❖Health Effects Review❖

GREAT LAKES CRITICAL POLLUTANTS

Introduction

In 1985, the Great Lakes Water Quality Board identified persistent toxic pollutants as the principal issue confronting the Great Lakes, and developed a list of eleven "Critical Pollutants" deserving an early focus by remedial action programs. This newsletter continues the examination of recent medical literature on selected persistent organic pollutants from this list, including DDT, dieldrin, and hexachlorobenzene. Recent literature includes mortality studies for organochlorine manufacturing workers, reports of organochlorine residues in tissues of diseased and healthy persons, and morbidity studies among termiticide-exposed populations. The literature was identified by searching computerized data bases (NIOSHTIC, National Library of Medicine) and is not limited to Great Lakes populations. Literature specifically related to breast cancer and the estrogenic effects of xenobiotics as well as additional literature on mirex and hexachlorobenzene, will be reviewed in a subsequent issue.

Organochlorine Residues in Normal and Diseased States

Investigators in Germany have carried out a series of studies to measure the levels of organochlorine pesticides (termed chlorinated hydrocarbons by these authors) in normal and diseased bone marrow, and in other tissues in normal and diseased states. All studies were conducted in Germany. In the first, the authors attempt to address the question whether these agents, many of which have mutagenic, carcinogenic or teratogenic effects in animals, contribute to pediatric tumors and malformations.[1] They analyzed fat samples taken from 262 children and adolescents aged zero to 18 years. The samples were collected during operations required for other reasons. The children were divided into three groups: Group A, 183 healthy children (babies and children operated on primarily for inguinal hernia or inguinal testis), including 12 neonates sampled before the first meal; Group B, 46 patients with malignant tumors (neuroblastoma, Wilm's tumor, soft tissue sarcoma, and others); and Group C, 33 babies and children with congenital malformations or benign tumors (renal and urethral malformation, lipoma, lymphangioma and others). The specimens were analyzed for PCB's, DDT and metabolites, HCH isomers and cyclodienes. The results showed that alpha-, beta-, and gamma-HCH, dieldrin, p,p'-DDE, total PCB and certain PCB isomers various were detected in either all or most samples. Heptachlor was detected in approximately half of samples. The highest levels were found for total PCB, DDT, HCB and HCH isomers. Of the cyclodienes, only dieldrin was detected at significant levels. The concentrations of PCB, DDT, and HCB were highest in neonates who not yet been fed, were significantly lower in infants six months old, and rose again to neonatal levels at the end of the first year of life. The concentrations changed little in the older childhood age groups. There were no significant differences in CHC concentrations between normal children and either babies with malignant tumors or babies with congenital malformations or benign tumors. The authors interpret the drop in concentrations between birth and six months to CHC distribution in the disproportionately increased body fat relative to non-fat tissue, and the apparent rise in the second half of the first year to the decrease in relative fat mass. The steady concentrations during the rest of childhood are interpreted as intake of CHC's which corresponds to the increase in fat occurring with age. Noting the small sample size, the authors warn against using these negative results to conclude that there is no association between CHC levels and tumor or malformation in children.

In another study, bone marrow from 35 children with leukemia (35 with ALL and 3 with CML) and 15 controls (9 children with ITP and 6 normal bone marrow donors) were analyzed for the following compounds: alpha-HCH, beta-HCH, total HCH, dieldrin, HCB, p,p'-DDE, p-p'-DDT, total DDT, PCB-138, PCB-153, PCB-180, total

PCB, and total CHC.[2] None of the CHC showed a normal distribution (as expected) with the median concentration for each agent being lower than the mean. There were no significant differences in concentrations of any of the compounds between children with and without leukemia.

Noting that the partitioning of chlorinated hydrocarbons (OC) and polychlorinated biphenyls is in part dependent on the fat content of tissues, the investigators then compared the concentrations of CHC and PCB in bone marrow with that of depot fat and breast milk.[3] They found that for Beta-HCH, HCB, Total-DDT, PCB-138, -153 and -180, the highest concentration (in mg/kg fat), (most cases significantly), were in the bone marrow, compared to breast milk and fat tissue. They postulate selective partitioning into bone marrow. Note that the sources of the samples were not the same patients (surgical sources for fat, children for bone marrow, nursing mothers for breast milk).

Finally, bone marrow specimens obtained from 13 adults with hematologic malignancies (3 with AML, 3 with CLL, 3 with plasmocytoma, 2 with CML, 1 with Hodgkin's lymphoma, and 1 with ALL) and from 16 patients without leukemia (6 with ITP and 10 bone marrow donors) were analyzed for a variety of CHC insecticides.[4] The following compounds were detected in all 29 samples: alpha-hexachlorohexane, beta-hexachlorohexane, dieldrin, hexachlorobenzene, p,p'-DDT, and DDE. When leukemia/lymphoma patients were compared to controls, the medians of total HCH, HCB and total DDT concentrations were increased by 37%, 48% and 17%, respectively. These increases were not statistically significant for any compound, which was attributed to the small sample size. The authors recommend that larger numbers of subjects be studied to evaluate the potential association between leukemia and lymphoma and CHC exposure.

These data provide evidence that there is partitioning of DDT, HCH and HCB into the bone marrow, and that in a small group of adult leukemia patients, their concentrations were higher than in those without leukemia. The clinical significance of these findings is currently unknown.

Occupational Aldrin Exposure, Enzyme Induction, and Genotoxicity

Australian investigators studied an occupational cohort for sub-clinical effects of aldrin exposure. They note that aldrin, used in termite control in South Australia, is converted to dieldrin by the mixed function oxidase system, and that dieldrin has a long biological $t_{1/2}$ (266 days in exposed workers).[5] They also note that previous reports concluded that neither aldrin nor dieldrin is mutagenic in microbial systems, and that testing in mammalian systems has given conflicting results. This study was undertaken in pesticide applicators in South Australia to determine (1) whether levels of plasma dieldrin and frequency of sister chromatid exchanges (SCE) reflect exposure to aldrin in humans, and (2) whether there is significant hepatic enzyme activity (and thus induction) in this occupationally exposed group. The study group consisted of 33 employees of two pesticide treatment companies, who were classified by job category and thus presumed exposure level. The employees also had other potential OC pesticide exposures. Subjects were tested for plasma dieldrin, urinary D-glucaric acid (DGA, an index of hepatic enzyme activity), and peripheral lymphocyte SCE. Exposure groups included (1) office and sales, (2) vehicle and plant maintenance, (3) termitocide applicators, and (4) applicators performing pre-building treatments prior to building construction. Results showed that Groups 2-4 had significantly higher mean dieldrin levels compared to Group 1 (median values 7.0, 5.3 and 16.0 ng/ml in Groups 2,3,4, respectively vs. 4.8 in group 1). Urinary DGA levels were also significantly higher in Groups 2,3 and 4 than in Group 1. There were no significant differences between the groups in the frequencies of SCE, and there was no correlation between SCE and plasma dieldrin concentration. Plasma dieldrin levels were strongly correlated with age and weight. The correlation with age was shown to be largely due to duration of employment. Urinary DGA was more strongly correlated with exposure group than with plasma dieldrin level. The authors offer the following interpretations: that the nominally non-exposed office staff were indeed exposed to aldrin; that dieldrin accumulation due to long employment history is suggested; and that the correlation between urinary DGA and exposure group but not plasma dieldrin suggests that exposure to other enzyme-inducing organochlorines are at play. Finally, the authors suggest that the absence of SCE correlation with aldrin exposure supports that idea that aldrin is not genotoxic.

Mortality Studies of Organochlorine Manufacturing Workers

There are several recent reports of the mortality experience of organochlorine manufacturing workers. These include updates on a cohort in Pernis, the Netherlands and on OC workers at four U.S. plants; and a Denver, Colorado cohort (included in the aforementioned U.S. group) newly reported on in detail.

An update of the mortality experience of workers at four different U.S. OC manufacturing plants, previously studied by NIOSH (Ditraglia, 1981[6]), is presented.[7] The purpose was to assess the risk of exposure to chlordane (plant 1); heptachlor and endrin (plant 2); aldrin, dieldrin and endrin (plant 3); and DDT (plant 4). Included were all white males employed for at least 6 months at the plants under study, from 1964 through 1987. SMR's were calculated for specific causes of death using national mortality rates as controls, and also, for plant 3 (the Colorado cohort), state and regional controls. There were no exposure data available for this study, except for limited data on DDT among workers at plant 4. The results showed reduced overall mortality and reduced cause-specific mortality for all causes except cerebrovascular and respiratory disease in the four groups combined. (A reduced overall mortality is commonly observed in occupational cohorts, consistent with the "healthy worker effect." This reflects the fact that to be a worker, one has to be relatively healthy, and the rate of cardiovascular mortality and thus overall mortality is usually lower in a working population than the general population.) Regarding cancer-specific mortality, there were excesses for stomach and hepatobiliary cancers in the groups combined; stomach cancer was non-significantly elevated in 3 of the 4 plants; and there was a significant increase in bladder cancer in one plant. In plant 3, there was a statistically significant increase in hepatobiliary cancers (5 observed, SMR 3.93, 95% CI 1.27-9.20). The five deaths included 4 from biliary tract, bile duct, or gall bladder; only one was a hepatoma. All hepatobiliary cancers occurred after at least 15 years of latency; there was no evidence of an exposure/response relationship (using duration of employment as a marker for exposure). The hepatobiliary SMR did not remain significant for all 4 plant combined. The authors note that the study is limited by the absence of exposure data.

A retrospective follow-up study reports the mortality experience of 2384 workers at the plant in Denver, Co. (the above mentioned "group 3") which produced organochlorine insecticides (aldrin, dieldrin, endrin); several organophosphates (azodrin, vapona); nitralin, and dibromochloropropane.[8] This paper reports on the cohort in greater detail, and includes limited exposure data. The study includes employees at the plant from 1952 through 1982, including non-whites and women. Work history information allowed assignment to broad work areas (maintenance , production operations, etc.). SMR's were calculated using Colorado rates for the comparison. Results show that the cohort was 87% white males; roughly 50% were hired by 1954; and close to 66,000 person-years were accrued in the study period. There were 496 deaths, resulting in an overall mortality rate similar to that of the state. There was an increase in the pneumonia death rate (20 observed, SMR 1.50, CI 0.92-2.32). The overall cancer mortality was similar to the state rate, with slight increases in death from lymphopoietic cancer (16 observed, SMR 1.46, CI 0.83-2.37) and hepatobiliary cancer (5 observed, SMR 2.49, CI 0.81-5.81). All the hepatobiliary deaths occurred in the "ever-hourly" job category (SMR 0.67, CI 0.45-9.00). Roughly 90% of this category had worked in Maintenance or Operations. There was no evidence of an exposure-response relationship, using duration of employment as the marker for exposure. The five hepatobiliary cancers were comprised of gall bladder (1 case), biliary tract (2 cases) hepatobiliary (1 case, unconfirmed) and diffuse hepatoma (1 case, unconfirmed). Three of these had worked in the plant for less than 1.5 years. The excess of lymphopoietic cancers occurred primarily in black men (3 observed, SMR 13.18, CI 2.72-38.55). The authors note that the excess in hepatobiliary cancers occurred in job categories that were likely to have the highest exposure to pesticides; unfortunately, there is no mention of the job assignment of the black workers with lymphopoietic cancers. The authors also note that unlike for hepatomas, there is no experimental animal data suggesting that aldrin and dieldrin cause biliary tract cancer.

Finally, there is a report for the Dutch cohort (originally reported on by deJong [9]) which is much smaller than the Denver cohort but for which there is detailed exposure data.[13] The study group consisted of 570 workers manufacturing aldrin and dieldrin, followed for mortality from 1952 through 1992. Blood dieldrin concentrations available for 60% of the cohort were used to estimate the daily intake of dieldrin for each subject, and allowed for assignment to a low, moderate or high dose group. Results show that the overall mortality and cancer mortality was lower than expected. Elevated SMR's occurred for liver (2 observed, SMR 2.25, CI 0.27-8.13) and rectal cancers (6 observed, SMR 3.90, CI 1.43-8.50). Stratification by dose did not show evidence for an exposure-response relationship for either cancer. The authors note that (1) there is no experimental evidence suggesting a link between aldrin/dieldrin exposure and rectal cancer, and (2) more than 75% of the cohort had dieldrin doses exceeding the assumed human equivalent that corresponds to the lowest possible dose rate showing an increased tumor response in experimental animal. Thus they conclude that this study does not provide evidence of carcinogenicity in a highly exposed occupational

cohort.

Conclusions

Demonstrating health effects in humans from chronic, low-level exposure to these persistent organic pollutants is a challenge for researchers. Effects may be subtle and their detection requires studying large populations. The potential long-term effects have implications for future generations, and thus should remain a priority for public health investigation.

Abbreviations used:
ALL: acute lymphocytic leukemia
AML: acute myeloid leukemia
CHC: chlorinated hydrocarbons
CI: confidence interval
CLL: chronic lymphocytic leukemia
CML: chronic myelocytic leukemia
DDE: dichlorodiphenyldichloroethylene
DDT: dichlorodiphenyltrichloroethane
DGA: D-glucaric acid
HCB: hexachlorobenzene
HCH: hexachlorocyclohexane
ITP: idiopathic thrombocytopenic purpura
NIOSH: National Intsitute for Occupational Safety and Health
OC: organochlorine
PCB: polychlorinated biphenyls
SCE: sister chromatid exchanges
SMR: standardized mortality ratio
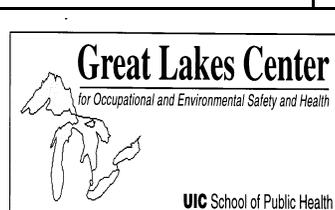
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