

EPIDEMIOLOGIC STUDY OF A POPULATION PREVIOUSLY EXPOSED TO HEXACHLOROBENZENE

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In several areas in Eastern Turkey during a 3-year period from 1956-59, approximately 4,000 people were inadvertently exposed to hexachlorobenzene (HCB) which was utilized as a herbicide for seed grains. These exposures occurred during periods of austerity when individuals ingested seed wheat unintentionally diverted to replace edible wheat stores.

Original Turkist government records for precise areas of distribution of wheat have been obtained. The seeds that were treated with HCB to control a wheat fungus were distributed mainly to South Eastern Anatolia between 1954-1959.

Distribution of the seed wheat included the areas surrounding the cities of Diyarbakir, Urfa, Siirt, Mardin, Gaziantep, Mus, Elazig, Nigde, and Adapazari.

Several unique clinical features were noted during the initial exposure period from 1956-1959. The interval between HCB ingestion and development of symptoms was calculated to be approximately six months. The initial symptoms mentioned by most subjects were weakness, loss of appetite, and sunlight sensitivity. Hyperpigmentation was maximum in exposed areas of skin and hypertrichosis occurred principally on the forehead, cheeks, arms, and legs and was sufficiently distinctive in the five to fifteen year age group for them to be described as "monkey children." Development of bullae often up to 5 cm in size occurred frequently, healing with severe mutilating scars. The porphyria was known as Kara yara (black sore). During the early period of active porphyria the affected persons continued to be irritable with colic, loss of appetite, weakness, and they excreted red or brown urine (porphyrinuria). Many adults and children died from this initial acute toxicity. It was estimated that nearly 14 percent of the exposed individuals died during the initial acute exposure phase. Survivors developed porphyrinuria with concomittant neurologic, cutaneous, hematologic, and mental aberrations characteristic of a syndrome called porphyria turcica. Arthritis was common in the younger age group with swelling and spindling of the fingers but very little pain. In addition, children born to mothers who had ingested the HCB-treated grain developed a condition called "Pembe yara" (pink sore) that was followed by a high infant mortality within two years. It has been estimated that more than 2000 children died from this condition in which many were breast-fed by mothers who had been exposed to HCB.

Preliminary data on a sampling of over 100 members of this population, 20 years after their initial exposure, indicate continued clinical symptoms and signs such as hyperpigmentation, hirsutism, cutaneous scarring, small stature and hands, painless arthritis, enlarged liver, and enlarged thyroid.

This is a picture of two sisters. The younger sister who is age 17 years appears on the left. She has a normal appearance and is of normal stature. The sister on the right was exposed to HCB during her childhood. As you can see, the HCB exposed individual had scarring on the face and hands. You can also see the smaller hands, the short fingers, and the arthritis of the hands. These characteristics are common among many of the HCB survivors.



This picture depicts the enlarged thyroid observed in several of the HCB exposed individuals.



This picture depicts another example of an HCB-exposed individual with an enlarged thyroid. The presence of enlarged thyroids in the HCB exposed population are presently being viewed with suspicion in light of recent experimental studies in which thyroid tumors have been observed in hamsters exposed to HCB. We are presently trying to determine whether the enlarged, goiter-like symptoms are endemic to this Turkish population or are a manifestation of the HCB exposure. We plan to request the pathologic findings on those individuals who elect to have their thyroid condition treated surgically and have requested thyroid scan data on all individuals whether surgically treated or not. As necessary, individuals with thyroid adenoma will be studied in more detail at the Hacettepe Hospital in Ankara.



This picture depicts the extensive facial scarring, the shortened fingers, and the painless arthritis observed in several of these HCB exposed individuals.



This study represents a unique opportunity to observe the human effects of HCB exposure. The current health status of previous exposed individuals may provide us with additional information relevant to the potential chronic effects of HCB. We have a particular interest in the status of youngsters born of mothers who were 6-12 years of age at the time of their initial exposure.

We have been most fortunate and very appreciative of the cooperation shown by the Turkish authorities and clinicians. Dr. Ayhan Gocmen, a Turkish clinician from Hacettepe Medical School of Ankara, Turkey, has been indispensable in his efforts to assist us in the clinical aspects of the study. Dr. Gocmen was initially involved in this problem when he was a resident working in Eastern Turkey on this particular problem shortly after the initial incidence was observed and has been associated with evaluating the problem ever since. He has been able to assist us in visiting a total of 10 villages in which over 100 individuals have been identified as survivors of their initial acute exposure some 20 years ago. Records indicate that nearly 5,000 villages may have been involved to various extents in this epidemic area suggesting a sizable population for study. Dr. Gocmen continues to expand our investigation and has acquired the services of several paramedical personnel to assist him in identifying HCB exposed individuals. Indoctrination of personnel at various medical centers throughout the epidemic area has also made them more aware of these disorders.

Preliminary information to date indicate that fecal and urinary porphyrins are still being excreted in significant amounts by several individuals. Urine and stool porphyrins have been obtained on 100 individuals with clinical evidence of porphyria. These data are being compared with Turkish and U. S. control individuals. The preliminary results indicate that five subjects are still porphyric after 20 years. Four of these subjects have moderately increased excretion of porphyrins whereas the fifth subject had a urinary uroporphyrin of 1,607 micrograms/liter compared with Turkish and U. S. controls of only 5.17 and 9.0 micrograms/liter, respectively. This latter individual also had a stool uroporphyrin of 189.2 microgram/gram dry weight compared with controls of 2.09 and 2.80 micrograms/gram, respectively.

Further follow-up studies are under way including the identification of additional exposed individuals and quantitative analysis of HCB and porphyrin levels.

In addition, animal studies are also in progress in an attempt to correlate animal and human symptomology as a result of a range of HCB exposures. These correlations will be based upon both acute and chronic animal exposures and those estimated in HCB exposed human populations.

In summary, we have observed clinical symptoms of porphyria including the excretion of urinary and stool porphyrins as well as HCB in maternal milk from HCB exposed individuals. These data suggest that HCB was accumulated in body tissues and fat stores for at least 20 years from initial exposure. These findings would support our continuing concern regarding the potential chronic effects of chlorinated hydrocarbons and, in particular, the chlorinated benzenes, on human health and the environment.

Discussion

Dr. Kraybill, NCI: Is there a parallelism in the United States, because there was an episode, I believe in Louisiana or Texas, where cattle got quite an insult from HCB? Would this be a population that one would be looking at?

Dr. Morris, EPA: There is a strong possibility that some of the clinical data that we developed in the Turkish incident can be correlated to other situations here in the United States. Certainly, the Louisiana incident is a prime example. The Agency does have a fairly sizeable data base on some of that and we are going to be looking at that data base as we proceed in this particular study.

Dr. Plotnick, NIOSH: Is there any indication of the levels of HCB in the original grain that was eaten. Also, are there samples still available and have impurities been analyzed. Some of these things appear to me to be more related, or possibly related, to the impurities than to the unchanged HCB itself.

Dr. Morris, EPA: Dr. Gocmen's brother-in-law is a member of the Turkist Department of Agriculture. In fact, he was very helpful in getting us the records of distribution. We are attempting now to methodically go through the list and identify storage facilities at distribution points to see if there might be any residual sacks of grain which might be made available to us for analysis.

In terms of your question about contamination, we would agree with you. A variety of potential contaminants with which many of us are aware may be of equal concern. I am hopeful that when our research team returns from their next visit that we might have some samples to analyze. Of course, after 20 years, I do not know exactly what this is going to mean either, but it certainly needs to be evaluated.

Dr. Fraumeni, NCI: Are there some clinical or experimental observations suggesting a relationship to cancer with this agent?

Dr. Morris, EPA: Yes. There are animal experimental data showing an oncogenic response in hamsters and mice when they are exposed to hexachlorobenzene.

Dr. Fraumeni, NCI: Do you know what type of cancer?

Dr. Morris, EPA: The thyroid gland appears to be a major target organ. This is why I indicated in my talk that we are interested in these particular patients with enlarged thyroids. I believe there has also been liver involvement.

Dr. Fraumeni, NCI: There is a condition called porphyria tarda, which is associated with cirrhosis, which in turn predisposes to liver carcinoma. Do these patients have cirrhosis?

Dr. Morris, EPA: I do not recall seeing it. We have noted enlarged livers in some of these patients; that is true. During my last visit in October 1979, we had one of the patients die of leukemia. I do not know what that means, because it is just one patient and he was only 26 years old. I think there may be a lot more pathology once we have identified the population. I appreciate that the study presently funded through the NCI/EPA activity is a five year study, but we are just now at the breakpoint of 20 years. I think in the next 20 years this particular population may provide us with a lot more data. So it is possible that this may be one of those activities, which Dr. Kraybill mentioned, that we might consider extending.



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