

特集

「国際臨床環境医学会 旭川」

The influence of chlorinated hydrocarbons (PCB, HCB, PCP) on cellular immune parameters in patients with allergies and chemical sensitivities

Klaus—Dietrich Runow, M. D. ¹⁾ Karlheinz Schmidt, M. D., Ph. D. ²⁾

1) Institut for Environmental Diseases, Bad Emstal, Germany

2) University of Tübingen, Germany

Toxic effects caused by pollutants must be considered as a possibility in cases of chronic allergy. The cytotoxic effects of environmental pollutants increases the number of allergic reactions. With a growing number of allergens the threshold of tolerance decreases. Thus the risk of getting asthma bronchiale is almost three times higher for children living in high—pollution areas in coparison to children living in low—pollution areas. Furthermore, pollutants can modulate the functions of the immunological system.

We examined 52 patients who suffered from chronic allergies or hypersensitivity. We not only took them into the standard diagnostic programe but also looked at their body load with chlorinated hydrocarbons, solvents and their immune status.

1. Symptoms

The patients that we included in our study complained of the following symptoms as shown in fig. 1:

Fig. 1 Symptoms in patients with allergies and chemical sensitivity.

Headache:	27
Dizziness	25
Lack of concentration	25
Tiredness	22
Burning eyes	18
Flatulence	17
Hypersensitive smelling	15
Drug intolerance	13
Gastric disorder	12
Obstipation	12
Somnipathy	12

Rhinitis	12
Alopecia	11
Sore lips	10
Diarrhoea	9
Irritation	9
Depression	8
Eczema	8
Swollen hands	7
Prurigo	7
Urticaria	5
Cramps in the leg	5

It is striking to see, that most of the patients showed neurological symptoms.

In the next step, we examined the patient's body load with chlorinated hydrocarbons, such as chemical solvents, pesticides, PCB's and PCP's.

2. The following chemicals had been measured in the blood of our patients:

Pesticides: Alpha—Chlordane, Gamma—Chlordane, Oxychlordane, Heptachlorine, Heptachlorepoide, Trans—Nonachlorine, Alpha—HCH, Beta—HCH, Gamma—HCH (Lindane), Aldrine, Endrine, Dieldrine, Hexachlorbenzole, Endosulfane I, Endosulfane II, DDT, DDD, DDE and Pentachorphenole.

(Method:GC, ECD)

Chemical Solvents: Benzene, Toluene, Xylene, Ethylbenzene, Trimethylbenzene, Dichlorbenzene, Styrene, Chloroform, Dichlormethane, 1, 1, 1—Trichlormethane, Trichlorethane, Trichlorethylene, Tetrachlorethylene.

(Method:GC, MS)

Polychlorinated Biphenyles (PCB): 23"44 Tetra;23'44'5

Penta;233'44 Penta;22'44'55 Hexa;22'344'5 Hexa;22'344'5
Hexa;22'344'5'6 Hepta;22'33'44'6 Hepta;22'344'55
Hepta;22'33'44'5 Hepta;Total-PCB
(Method:GC, ECD)

3. Results

The most alarming results were the remarkably increased values of Hexachlorbenzene, Polychlorinated Biphenyles and Pentachlorphenol.

Other chlorinated hydrocarbons-values (CH-values) such as chemical solvents were only slightly increased referring to US-average values, whereas mainly Toluene, Benzene, Trimethylbenzene and 1, 1, 1-Trichlorethane could be measured. It is interesting, that cyclodienes (such as Endrine, Aldrine, Dieldrine) could often not be measured. But the fact, that we could not measure them does not mean, they were not there:One could speculate, that these chemicals are too lipophile for dissolving in the blood. Another hypothesis is, that they are metabolized to substances, that we don't know yet. The third possibility lies in the fact, that these substances are more likely to be found in the urine due to their polarity. We know this phenomenon from the Heptachlorepoxid.

Now that we knew more about the patients body load with these chemicals, we wanted to know:What do they do to the immune system? HCB for example is known as being highly immunotoxic.

4. The Immune-Status

In order to find out more about it, we determined the immune status of the patients as well:We measured Leukocytes, B-lymphocytes, monocytes, granulocytes, Total-T-lymphocytes, activated T-cells, T-helper-Cells, T-suppressor-cells, natural killer cells (NK), cytotoxic T-cells and the ratio of T-helper versus T-suppressor-cells.

We found a highly significant negative correlation between HCT and the natural killer cells. PCB correlates negatively with the T-suppressor-cells. For pentachlorphenole (PCP) we could not find any statistically significant correlations in terms of the immune system. But this does not mean, we can forget about this substance at large:PCP is metabolized in the body to HCB. Also HCB is a side-product in the process of

PCP-combustion. In addition I would like to empha size, that research on chlorinated hydrocarbons (CH) should concentrate on the individual metabolism-rates.

Fig. 2 ~ 5 HCB-NK und PCB Suppr. Cells

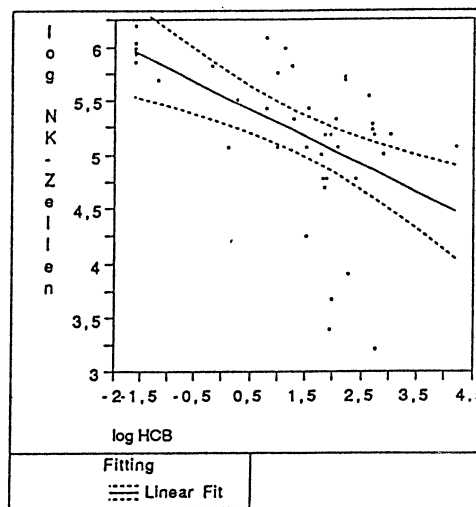
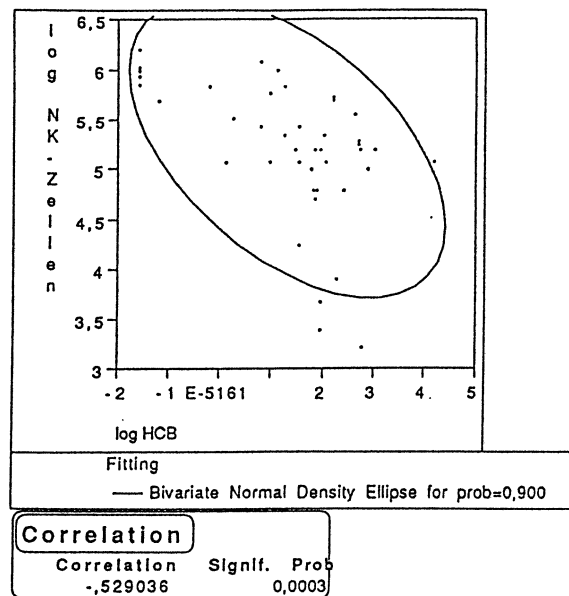
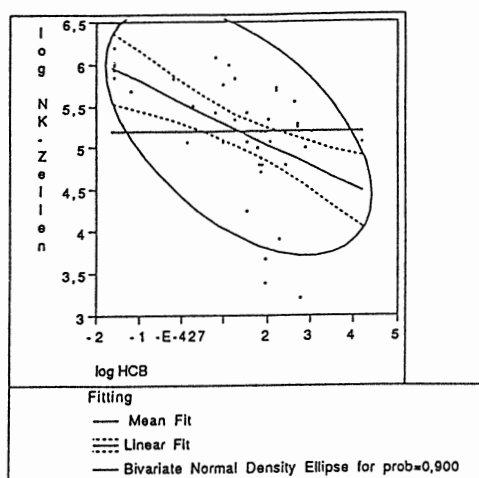


Abb. 2 : Ellipse, die einer zweidimensionalen Normalverteilung entspricht und im Mittel 90 % der Beobachtungen enthält. (log HCB zu log NK)

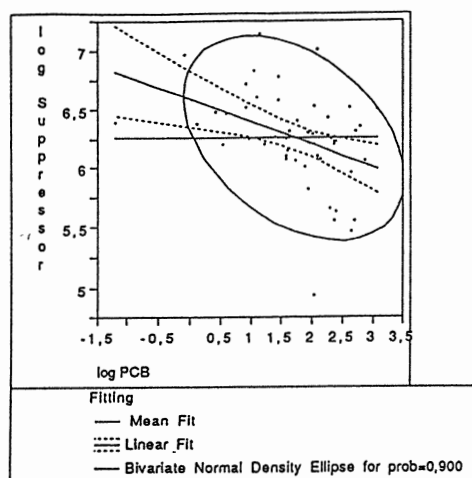
Abb. 3 : Regressionsgerade mit Vertrauenshyperbel



Mean Fit	
Mean	5,209172
Std Dev [RMSE]	,6981089
Std Error	,1077205
SSE	19,98160

Linear Fit				
Summary of Fit				
Rsquare	,2798800			
Root Mean Square Error	,5997739			
Mean of Response	5,209172			
Observations (or Sum Wgts)	42			
Analysis of Variance				
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	5,592451	5,59245	15,5463
Error	40	14,389151	0,35973	Prob > F
C Total	41	19,981602		0,0003
Parameter Estimates				
Term	Estimate	Std Error	t Ratio	Prob> t
Intercept	5,5475883	,126220	43,95	0,0000
log HCB	-,2563569	,065017	-3,94	0,0003

Correlation		
Correlation	Signif.	Prob
-,529036		0,0003



Mean Fit	
Mean	6,260368
Std Dev [RMSE]	,4049679
Std Error	,0572711
SSE	8,035951

Linear Fit				
Summary of Fit				
Rsquare	,1674969			
Root Mean Square Error	,3733283			
Mean of Response	6,260368			
Observations (or Sum Wgts)	50			
Analysis of Variance				
Source	DF	Sum of Squares	Mean Square	F Ratio
Model	1	1,3459974	1,34600	9,6574
Error	48	6,6899539	0,13937	Prob > F
C Total	49	8,0359513		0,0032
Parameter Estimates				
Term	Estimate	Std Error	t Ratio	Prob> t
Intercept	6,5953004	,120013	54,95	0,0000
log PCB	-,1959057	,063039	-3,11	0,0032

Correlation		
Correlation	Signif.	Prob
-,409263		0,0032

5. Hexachlorbenzene (HCB) — The German Marker

Hexachlorbenzene belongs to the chlorinated aromatic substances. It is known as the most potent immunotoxic substance. Due to its chemical structure, it can hardly be catabolized. It can have acute and chronic effects. The acute oral toxicity of HCB lies under the one of Lindane or DDT. An overdose of HCB has a lethal neurotoxic effect. But because of its persistence and its accumulation in the food chain, its potency to cause chronic effects plays an even more important role. Tests with animals have shown, that even minimum amounts do show certain effects. First of all there is the interference of HCB with the haemobiosynthesis in the liver, that can even cause a chronic hepatic porphyrie moreover there is the induction microsomal hepatic multifunctional

oxidases and neurotoxic effects. Rats have shown that the main metabolite PCP is synergetic to the porphyria.

When we look at the cellular immune parameters in our patients we see the tendency that HCB increases the cytotoxic cells.

Is it a compensation of the decreased number of killer-cells? In Germany, HCB has been prohibited in the agriculture since 1980. But it evaporates in high concentration in the process of waste-incineration. But most of the HCB — some say up to 90 percent — derive from the waste of the chemical industry. This way, it is unleashed into the environment.

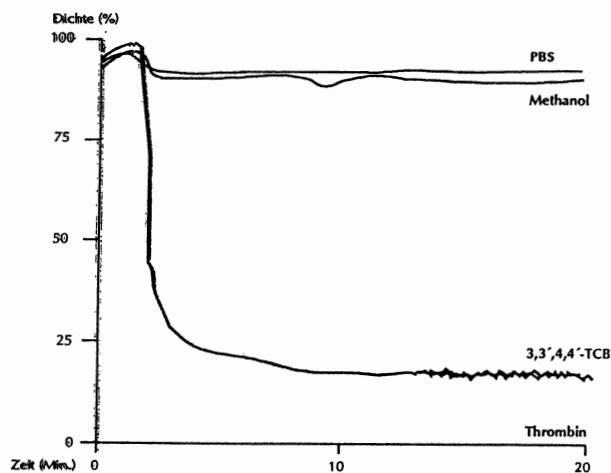
6. Polychlorinated Biphenyls (PCB)

They belong to the group of chlorinated hydrocarbons with a

very slow catabolization.

They are hazardous to the fertility. Also it has been shown, that 3, 3', 4, 4'-TCB can cause an aggregation of the thrombocytes.

Fig. 6 Dia Trombozytenabfall



Aggregation von menschlichen Thrombozyten ($2 \times 10^8/\mu\text{l}$) in Gegenwart von 3,3',4,4'-TCB ($0,6 \mu\text{M}$), Methanol ($10 \mu\text{l}$) oder Thrombin ($2,5 \text{ U/ml}$). Die Thrombozytenaggregation wurde als Änderung der Transmission bestimmt. (Quelle: Monika Raulf, W. König, Einfluß von PCB auf zelluläre Effektorfunktionen *in vitro* Allergologie, Jahrg. 14, Nr. 9, 1991, S. 354)

These PCB's can reach up to 80 per cent of the aggregative power of thrombin. PCB's are lipophile, so that they are stored in the body fat. Here the values lie 100 until 200 times above the values measured in the blood. They accumulate in the food chain.

PCBs are a constantly increasing problem in Germany, research has shown, that the body load of german children with PCB is sometimes even higher than the one of adults from Japan, Great Britain, New Zealand or Canada.

Another problem we will investigate is the problem of the coplanar PCBs.

They probably have effects like dioxins.

Summer 1992 I attendet together with Bill Rea and Jean Monro the first Czechoslovakian conference on global pollution, which had been organized by Lebuscha Gilka from Canada. We heard about the Czechoslovakian PCB desaster. The milk is highly contaminated but still bought from other countries; On the other hand cattle had been killed and many farmers lost their livelihood.

7. Pentachlorphenole (PCP)

PCP is a pesticide, widely used in Europe.

First of all, pentachlorphenole can cause severe neurological damages. One of the most common symptoms here is an unbearable headache, that most of the patients describe as hammering, knocking or drilling. The ache is located in the forehead and is not susceptible to analgesics. Many patients complain of dizziness, mostly in move, not in resting positions. Also they complain an insecure way of walking and speaking trouble. Almost every patient suffers from tremor. Also cold feet and hands and malsensations are quite common symptoms of intoxicifications with PCP.

In addition PCP causes internistic problems such as chronic sinusitis, dermatites of unspecific outsprig, furunculosis, swollen body parts, especially in the arms and legs. Here one can find severe angiopathic reactions such as an acrocyanosis. Also the patients report extreme transpiration, especially during the night. Furthermore there are digestive problems and flatulances, hiccups, stomachache and partly severe cramps. Some times one can find over a short time increased body temperatures, which can reach rectal 39 degrees centigrade. Finally, we have seen patients with bleeding from the gums and hair loss.

Immunological disorders are described by Huber from the Univ. of Heidelberg. The lymphocyte stimulation test showed disturbances with PCP levels already under 20 ppb.

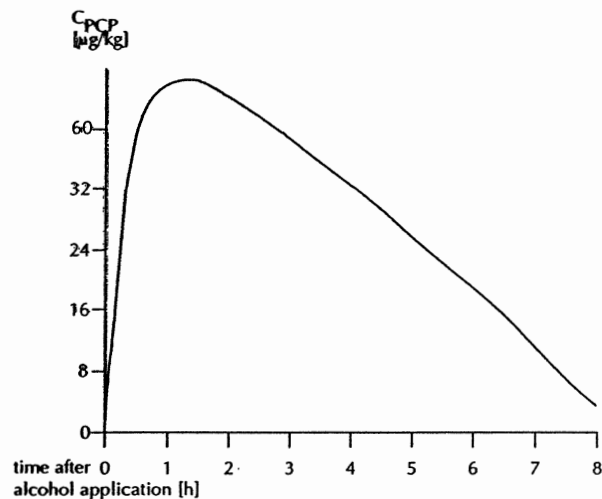
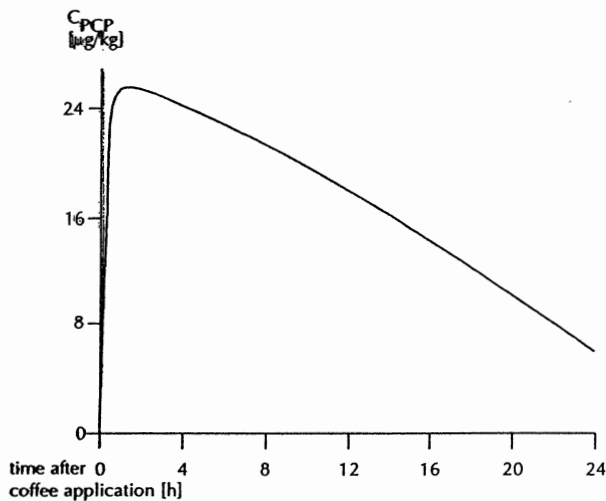
Thirdly there are psychiatric problems caused by PCP. Patients are phlegmatic, report of sudden changes in their personality, of forgetfulness, unrestfulness, aggressions and irascibility.

Some say, they simply have totally changed.

The tricky thing about PCP is, that it almost can't be measured in the blood: It is stored in the liver and the kidneys, which are the most affected organs.

We tried to prove this by provocatign the patients with alcohol — in order to stimulate the liver function — and coffee, which enforces diuresis. The PCP — value in the blood increases remarkably one and a half hour after the caffen intake. The same with alcohol.

Fig. 7 and 8 :PCP levels after alcohol and coffee



The reason for this increase could be, that the liver enzymes and the gluconidtransferase are stimulated. For this, it is very important, that patients who are hypersensitive to chemicals as PCP refrain from coffee or alcohol, even from certain drugs. For them, it is very important to avoid this abrupt increase of PCP—blood level, there have been cases reported, where patients have shown symptoms of acute intoxication or even shock.

Summary

We examined patients with allergies and chemical sensitivities

and measured chlorinated hydrocarbons, immunological parameters, vitamins, minerals, trace—elements, heavy metals (incl. teeth metals:mercury, palladium) .

In this special examination we correlated the values of chlorinated hydrocarbons (Hexachlorbenzene, Polychlorinated Biphenyls and Pentachlorphenol) with immunological parameters.

Hexachlorbenzene (HCB) belongs to the chlorinated aromatic substances.

It is known as the most potent immunotoxic substance. Due to its chemical structure, it can hardly be catabolized. It can have acute and chronic effects. The acute oral toxicity of HCB lies under the one of Lindane or DDT. An overdose of HCB has a lethal neurotoxic effect. HCB reduces the number of natural killer cells. Because of its persistence and its accumulation in the food chain, its potency to cause chronic effects plays an even more important role.

Polychlorinated Biphenyls (PCB) are lipophile, so that they are stored in the body fat. Here the values lie 100 until 200 times above the values measured in the blood. They accumulate in the food chain. They are hazardous to the fertility. Also it has been shown, that 3, 3', 4, 4'—TCB can cause an aggregation of the thrombocytes. These PCB's can reach up to 80 per cent of the aggregative power of thrombin. It could be shown that PCBs reduce the number of T—Suppressor—Cells.

Pentachlorophenole (PCP) can cause severe neurological damages. One of the most common symptoms here is an unbearable headache, that most of the patients describe as hammering, knocking or drilling. The ache is located in the forehead and is not susceptible to analgesics. Many patients complain of dizziness, mostly in move, not in resting positions. Also they complain an insecure way of walking and speaking trouble. Almost every patient suffers from tremor. Immunological disorders are described by Huber from the Univ. of Heidelberg:the lymphocyte stimulation test showed disturbances with Serum—PCP levels already under 20 ppb.

Discussion

It is a matter of fact that the reduction of the natural killer cells caused by HCB reduces as well the defensive power of

the body against bacteria, viruses and even tumor cells. That means, that not only the risk of infections increases, but also the risk of cancer.

At the same time, the reduction of the suppressor-cells promotes the T4/T8 quotient, that gives a strong hint of an over-reaction of the immune system, such as allergies or pseudoallergies. At the same time, it has been proven, that PCB can cause liver-cancer in rabbits.

To my opinion it is very important to clarify the way the cells are damaged. A hypothesis on this might be, that they are destroyed either by Lipidperoxidation, or by a disturbed cell-breathing, or inactivation of the lymphokines.