Passing Along Pesticides

Lymphoma Rises in Children of Applicators

A growing body of scientific evidence suggests there may be an association between parents' exposure to pesticides and cancer in their children. In this issue, Kori Flower of the University of North Carolina–Chapel Hill School of Public Health and colleagues report the results of their recent study investigating the possibility of increased cancer risk among the children of pesticide applicators [***EHP* 112:631–635**]. The associations they uncovered, although modest, underscore the need for careful evaluation of this issue.

Double exposure. Pesticide applicators can expose their children to chemicals from the job, particularly if protective gear is not worn at work. The result may be more cancers in these children.

The authors used detailed parental pesticide application data derived from questionnaires gathered by the Agricultural Health Study, a large prospective study of pesticide applicators and their spouses in Iowa and North Carolina conducted by the NIEHS, the National Cancer Institute, and the U.S. Environmental Protection Agency. Flower and colleagues limited their study to Iowa workers and their families. The 52,395 Iowa pesticide applicators who enrolled in the Agricultural Health Study between 1993 and 1997 accounted for a total of 17,357 children born during or after 1975. By linking information about those children with data from the Iowa Cancer Registry, the researchers were able to identify 50 cases of cancer among children of Iowa pesticide applicators.

The team compared the cancer incidence rate in the cohort to that expected in the general population to generate a standardized incidence ratio, and found an increased cancer incidence rate among children of the Iowa workers. The risk of all childhood cancers combined was 36% greater in children of applicators compared to all Iowa children; the risk of all lymphomas more than doubled, and that of Hodgkin lymphoma was 2.5 times greater. Further, the team found an increased risk of cancer among children of pesticide applicators who did not wear chemical-resistant gloves during application, as opposed to the children of those who did. As the authors point out, this could indicate direct pesticide exposure in the applicators (who would then carry the chemicals home) or less meticulous chemical practices on the farm, both of which could increase the opportunity for exposure among the children.

What the authors didn't find may be just as interesting as what they did. For example, no association was found between frequency of parental pesticide application and increased childhood cancer risk, nor was there evidence of a dose–response relationship between parental exposure and children's risk. Although those findings may have been due to the small number of cases involved and the resulting limited statistical power, the investigators stress that "the possibility that increased cancer risk within the cohort is unrelated to pesticide exposure must be considered."

Of the 50 specific pesticides studied, exposure to 1 was significantly associated with increased cancer risk: Flower and colleagues detected a 2.5-fold greater cancer risk in association with exposure to aldrin prior to conception. However, aldrin has not been clearly linked to human cancer. No significant associations were detected between exposure to classes of pesticides (organophosphates, organochlorines, carbamates, chlorphenoxy compounds, pyrethroids) and increased risk.

Despite the limitations of the study, Flower and colleagues point out that "the identification of excess lymphoma risk suggests that farm exposures including pesticides may play a role in the etiology of childhood lymphoma." That conclusion underscores the need for larger studies to clarify potential cancer risks from pesticides. **–Ernie Hood**

When PCBs Act Like Thyroid Hormone

Mysterious Mimicry in the Fetal Brain

Children exposed to relatively high levels of polychlorinated biphenyls (PCBs) can have deficits in general intellectual ability, poor short-term memory, and short attention span. Some researchers propose that this may be caused by the ability of PCBs to interfere with thyroid hormone action. Thyroid hormone plays an important role in directing brain development, an action that is largely accomplished by binding to nuclear receptors that either amplify or dampen the expression of genes in specific brain regions at specific developmental times. In this issue, Kelly J. Gauger of the University of Massachusetts Amherst and colleagues report that PCBs can act like thyroid hormone in the fetal brain, but that they don't bind to thyroid hormone receptors; instead, the activity happens through a mechanism that is not yet understood [***EHP* 112:516–523**].

Experimental studies consistently find that PCB exposure decreases levels of the thyroid hormone thyroxine in rats. Therefore, some researchers conclude that PCBs might affect brain development by causing a reduction in thyroid hormone when the developing organ needs it the most. On the other hand, PCBs

could act directly on thyroid hormone signaling in the fetal brain—one theory has held that perhaps PCBs bind to thyroid hormone receptors in the brain and either block their action or inappropriately stimulate them. This distinction has important implications for designing a test that can effectively screen for thyroid hormone disruptors.

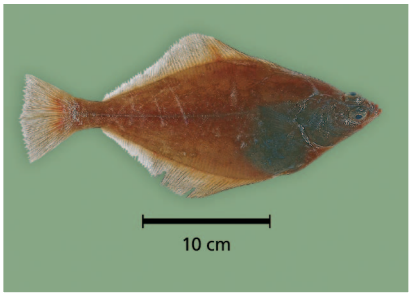
To study whether PCBs act on the fetal brain through a reduction in maternal thyroid hormone levels or by exerting a direct action on the brain, the team fed the PCB mixture Arochlor 1254 to pregnant rats from gestational days 6 to 16. Six rats received a dose of 1 milligram per kilogram, six received 4 milligrams per kilogram, and six were controls. On gestational day 16, the researchers examined the brain of one fetus from each litter using gene probes and *in situ* hybridization to obtain a quantitative measurement of gene activity. This was done on gestational day 16 because the fetus cannot make its own thyroid hormone at this time. Therefore, the team could test whether PCB-induced reductions in maternal thyroid hormone would produce effects on the fetus that are similar to those caused by maternal hypothyroidism.

The team found that both doses of Arochlor 1254 reduced thyroid hormone levels in pregnant rats on gestational day 16. Other measures of hypothyroidism, such as maternal weight gain and changes in litter size, were not observed.

The team further found that the Arochlor 1254 exposures caused an increase in the expression of genes normally upregulated by thyroid hormone—strong evidence, the authors write, that PCBs can produce thyroid hormone–like effects in the fetal brain. This and other details of the results suggest that PCBs must be directly activating thyroid hormone receptors, according to the authors. Because they could not identify individual PCBs or their metabolites that exhibited strong binding to thyroid hormone receptors, the mechanism by which PCBs might affect these receptors will likely be a novel finding. **–Rebecca Renner**

Gill Damage in Puget Sound Fish

Industrial Chemicals Associated with DNA Changes



Chemical pollutants in parts of Puget Sound appear to be damaging the DNA of fish that live there, according to findings published this month by Donald C. Malins of the Pacific Northwest Research Institute Biochemical Oncology Program and colleagues [*EHP* **112:511–515**]. The researchers compared DNA extracted from the gills of English sole in the Duwamish River (which flows into the sound through a heavily industrialized area in south Seattle) to DNA taken from fish in the relatively clean Quartermaster Harbor. They found significantly more structural damage in the DNA of fish taken from the Duwamish compared to samples from Quartermaster Harbor.

For this study, the researchers used two chemical markers to characterize the levels of pollution in bottom sediments: polynuclear aromatic hydrocarbons (PAHs), by-products of fossil fuel combustion that are readily metabolized in fish, and polychlorinated biphenyls (PCBs), which were banned in the United States in 1979, but persist in the environment due to their slow rate of degradation. PCBs accumulate in fish tissue and have been responsible for many advisories to limit human consumption; the Washington State Department of Health warns of the possible adverse health risks of consuming English sole and other bottom-feeding fish from the lower Duwamish River due to the presence of PCBs, PAHs, and other toxic chemicals.

The team used expression of cytochrome P450 1A (CYP1A) as a measure of exposure to the contaminants of interest. CYP1A is involved in the oxidation of chemicals including PAHs and PCBs, and when it reacts with hydrocarbons, including PAHs, it can create metabolic by-products that can alter DNA. Also, certain PCBs can cause CYP1A to form reactive oxygen, which can damage DNA. Higher levels of CYP1A expression may lead to a greater risk of damage to DNA and more potential for mutations. The Duwamish is substantially more contaminated with PAHs and PCBs compared to Quartermaster Harbor, and the levels of toxic chemicals in the sediments at both sites were consistent with the degree of expression of CYP1A in the gills of fish from the respective sites.

The researchers used Fourier transform infrared (FT-IR) spectroscopy statistical models to identify subtle structural changes in gill DNA including differences in base functional groups and conformational disruptions that have the potential to affect transcription and replication. This technology had been previously used to identify changes in the structure of fish liver DNA and to predict prostate and breast cancer in humans. The researchers applied logistic regression analysis to these models to assess the effects of contaminants on fish gills. This yielded a "DNA damage index" based upon the different spectral properties of gill DNA from each fish group.

This index could be used in the future to gauge the effectiveness of cleanups at polluted sites. For example, if gill tissue from fish at a site undergoing remediation had a DNA damage index close to that of fish from a clean reference site, it would be an indication that remedial efforts had been successful. An added environmental benefit of the technique is that researchers can take small biopsies of gills in the target fish and return the fish to the water alive.

The researchers hypothesize that fish with gill DNA damage might also have damage to DNA in other parts of the body. They are presently examining the liver, gonads, and kidneys of the fish sampled in the current study to determine the potential correlation between gill DNA damage and internal organ damage. They are also applying the FT-IR models to fish from polluted and clean sites in California to see if the DNA damage index is equally useful in other contaminated environments. Further research is necessary to determine if a high DNA damage index score is an accurate predictor of health problems in fish and risks to people who consume them. **–Carla Burgess**

A better biomarker. Gill biopsies like those used with English sole (inset) from the Duwamish River (above) could offer a better way to assess the effectiveness of remediation efforts.

Ned Ahrens/King County; inset: U.S. FDA