Elimination of β-hexachlorocyclohexane (β-HCH) in occupationally exposed persons

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1 Introduction:

In the production of the insecticide lindane (γ-hexachlorocyclohexane (γ-HCH), purity>99%) several by-products occur, of which α-HCH and β-HCH are the most important ones. Though the amount of α-HCH in technical grade HCH is larger (65-70%) compared to β-HCH (7-10%), β-HCH is of major toxicological importance because of its tendency to accumulate in fatty tissue. There is only scattered information about the half-life time (HLT) of this substance[1,7,9], which estimate a HLT between one and several years. The fact that after chronic exposure to technical HCH the correlation of the HCH-isomers in blood (α-HCH/β-HCH 59/160 [2] and 97,2/206,7[8] µg/ml blood) are profoundly different to the spectrum of isomers in the product, as well points to a long HLT of β-HCH.
Today β-HCH concentrations up to 3 µg/l blood (average of ~1 µg/l) can be detected in persons due to environmental background exposure.
β-HCH is being suspected to cause neuronal diseases[4,8], although results in literature are inconclusive[3]. As well β-HCH is in the discussion because of its carcinogenic potency[10]. Therefore clearer knowledge about HLT of β-HCH in humans is highly desirable.

2 Methods

In a cohort of former workers of a pesticide producing plant of 41 workers two deep frozen blood specimens, in three workers three blood specimens of different times were available. Whilst the second specimens except of one were collected during a clinical investigation in 1992-4, the first specimens were collected between 1985 and 1991.
Of both times there exist clinical and laboratory data of most of the workers. Whole blood (WB) samples were stored at -20°C until analysis (for further information see [6]).
Each sample was analysed for concentration of β-HCH twice by high-resolution gas chromatography/high resolution mass spectrometry. The correspondent blood specimens for each person were analysed at the same time. Extractable lipids (EL) were measured as well.

Concentration in extractable lipids c_{EL} was than calculated by

$$c_{EL} = \frac{c_{WB}}{\%EL/100}$$

For statistical analysis 1µg/l blood (the mean of momentary background concentration) was subtracted from achieved concentrations. After that, using a model of first order kinetic, individual decay rates were calculated by

$$\lambda_i = \frac{Y_{i,first} - Y_{i,last}}{\Delta t_i} \qquad i = 1, .., n$$

with $Y_{i,first}$ and $Y_{i,last}$ as natural logarithm of first and last measured blood level minus background and Δt as respective time difference in years. Transformation of the decay rate to HLT can be done by

$$HLT_i = \frac{\ln 2}{\lambda} .$$

3 Results

For 40 of the 44 workers, who had blood levels of β-HCH well over background contamination at every sample (at least > 3µg/l blood), the individual decay rate (DR) was calculated. Tab.1 shows the individual DRs calculated either on the basis of whole blood or extractable lipids.
Fig.1 shows a scatterplot of the β-HCH concentration at time of first sample vs. individual decay rate. The decay rate does not appear to be concentration dependent (Pearson's correlation coefficient =0,094), thus giving no hints that excretion does not follow a first order kinetic.
In Tab.2 median, range, lower and upper quartile of both DRs are given. On whole blood basis median of DR is 0,097, range 0,007-0,638 (median HLT=7,´3 years), on extractable lipids basis median DR is 0,091, range -0,003-0,290 (median HLT=7,46 years).
It is worth mentioning that three of the four persons with the lowest decay rates (longest HLT) show laboratory signs of severe liver disease.
Correlation of DRs of all 40 persons results in a Pearson's correlation coefficient of 0,70. Neglecting all persons with a difference in the concentration of extractable lipids between their first and second sample of more than 25% results in a correlation with Pearson's coefficient of 0,95 (s. Fig.2).

4 Discussion

The study presents the hitherto largest study about the DR (resp. HLT) of β-HCH in the human. Median HLT is around 7 years (DR ~ 0,09/year), independent on calculation of

concentration in whole blood or refering to lipid contents. Variation is large and covers all the hitherto measured HLTs, including those of about one year[1].
Obviously the agreement of decay rates based on whole blood or on extractable lipids contents is strongly influenced by differences of the concentration of extractable lipids between the samples. Regarding the lipophilicity of β-HCH (Octanol/water-coefficient (log p_{OW}) =3,8)[10] the HLT based on lipid contents seems the most reasonable one.
Although momentarily based on case description only, there are hints that an intact liver function is essential for the elimination of β-HCH and that liver damage results in a delay of elimination. Findings of the metabolism of β-HCH in humans[5] fit well with this hypothesis. This and the impact of several factors on half life time of β-HCH are currently under investigation.

5 References

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Tab.1: ß-HCH concentrations and decay rates of the individuals (n=40)

nr	HCH-wb 1	HCH-wb 2	HCH-el 1	HCH-el 2	delta-time	DR-wb	DR-el
1	71,7	48,5	15587	10104	4,25	0,09198	0,102
2	49,9	13,3	11089	3244	6,33	0,20878	0,19408
3	467	155	80517	38750	6,9166	0,15946	0,10574
4	395	224	79000	48696	6,1[1]67	0,09198	0,07846
5	64,7	45,3	13766	10295	1	0,35645	0,2905
6	41,3	16,2	7121	3447	6,75	0,13864	0,10749
7	142	92,2	35500	22488	2,25	0,19194	0,20292
8	30	27,4	7692	6683	1,667	0,05439	0,0844
9	289	211	65682	47954	8,0833	0,03892	0,03892
10	74,8	29,2	18700	8588	6,5833	0,14288	0,1182
11	21,3	18,5	3804	3190	7,333	0,01922	0,024
12	215	106	44792	22083	7	0,10103	0,10103
13	126	54,2	24706	11292	9	0,09373	0,087
14	84,1	62,1	16173	15923	1,333	0,22745	0,01168
15	452	386	80714	60000	6,833	0,0434	0,0434
16	154	92,8	24444	17846	6,25	0,08104	0,05034
17	719	276	74124	55200	1,5	0,63831	0,19652
18	191	127	43409	33421	6,1666	0,06618	0,0424
19	212	116	36552	22308	6,91667	0,08718	0,07139
20	45,7	8,5	10156	1848	6,25	0,26913	0,27264
21	189	60,7	40213	9951	6,8333	0,16622	0,20437
22	72,3	17,6	17214	4293	6,333	0,22309	0,21929
23	42	30	8077	5882	1,91667	0,17555	0,16542
24	156	70,8	36279	14449	6,91667	0,11422	0,1331
25	100	58	25641	13810	6,5833	0,08274	0,094
26	99	92,5	18333	11420	6,16667	0,01101	0,07676
27	36,5	20,9	6293	3266	6	0,09293	0,10933
28	80,9	29,2	17587	6489	6,41667	0,15881	0,15539
29	283	149	65814	38205	6,3333	0,10129	0,08587
30	215	156	52439	30588	6,08333	0,05273	0,08861
31	24,6	12,7	4920	2953	7,91667	0,08351	0,06446
32	155	89	32292	18936	6,33333	0,0876	0,08427
33	24	13,3	4446	3022	6,08333	0,10309	0,06344
34	13,8	3,5	2555	778	6,91667	0,19835	0,17199
35	340	221	69388	44200	6,25	0,06893	0,07216
36	105	72,1	22826	16022	6,25	0,06015	0,05663
37	6,5	2,5	1625	676	6,66667	0,14333	0,13163
38	36,5	36	7300	7347	1,91667	0,0072	-0,0033
39	19	11	4222	2750	7	0,07808	0,06125
40	6,6	4,4	1269	978	1,5	0,27031	0,17392

[1] *nr=running number; HCH=ß-HCH-concentration in µg/kg; wb=whole blood basis; el=extractable lipids basis; 1=first sample; 2=second sample; delta time=time between samples in years; DR=decay rate*

Fig.1: Plot of individual decay rate (DR) vs. concentration of ß-HCH (HCH) related to extractable lipids (EL) in the first sample (n=40)

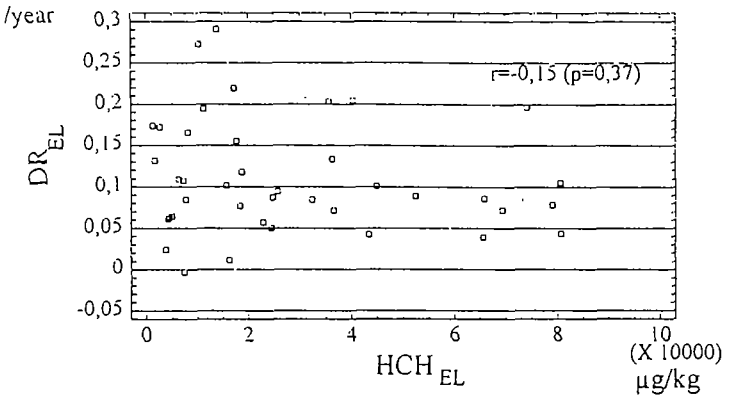
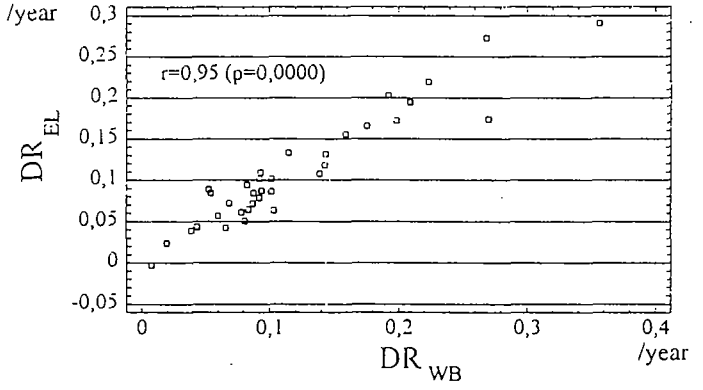


Fig.2: Plot of decay rate (DR) on whole blood (WB) vs. decay rate on extractable lipids (EL) basis (n=35)



Tab.2: Decay rate (DR) of ß-HCH on whole blood (WB) or extractable lipids (EL) basis

	n	median	min-max	25%-percentile	75%-percentile
DR-WB	40	0,097	0,007 - 0,638	0,074	0,171
DR-EL	40	0,091	-0,003 - 0,290	0,064	0,160