No 850/2004, the use of lindane has been banned in Europe since the beginning of 2008. Lindane has not been produced in the United States since 1976 (ATSDR 2005), but it has been imported in large quantities. In August 2006, the U.S. EPA cancelled all registrations for agricultural uses of lindane (US EPA 2006). However, it is still used to treat scabies mites and lice, among others in the United States, and probably in other countries as well.

The synthesis of hexachlorocyclohexane (HCH) from benzene and chlorine produces a mixture of isomers (technical HCH), which is composed of 65–70% α-HCH, 7–20% β-HCH, 14–15% γ-HCH, 6–10% δ-HCH and 1–2% ε-HCH. The insecticidal activity can only be attributed to the γ-isomer. Lindane is the name of the product consisting of at least 99% γ-HCH (UBA 2018). Only those studies are described in the following that were carried out with lindane.

The BAT value of 25 µg lindane/l serum was established on the basis of studies performed on workers occupationally exposed to lindane. Long-term exposure resulted in only slight elevations of liver enzymes, which were within the normal range and not significant compared to a control group. Blood lindane concentrations in workers involved in the production of lindane were found to be in the range of 37 or 64 µg/l serum (see Table 1). In addition, up to two to five times higher α- and β-HCH levels were measured. It can be assumed that the doses effective in animal studies are similar to those which cause corresponding effects in humans. It is very likely that the effects of the individual HCH isomers act additively.

Target organs that are primarily affected by the toxic effects of lindane are also the central nervous system and the reproductive system. According to present knowledge, immunotoxic and immunomodulating effects must also be taken into account in the evaluation.

**Tab. 1** Serum concentrations of lindane as well as α-HCH and β-HCH in workers following exposure to lindane and H isomers

| Exposed workers | Lindane [µg/l serum] | α-HCH, β-HCH [µg/l serum] | Effect | References |
|---|---|---|---|---|
| 57 workers, lindane production | Mean: 36.9 ± 39.9<br>Median: 23 (15–188) | Mean: 69.6 ± 51.5, 190.3 ± 153.4 | no statistically significant elevation of liver enzymes compared to the control group (γ-GT, ASAT, ALAT, LDH), slightly elevated γ-GT levels in both collectives | Baumann et al. 1980<br>Brassow et al. 1981 |
| 21 workers from this collective, exposed to lindane only | Mean: 64.3 ± 53.5<br>Median: 42 | | | |
| forestry workers | up to 36 | | no evidence of hepatotoxicity (alkaline phosphatase, γ-GT, ASAT, ALAT) | Drummond et al. 1988 |

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; γ-GT: γ-glutamyl transferase; LDH: lactate dehydrogenase

## Exposure and Effects

The only study available on the evaluation of immunotoxic effects in correlation with internal exposure is the one by Seth et al. (2005). Between 1997 and 2001, 20 patients were treated with the acetylcholinesterase inhibitor atropine after lindane poisoning. The patients were treated for 7 to 21 days. The control group consisted of 20 healthy subjects with no history of lindane or organochlorine pesticide exposure. Blood samples were collected within 24 hours and 10 days and tested for IgG, IgM, IgA, IgE and cytokines (IL-2, IL-4, TnF-α and IFN-γ). The blood lindane concentrations were 0.25–1.3 mg/l. No lindane was detected in the blood of the control subjects. Routine haematological and biochemical parameters were found to be within the normal range in the patients. There was no statistically significant decrease in acetylcholinesterase activity in patients compared to control subjects. No significant alteration in serum immunoglobulin concentrations was observed as compared to the control group. The serum levels of the cytokines IL-2, IL-4 and TNF were significantly increased in the patients and correlated positively with blood lindane levels. IFN-γ levels were significantly reduced. To date, atropine is not known to have any effect on cell-mediated or humoral immune responses (Seth et al. 2005). Data on external exposure are not available.

## Background Exposure

Background exposure in Germany is constantly decreasing. In 1998, the population not specifically exposed to lindane had background levels of less than 0.1 µg lindane/l blood plasma or serum. These data were collected from 130 children and adolescents who lived in urban areas and had not come into contact with lindane (Heudorf et al. 2003). Children living in malaria-endemic areas in Mexico had blood lindane levels of 0.35 to 6.15 µg/g lipid (Trejo-Acevedo et al. 2012).

## Re-evaluation of the BAT value

There are no new studies on internal exposure and possible effects.

The MAK value of 0.1 mg/m³ was maintained taking into account the latest immunotoxic findings (Hartwig and MAK Commission 2019). As there are no studies indicating an immunomodulating effect at a serum concentration of 25 µg lindane/l,

**the BAT value of 25 µg lindane/l serum is also confirmed.**

### Evaluation of the pregnancy risk group

A NOAEL for prenatal developmental toxicity of 10 mg/kg body weight/day each for both rats and rabbits and a NOAEL for perinatal toxicity of 3.4 mg/kg body weight/day for rats was derived. The assignment to Pregnancy Risk Group C at a MAK value of 0.1 mg lindane/$m^3$ is based on the sufficiently large difference between the NOAEL for developmental toxicity in rats and rabbits, converted into air concentrations, and the MAK value of 175 and 290, respectively, and between the NOAEL for perinatal toxicity in rats and the MAK value of 83. Therefore, the assignment of lindane to Pregnancy Risk Group C was confirmed (Hartwig and MAK Commission 2019).

There are no studies on developmental toxicity providing information on serum concentrations. Therefore, the NOAEL of 10 mg lindane/kg body weight from the developmental toxicity studies is compared with the serum concentration from oral studies in the same dose range. After administration of 10 mg/kg body weight to male Wistar rats by oral gavage for 25 days, a blood concentration of 1000 µg lindane/l blood was measured (Joy et al. 1982). In a 20-week feeding study on female Wistar rats, a concentration of 180 µg/g adipose tissue was reported at a dose of 10 mg lindane/kg body weight (Schröter et al. 1987). Since the fat:blood ratio of lindane is approximately 200 (Greim 2001), 10 mg/kg body weight correspond to about 900 µg/l blood. The blood concentration roughly corresponds to the serum concentration. Assuming that the serum concentration in pregnant rats is similarly high, the serum concentration at the NOAEL for developmental toxicity is about 40 times the BAT value.

**For this reason, assignment to Pregnancy Risk Group C applies if the BAT value is not exceeded.**

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