

Organochlorine Compounds: Risk of Non-Hodgkin's Lymphoma and Breast Cancer?

WOLFGANG HOFFMANN
School of Public Health-Graduate School
Department of Epidemiology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

ABSTRACT. Organochlorines (i.e., synthetic chlorinated hydrocarbon compounds) are widespread, environmental contaminants that are present throughout the United States. Strong epidemiological evidence has linked occupational exposure to a high incidence of non-Hodgkin's lymphoma. Recently, it has been postulated that exposure to organochlorines increases the risk of developing breast cancer. Human data on this issue remain insufficient, but recent results are very consistent. Observations in human populations of the immunotoxic and hormone-mimicking properties of some organochlorines add biological plausibility to the epidemiologic findings. Limitations in our ability to measure organochlorine exposure still preclude a quantitative risk assessment, relative to these cancer endpoints. Public health action with respect to restriction of ongoing production and use of organochlorines, however, appears warranted for purposes of prevention.

ORGANOCHLORINES (i.e., synthetic chlorinated hydrocarbon compounds [OCs]) refer to a heterogeneous group of man-made organic compounds, which contain covalently bound chlorine atoms. Many organochlorines have been used as pesticides, including both insecticides (e.g., dichloro-diphenyltrichloroethane [DDT], lindane, aldrin, dieldrin, methoxychlor) and herbicides (e.g., 4-chloro-2-methylphenoxyacetic acid [MCPA], dichloprop, 2, 4-dichlorophenoxyacetic acid [2,4-D], and 2,4,5-trichlorophenoxyacetic acid [2,4,5-T]). Other OCs (e.g., polychlorinated biphenyls [PCBs]), are used as flame retardants, coolants in hydraulic systems, dielectrics in transformers, and for a variety of other—mostly industrial—purposes.

Use of DDT as a potent insecticide became widespread in the United States after 1945. Annual production peaked (i.e., 82 000 tons/y¹) during the early 1960s. In the early 1970s, evidence of persistence in environmental media and accumulation in the food chain led to a ban of DDT, as well as most other organochlorine pesticides in the United States. Domestic

production of PCBs in the United States was discontinued for similar reasons in 1977.² Nevertheless, both DDT and PCBs are measurable in almost 100% of human serum and fatty tissue samples taken today.²⁻⁴ There exists, however, considerable interindividual variation. Higher average concentrations are associated with residing in the South; living on farms; and being nonwhite, male, older, or below the poverty level.⁵

Non-Hodgkin's lymphoma (NHL) and, recently, breast cancer have been linked to OC exposure. Few OCs are complete carcinogens (e.g., aldrin/dieldrin,^{6,7} chlordane,^{8,9} some PCBs¹⁰). Other OCs act as immunotoxicants and/or mimic thyroid and steroid hormones and could, therefore, be involved as promoters in the carcinogenic process. Humans exposed to either PCBs or 2,4-D/2,4,5-T showed depressions of total T lymphocyte and T helper cell counts—both of which are crucial in the immunological defense against early stages of cancer—as well as increases of undetermined (immature) lymphocytes, possibly reflecting neoplastic stimulation.^{1,2,11} Methoxychlor, DDT, and some PCB con-

geners bind competitively to the cytosolic estrogen receptor.^{12,13} DDT is a suspected human goitrogen, which is attributed to its interference with thyroid hormones.^{1,14}

Estrogenic effects in humans have been measured at environmental levels. Human females with high DDE/PCB contents in breast milk had markedly shorter lactation periods (i.e., approximately 1 wk reduction per ppm of either chemical), compared with controls, in a prospective cohort study conducted in the United States.⁴ The authors reported similar findings in Mexican women.¹⁵ Estrogenic action could link organochlorine exposure directly to established breast cancer risk factors (e.g., early menarche, late menopause, number of full-term pregnancies, obesity).¹⁶ Alternatively, it has been hypothesized that these factors might modify the susceptibility of the breast tissue to the carcinogenic properties of OCs.¹⁷ The protective effect of lactation could be accounted for by the observation that lactation is the single most effective pathway of organochlorine excretion.¹⁸ Recently, DDT/DDE levels in young Canadian women were found to be nearly twice as high in women who had never breast-fed, compared with women with a breast-feeding history of at least 12 mo.¹⁹

Risk of NHL from exposure to OCs has been addressed extensively in the epidemiologic literature (i.e., more than 50 publications since 1970¹). Among the more recent studies are two prospective population-based case-control studies that used incident cases ($N = 622$ and $N = 172$, respectively)^{20,21}; a retrospective case-control study in which death-certificate data were analyzed ($N = 1\,101$)²²; and three cohort studies²³⁻²⁵ of occupationally exposed workers (e.g., farmers, pesticide applicators, grain millers, $N = 20\,245-70\,000$).

Two consistent findings of these investigations were (1) a marked "healthy-worker effect" for farmers and (2) increased risks for NHL that were associated with pesticide exposures (statistically significant in 5 of the 6 studies). Risks were increased even further after the investigators stratified for various surrogate exposure measures (i.e., early year of first pesticide use, duration of exposure, acres sprayed, fuel purchased, use of protective equipment). Ratio measures of association ranged from less than 2 to 8.0. In the investigations in which differentiations were made, herbicides were associated with greater risk, compared with insecticides. In those instances in which exposure to particular compounds could be evaluated, the highest risks were associated with 2,4-D and 2,4,5-T.

In five recent case-control studies, breast cancer risk from OC exposure was addressed. A pure retrospective approach was used in three studies; OC levels (i.e., DDT/DDE, PCB; in two studies, hexachlorobenzene (HCB), hexachlorocyclohexane (β -HCH), heptachloropoxide, and oxychlorodane were also included) in breast tissue of breast cancer patients were compared with levels in controls. Sample sizes comprised 20-44 cases and 20-56 unmatched controls (i.e., patients with benign breast disease and autopsy specimens obtained from patients with nonmalignant diseases). In only one of these studies was it reported that essentially no dif-

ference existed in concentrations of PCBs and DDT/DDE in breast tissue samples obtained from deceased patients with breast cancer, compared with controls.²⁶ In the other two retrospective studies, cases had significantly higher tissue levels of DDT, DDE, PCB,²⁷ and β -HCH.²⁸

The two remaining studies were nested case-control studies of DDE and PCB exposure drawn from prospective cohort studies. Stored frozen blood specimens and extensive questionnaire information were obtained prior to diagnosis. Samples comprised 58 prevalent cases and 171 matched controls from a cohort of 14 290²⁹ and 150 cases and 150 matched controls from a cohort of 57 040.³⁰ Wolff et al.²⁹ found a significant association between DDE exposure and breast cancer (odds ratio [OR] = 4 for 90% versus 10% percentiles, $p = .031$). Risk associated with exposure to PCBs was of borderline significance (OR = 2, $p = .058$). Krieger et al.³⁰ performed strictly separate analyses for subgroups (i.e., 50 white, 50 black, and 50 Asian women), and whereas risks did not reach statistical significance, positive dose-response relationships were reported for DDE in white and black women (OR highest versus lowest tertile = 2.4 and 3.9, respectively) and for PCB in blacks (OR = 2.2).

Methodologic Issues

NHL studies. Assessment of exposure depends on surrogate or proxy measures. External data on the use of particular OCs from employer and supplier records are usually not available. Recall bias usually occurs for specific compounds, particularly for those cases in which subjects have been exposed during earlier years and to a variety of compounds. The resulting misclassification is likely to be nondifferential and, therefore, the actual risk would tend to be underestimated.

The attribution of observed risks to particular compounds is difficult because subjects have usually been exposed to various classes of OCs. Contaminants in technical preparations of pesticides (i.e., up to approximately 30% contaminants) can be far more toxic than the active substances (e.g., *o,p'*-DDT in DDT, dioxins in 2,4-D, and 2,4,5-T).^{1,14}

Confounding via other farming-related exposures (e.g., solvents, paints, dust, diesel exhausts) is possible and cannot usually be controlled adequately.

Breast cancer studies. Measurements of OCs have been performed at only one point in time: either after death or several years prior to diagnosis. In three of the studies, separate results were given for different OCs. Simultaneous inclusion of DDE and PCB in logistic models levels reduced the coefficients for PCB in the two nested case-control studies (i.e., only slightly³⁰ and by as much as 53%,²⁹ respectively). However, risk associated with DDE exposure remained essentially unchanged in both studies. Potential confounding from other OC compounds could not be assessed because only DDE and PCB were measured.

Persistent OCs in breast tissue may not represent the only—or even the most significant—risk agents. Other

OCs (e.g., phenoxy acids, endrin, methoxychlor, pentachlorophenol) are more rapidly metabolized and excreted and, therefore, might no longer be measurable at the time of a study, although their mutagenic and carcinogenic potential has been well established.^{1,11,14,31}

In three of the five case-control studies cited, cases numbered fewer than 50, controls were not matched, and information on established risk factors and other potential confounders was insufficient. In the largest study, only subgroup analyses were conducted.³⁰ The largest number of cases analyzed to date is 58.²⁹

Conclusion and Recommendations

Currently, OCs are considered to be an established risk factor for NHL. Although NHL represents only 3.7% of all incident cancers,³² these findings may have considerable public health implications because incidences of NHL have increased steadily and with rapidity worldwide (i.e., on average + 4% incidence/y³³). Other known risk factors account for only a small proportion of cases. Risk seems to be higher for herbicides (i.e., particularly for the phenoxy acids 2,4-D and 2,4,5-T) than for insecticides.^{11,31,34} In 1972, 2,4,5-T was banned in the United States; however, 2,4-D is the most commonly used herbicide in the United States today (i.e., 30 000 tons/y^{1,31}).

Results for breast cancer are less conclusive. Although a relationship had been hypothesized initially in 1976,³⁵ this potentially important risk has been assessed in only a few epidemiologic studies. The significant findings, however, are quite consistent and are substantiated even further by several other nonsignificant positive associations. The results of the most recent study by Krieger et al.,³⁰ although labeled initially as "negative," are consistent with those of Wolff et al.,²⁹ and Krieger's results generally accord with the findings reported in earlier case-control studies.³⁶

The recent observation of higher concentrations of DDE in tissue samples from estrogen receptor positive carcinomas, compared with estrogen receptor negative carcinomas, may account for some of the variability in the case-control studies reported to date.¹⁶

Biological plausibility (i.e., direct carcinogenicity, promoting effects through estrogenic action and immune alterations) adds further fuel for causality. The finding of greatest risk among blacks (i.e., mean average OC concentrations have been reported to be twice that in whites) indicates that socioeconomic factors must be accounted for in public health strategies.^{2,5,17}

Clearly, further studies are necessary. Ideally, individual exposure assessment requires prospective cohort studies with close follow-up and biochemical monitoring. Serum, rather than fatty tissue, may be analyzed to avoid invasive biopsies. The partition ratio of fatty tissue to serum will have to be accounted for carefully (i.e., about 300:1; range of 150–600).^{37,38} The application of biomarkers of exposure,³⁹ including chromosomal aberrations^{31,34,40} and the 2,3,7,8-TCDD-specific Kahn-Gochfeld-serum marker¹¹ for monitoring purposes, needs to be better evaluated and standardized.

Existing evidence already warrants improved protection for occupationally exposed workers, including high-risk groups (e.g., farmers, pesticide mixers/loaders/applicators, fruit pickers). The following list contains further recommendations:

1. Persisting OCs should be banned completely from production and use.
2. Occupational cancer risk should be acknowledged in pertinent compensation lawsuits.
3. Thresholds for contaminants in technical preparations of OCs should be lowered, and control of toxic contaminants needs to be improved.
4. Test procedures for new pesticides must include both immunotoxicity endpoints and endocrinological effects.
5. Pesticide application, including herbicide application in private lawns, golf courses, along railway lines, etc., should be monitored more closely (e.g., through establishment of independent registries).
6. Precautions should be taken against attempts to "liberalize" pesticide control in transnational trade agreements (e.g., GATT⁴¹).
7. Epidemiological findings, as well as results of research for less toxic alternatives, should have immediate consequences for export strategies.^{1,34,42}

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Requests for reprints should be sent to Wolfgang Hoffmann, M.D., Bremen Institute for Prevention Research and Social Medicine, Gruenenstrasse 120, D-28199 Bremen, Germany.

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