EXPLORING THE RELATIONSHIPS BETWEEN EXPOSURE TO PCDDS/FS AND NEUROLOGICAL HEALTH EFFECTS IN HUMANS

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Introduction

In Germany from 1949-1984 high human exposure to dioxins and furans (PCDD/Fs) occurred to workers in chemical industry mainly during the production of trichlorophenol (TCP) and 2,4,5 T-acid and to some extent also in the production of chlorphenols (CP), pentachlorophenol (PCP) and trichlorobenzol (TCB). In its sequel, a few cohorts of occupationally exposed workers were identified and could be studied for human health effects and their possible relation to dioxins which has contributed substantially to human risk assessment of polychlorinated dibenzodioxins and -furans. The earliest studies in Germany used surrogate biomonitoring, e.g., absence or presence of a chloracne history[1]. Another surrogate variable was based on the categorization of possibly exposed persons into occupational exposure classes, e.g., certain, likely, unlikely or non-exposed, on the basis of job matrices and records kept in the company or stored in the files of trade unions. Those studies were unfortunately unable to examine the effects of dioxin on human health unambiguously and no convincing dose-response evaluation was possible until dioxin levels could be determined in human tissue, around 1980-1985 determined in adipose tissue samples and later in blood lipid of blood serum samples. Neurological effects were amongst the first studied human health effects related to dioxins. Baader and Bauer[2] reported in a study of 17 workers of a pentachlorophenol producing plant suffering from chloracne on the simultaneous occurrence of weakness in limbs, paraesthesia, heart pain and psycho-vegetative disorders. Neurological effects, e.g., muscle pain, weakness in extremities, fatigue, increased excitability, demotivation, decreased libido, were reported by Bauer et al.[3] in 9 workers of a plant in Hamburg.

Effects of dioxins and furans on the neurological system have been studied continuously since then[4]. This comprises a large range of symptoms and diseases: cognitive and neuropshychiatric symptoms (neurobehavioral, personality change, fatigue, muscle ache, anxiety, depression, distal paresthesia, encephalopathy, decreased attention, decreased concentration), motor/coordination dysfunction and other CNS effects (tremor, dystonia, tendon jerks, ataxia, extra pyramidal signs ascular lesion, stroke), peripheral neuropathy, decreased libido, pin sensation, neurological dysfunction, nerve conduction velocity, cranial nerve symptoms. Studies reviewed by Goetz et al.[4] yielded mixed results for most of these health effects and a conclusive answer on a causal relationship between exposure to dioxins and furans and neurological health effects in humans is, still pending. One of two previous studies of a sub-sample of a German workers cohort showed a significant dose relationship of an effect of dioxin body burden on the autonomous nervous system (color vision impairment, but another investigating heart rate variability did not. The present study summarizes findings about neurological health effects of dioxins and furans using data of systematically investigated German cohort of workers occupationally exposed to PCDDs/Fs, thereby complementing recently reported results on neurological toxicity mediated through an impairment of the autonomous nerveous system [5,6].

Methods and Materials

In Germany occupational exposure to dioxins and furans occurred mainly in six plants of 4 companies, denoted A,B,C,D Table 1. The *Berufsgenossenschaft (BG) Program* investigated comprehensively health effects in a cross-sectional examination. In a follow-up study biomonitoring data were produced and collected in order to investigate for the existence of a dose-response relationship. Both studies overlap with the subsequently described investigation programs. The *IARC Phenoxy Herbicide Program* recruited for a mortality study 2479 persons of three companies where exposure during the herbicide production was plausible. The *Boehringer Hamburg Program* investigated the largest cohort consisting of 1583 regular workers of one plant[7]. The program included both mortality studies and morbidity studies of sub-cohorts. and a biomonitoring program. The *Boehringer Mainz Program* was restricted to a cohort from two plants of workers alive at start of the investigation in 1984 and working longer than 6 months in dioxin related production sites or dioxin related jobs including workers who wanted medical examination[8]. *The BASF Program* considered workers related to the accident of November 1953 and its subsequent clean up[9]. *Other Cohorts Programs* comprise separate investigations of workers originating mainly of two companies (C,D) which overlap with the BG program. Medical examinations and the collection and recording of morbidity and mortality data of the investigated persons of the Boehringer Mainz Program were described earlier[5,8,10].

Table 1. Six investigation programs for health effects of dioxins in workers of Germany exposed after 1950 with study identification, type of exposure and sample sizes. *biomonitoring data;

1. Berufsgenossenschaft (BG) Program				
1959/51 - 1984	TCP, 2,4,5 T-acid,		n=455	n=171*
	CP, PCP	A:	98	48*
Four companies A,B,C,D		B:	222	93*
(B: two plants, C: two plants)		C:	48	12*
		D:	97	18*
2. IARC Phenoxy Herbicide Program *(overlap with all others)*		n=2479		
1951-1989	phenoxy herbicides	A:	680	-
	and dioxins	B:	1144	130*
		C:	655	8*
3. Boehringer Hamburg Program *(overlap with 1. and 4.)*				
1950/51-1954	TCP (*one plant)*		n=1583[#]	1177*
1957-1984	TCP, 2,4,5T-acid, TCB, CP, Lindane			
4. Boehringer Mainz Program *(overlap with 1. and 3.)*				
1950/51-1954	TCP (*two plants)*	1st	n=183	-
1950-1984	TCB, CP, Lindane	2nd	n=192	185*
5. BASF Program *(overlap with 1.)*				
11/1953, 1968-1969	TCP		n=254	29*
6. Other Programs (*overlap with 1.)*				
1951-1976	TCP; 1968-1984 PCP		n=145	30*

Results and Discussion

Neurological effects were determined in *Berufsgenossenschaft (BG)* Program based on biomonitoring data through an interview during medical anamnesis and by a medical examination which included neurological measurements. Table 2 shows the number of incident cases of a battery of neurological symptoms subdivided into three exposure classes defined by the TCDD concentration at the time of medical examination. The incidence of neurological complaints was rather low. A few symptoms showed numerically an increase with increasing TCDD level which was, however, in no instance statistically significant. Multivariate regression analyses accounting for confounding effects of age, body mass, smoking, alcohol intake and company confirmed the negative findings[10].

Table 2. Neurological complaints of 153 (maximum evaluable) workers from the **BG-Biomonitoring Study** (where relevant, percentages are given in parentheses).

	Incidence of disease or symptoms	Exposure: 2,3,7,8 TCDD level (ppt) low < 20	medium 20-100	high >100
Upper and lower Limbs				
paralgesia, numbness, pains	50/149	10 (26)	20 (35)	20 (37)
muscletwitching, cramps	19/148	5 (13)	9 (16)	5 (9)
weakness	13/149	2 (5)	7 (12)	4 (7)
Neurological				
cranial nerve impairment	19/148	8 (22)	8 (14)	3 (6)
peripheral pareses	7/147	2	2	3
superficial sensitivity disorder	24/148	4 (11)	9 (16)	11 (20)
tingling	23/148	4 (11)	11 (19)	8 (15)
abnormal vibration sense	27/148	4 (11)	11 (19)	12 (22)
coordination disturbance	4/148	2	2	0
muscle impairment	6/148	2	2	2
proprioceptive reflex imp.	23/146	2 (5)	2 (16)	12 (22)
Autonomic disturbances				
red dermography	3/60	2	1	0
hyperhidrosis	12/148	2 (5)	3 (5)	7 (13)
moist, cold distal parts	3/148	1	0	2
fine finger tremor	4/148	1	2	1
Electrophysiological				
nervus peroneus	10/147	2 (5)	5 (9)	3 (6)
nervus suralis	13/147	3 (8)	7 (12)	3 (6)
VEP	15/143	5	5	5

Investigation of a sub-cohort of the BASF Study on the incidence and illness episodes of 158 exposed persons with 161 control revealed a statistical significant increase of effects on the PNS (3.2 % versus 1.8 %, p=0.018) but no effect on the central nervous system (0.6 % versus 0.5 %)[11]. Using biomonitoring data and back-calculation of the TCDD concentration the number of episodes of mental disorder per 100 person-years was 2.9 for the group exposed to less than 1000 ppt (n=73) and 2.2 for

the group exposed higher (n=85). The respective numbers of PNS episodes were 3.0 and 3.3. Hence, no dose-response relationship was observed when using TCDD levels back-calculated to the concentration at the time of the accident.

An increase of 12-23 % - although not statistically significant - of the occurrence of depressions when comparing low exposed (< 270 ppt TEQ) with high exposed (³ 270 ppt TEQ) workers was observed in a sub-cohort of the Boehringer Hamburg Program[12]. The proportion of persons being excitable and aggressive, feeling anxious, sad, or exhausted, showing emotional uneasiness and irritability, reporting libido and sexual dysfunction, or expressing suicidal thoughts was 10 % - 25 % higher in the high exposed group. Adjusted for age, smoking, education and prevalence of diseases confirmed a statistically significant effect for depression, excitability and aggressiveness, uneasiness and irritability, and suicidal thoughts ($p<0.05$) in this sub-sample.

So far the results discussed here as well as previous findings do not consistently support the hypothesis of the presence of such an effect. Tendencies and trends could be exhibited, but most of them were not statistically significant. Therefore, in summary, no final conclusion can be drawn on the presence of a causal relationship between exposure to dioxins and the occurrence of neurological diseases on the basis of the findings described above.

Further research is needed to confirm or dismiss the hypothesis of neurological effects of dioxins and furans. At the present stage it is questionable whether small or medium scale studies are the appropriate means to tackle this problem. Future efforts should discuss and fix what kind of effect and what minimum size of it is considered relevant. This specification would then allow the determination of the appropriate scale of the study and lead to a realistic assessment whether and where such a study could be performed.

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References

1. Schulz K.H. (1957). Arch Klein Exp Dermatol 206: 589-596.
2. Baader E.W., Bauer H.J. (1951). Ind med Surg 20, 286-290.
3. Bauer H., Schulz K.H., Spiegelberg U. (1961). Arch Gew.pathol und Gew.hyg 18, 538-555.
4. Goetz C., Bolla K.I., Rogers S.M. (1996). Neurology, 44, 801-809.
5. Heinzl H., Muttray A., Jung D., Hergert A., Rose D-M., Konietzko J., Hofmann H.C., Portier C.J., Edler L. (2000). Organohalogen Compounds 48, 195-198.
6. Edler L., Muttray, A., Jung, D., Rose D.-M., Konietzko J., Portier, C., Heinzl H. (2001). Organohalogen Compounds 53, 309-312.
7. Manz A., Berger J., Dwyer J.D., Flesch-Janys D., Nagel S., Waltsgott H. (1991). TheLancet 338, 959-964.
8. Jung D., Berg P.A., Edler L., Ehrenthal W., Fenner D., Flesch-Janys D., Huber C., Klein R., Koitka C., Lucier G., Manz A., Muttray A., Needham L., Päpke O., Pietsch M., Portier C., Patterson D., Prellwitz W., Rose D.M., Thews A. and Konietzko J. (1998) Environ Health Perspect 106(Suppl 2), 689-695.
9. Zober A, Messerer P, Huber P (1990). Int Arch Occup Environ Health 62:139-157.
10. Benner A., Edler L., Mayer K., Zober A. (1993). Berufsgenossenschaft der chemischen Industrie (Ed). ISBN 3-88383-336-3. Colordruck Kurt Weber, Leimen.
11. Zober A., Ott M.G., Messerer P. (1994).Occup Environ Med 51, 479-486.
12. Franzkeit U., Nienhaus A., Flesh-Janys D, Böhme K., Manz A., Berger J. (1996). Organohalogen Compounds 30, 329-332.