❖Health Effects Review❖

Volume 2 Issue 2 January-March 1997

IMMUNOTOXICOLOGY

INTRODUCTION

The immune system is both a target and a mediator of environment-induced injury. Chemicals and physical stressors such as ionizing radiation can damage the immune system resulting in impaired immunity and impaired auto-surveillance for cancer. The immune system can also mediate the damage produced by exogenous agents through mechanisms such as hypersensitivity and autoimmunity. Environmental chemical exposures have also resulted in combinations of toxic and allergic responses called “toxic allergic” syndromes. Examples of the latter include toxic oil syndrome in Spain and eosinophilia myalgia syndrome produced by L-tryptophan contaminants in the United States.

The human immune system is a complex combination of organs, cells and chemical mediators that act together to identify and sequestor or kill “foreign” substances. Immune organs include the thymus, spleen, and lymphatic system. Immune cells include lymphocytes, other white blood cells, and tissue macrophages. Lymphocytes are the primary actors in the immune response, and are divided into B, T, and natural killer (NK) cells. T-lymphocytes can be further subdivided into helper, suppressor, and cytotoxic cells. Chemical mediators of immune responses include antibodies, immunoglobulins, cytokines and the complement system of plasma proteins. Immune responses have been classified as cell-mediated and humoral. Cell-mediated responses are driven by proliferation and differentiation of immune cells, especially T-lymphocytes. Humoral responses are those which involve the production of antibodies (i.e. IgE, IgA, IgG and IgM) through differentiation of B-lymphocytes.[2]

Immunotoxic exposures, which result in direct damage to the immune system, can result in suppression of immune responses and decreased resistance to infections and malignancies. Some environmental contaminants have been found to be immunosuppressive in experimental models. These include heavy metals (mercury, copper, manganese, cobalt, cadmium and chromium), alkylating agents, and halogenated organic compounds (dioxins, furans, PCBs, PBBs, organochlorine insecticides).[2]

Some pollutants may also trigger immune responses resulting in hypersensitivity or autoimmunity. Common allergic reactions, such as hives, hay fever, and jewelry dermatitis are examples of hypersensitivity reactions to exogenous chemicals. Autoimmune disorders, such as lupus and scleroderma, result from the immune system’s attack on its host’s own tissues. Evidence is growing that at least some autoimmune reactions may result from exogenous chemicals’ interference with the immune system’s ability to differentiate host antigens from those of foreign invaders. Finally, some environmental chemical exposures can produce a dose-related toxicity in combination with hypersensitivity reactions. An example of this is an unusual syndrome characterized by pneumonitis, eosinophilia, and late neuromuscular disorders among thousands of people in Spain who ingested rapeseed oil contaminated with oleoanilides in Spain that was reported in 1981.

A quarterly summary of recent findings in the scientific literature on human health effects and environmental pollutants, with an emphasis on pollutants of the Great Lakes ecosystem. Prepared under the direction of the Health Professionals Task Force of the International Joint Commission. This does not represent the official position of the International Joint Commission.

Health Professionals Task Force
Secretary: Jim Houston
International Joint Commission
Canada Section
100 Metcalfe Street
Ottawa, Ontario K1P 5M1
phone (613) 995-0230
fax (613) 993-5583

In February 1995, a consensus statement on chemically-induced alterations in the developing immune system was drafted at the “Wingspread work session.” Briefly stated, the authors concluded that experimental lab studies demonstrate, with certainty, that exposure to synthetic chemicals can result in increases or decreases in measured immune parameters, hypersensitivity and autoimmunity. Immune changes are seen in some wildlife and human populations, and these changes are consistent with the results of laboratory studies. It is predicted that some synthetic chemicals can cause alterations in the developing immune system that translate into altered host resistance and susceptibility to disease later in life. Few well-controlled epidemiological studies have been conducted on immune function changes in human and wildlife populations; however, work session participants concluded that the risk is sufficient to warrant regulatory aproaches that would limit exposure to immunomodulatory chemicals.[4]

RECENT WILDLIFE STUDIES

Concern about immunotoxic effects of chemical pollutants has been heightened by reports of immunological effects in wildlife populations from polluted areas. A number of incidents of mass mortality of marine mammals from infectious agents have occurred, and it has been proposed that pollutant-induced immune system changes were a contributing factor to the epidemics. Animals affected by infectious disease outbreaks have been found to have higher levels of persistent pollutants such as the PCBs or dioxins. In laboratory studies, harbour seals fed a diet of Baltic sea herring (contaminated with organochlorine compounds and other pollutants) showed effects such as impaired NK cell activity and T-lymphocyte function when compared with animals on a diet of relatively uncontaminated Atlantic Ocean fish.[5] In a survey of Herring gulls and Caspian terns in five sites (four in the Great lakes region), prenatal exposure to organochlorine pollutants was associated with suppression of T-cell-mediated immunity. Of the pollutants assessed in gull and tern eggs, the strongest associations were found with the PCBs.[6]

DEVELOPMENTAL IMMUNOTOXICOLOGY

A number of recent studies in humans and animals indicate that the immune system may be altered by exposure to even low levels of contaminants during fetal or infant development, and the effects may be more dramatic and persistent that those from exposure later in life. A diverse group of chemicals, including heavy metals, insecticides, fungicides, PAHs, dioxins and mycotoxins (produced by fungi) have been implicated as agents that may affect the developing immune system. The endocrine-disruptors, or synthetic compounds that can mimic the actions of the body’s hormones, also have the potential to interfere with normal immune system development. The thymus appears to be the target for many developmental immunotoxicants, resulting in altered numbers and proportions of T-cells.[7]

Though few human studies have been conducted, there is some evidence of immune system changes in children exposed *in utero* to persistent organochlorines in studies in Michigan and of the Inuit Indians.[8] In these reports, there is evidence of not only alterations in immune cell numbers, but of increased rates of infections in children with higher *in utero* exposures. Newer results from the mother-child cohort in The Netherlands also indicate an association between perinatal organochlorine exposures and immune system effects, although clinical manifestations of immune systems changes were not found.[9]

ENVIRONMENTAL EXPOSURES

Among the more widely known cases of population exposures to environmental pollutants are the incidents of Yu-Cheng and or Yusho disease in Taiwanese and Japanese people who were exposed to PCBs and furans through the use of PCB-contaminated rice oil. Immune system changes have been found in studies of these two populations. The effects found were summarized: (1) persistent respiratory distress accompanied by Gram-negative bacilli-infected airways in about half of the Yu-Cheng cases; (2) significant decreases in IgA and IgM, but not IgG, were found two years after exposure but levels returned to normal after three years; (3) in the Yu-Cheng cases, a significantly reduced percentage of total T-lymphocytes, apparently due to reductions in T helper cells, was found, but the Yusho patients tested at 14 years after exposure showed a slight increase in T helper cells and a slight decrease in T suppressor cells; and (4) enhanced responses to mitogens (i.e. pokeweed, concavalin A).[8] There are reports of altered immune function in populations with environmental exposures to dioxins, though the results are not always consistent between studies.[10]

Recent results from the mother-child cohort study in The Netherlands found that prenatal exposure to PCBs or dioxins had immunotoxic effects. In a group of 48 infants, higher prenatal and postnatal exposure to PCBs and dioxins was associated with lower monocyte and granulocyte counts at three months of age, and with an increase in the number of cytotoxic T-cells at 18 months of age. No relationship was found with antibody production or the incidence of respiratory symptoms. However, the authors postulate that the lower numbers of monocytes and granulocytes at three months of age may have resulted in more subclinical infections during the first months of life and an increase in cytotoxic T-cells thereafter.[9]

In other recent studies, subtle changes in immune cell numbers or biochemical changes have been found, but there is no clear evidence of frank immune system disease in these studies. Immunological changes have been found in Swedish and Latvian populations with higher pollutant exposures via fish consumption, but no clinical manifestations of immunotoxicity were found. In one study, 68 subjects from 5 Latvian villages were categorized by fish consumption rates. There were significant positive correlations between all employed fish consumption parameters and both the proportions and numbers of B-cells, while fish consumption was correlated with a decrease in the proportion of suppressor T-cells. There was also a nonsignificant ($p=0.06$) increase in the proportion of NK cells.[11] However, a decrease in NK cells was significantly correlated ($p=0.04$) with increasing PCB levels in the blood in results from the Swedish study. Significant associations were found with p,p'-DDT, three PCB congeners (mono-ortho and non-ortho). No changes were found in other lymphocyte subsets.[12]

German investigators have found evidence for a general stimulation of the immune reaction as a consequence of exposure to air pollutants. Levels of immune system proteins and complexes were measured in over 500 women (55 years and older) in an industrial and a rural community. The industrial community had a greater proportion of women reporting chronic disease, allergy, smoking and occupational exposures. After adjusting for confounders, significantly higher levels of two complement proteins and IgG, IgA, and IgM antibodies were found in the blood samples from women in the industrial community.[13] A similar study was conducted using women from three German communities — one rural, one with coal mining and coke plant industries, and one with coal, iron , steel and oil industries — and women from the heavily industrialized community were found to have significantly higher levels of one complement protein (C3c), but no differences were found for other immune mediators. When comparing the coal mining community with the rural community, there were increased levels of IgG, IgM and C3c, but only the complement protein was significantly higher. The authors postulate that the immune system changes may be attributed to the increased levels of airborne particulates in the coal mining community.[14] These studies indicate increases in immune system activity with pollutant exposures; some clinical studies have demonstrated impairment of local lung defenses following exposure to ozone, a ubiquitous air pollutant.

In New Jersey, persons living near a chromium ore processing facility were found to have a decrease in interleukin-6 production (with pokeweed mitogen stimulation) when compared with residents from suburban or rural areas; there were no significant differences in numbers of immune cells.[15]

OCCUPATIONAL EXPOSURES

A number of occupational studies have found subtle changes in immune function with exposure to chemicals in the workplace. Clinical signs of immune disorders were not found in these studies; however, it is widely accepted that clinical signs of allergy or asthma have been found with some workplace exposures. Increased levels of IgG, IgM and IgA antibodies were found in studies of workers exposed to lead,[16] PAHs[17] and n-hexane;[18] the lead-exposed workers also had decreased numbers of T-helper cells and two complement proteins. In Italy, significant ($p<0.05$) decreases were found in proportions of T-cell types and NK cells, with farmers' exposure to chlorophenoxy herbicides (e.g. 2,4-D). There was also a nonsignificant ($p=0.08$) correlation between quantity of pesticide used and decrease in NK cell activity.[19] In Tokyo, increased numbers of one type of NK cells were found in dyestuff workers with exposure to aromatic amines while no changes were found in numbers of other NK cells; it was postulated that the increase was compensating for a decrease in T-helper cells, as has been found in patients treated with immunosuppressant drugs.[20] Workers in a dithiocarbamate fungicide plant with low-level exposures to mancozeb were found to have a significant decrease in one type (CD3/DR+) of T-cells ($p<0.05$) when compared with unexposed workers. No differences were found in antibody levels, complement levels or percentages and numbers of T- and B-cells.[21]

Great Lakes Center
for Occupational and Environmental Safety and Health
UIC School of Public Health

PREPARED BY:

Great Lakes Center for Occupational and Environmental Safety and Health
School of Public Health
University of Illinois at Chicago
2121 West Taylor Street
Chicago, Illinois 60612-7260
(312) 996-7887
email: mross1@uic.edu

Project Coordinator:
Mary A. Ross, PhD
Senior Science Advisor:
Daniel O. Hryhorczuk, MD, MPH

World Health Organization
Collaborating Centre for Occupational and Environmental Health

GREAT LAKES BASIN

A number of organochlorine pesticides (e.g. DDT, mirex, dieldrin) and organophosphate pesticides (e.g. malathion) have the potential to produce immunotoxicity, on the basis of results from occupational and lab animal studies. In occupational studies, changes in levels of antibodies or numbers of immune cells have been found, but reports of clinically-apparent changes in immune function (i.e. increased infections) are rare and the clinical significance of the biochemical or cellular changes is unknown. In a review of health effects from exposure to pesticides in the Great Lakes, Thomas[22] finds no definitive evidence for human immune system dysfunction with environmental exposures, but concludes that potential immunotoxic effects cannot be ruled out. Regarding exposure to dioxins and PCBs via dietary exposure, there is some evidence for clinically altered immune function with perinatal exposure to PCBs.[8] However, few studies have evaluated associations between pollutant exposures and immune function, and the results are not always consistent between studies.[10] Though the existing data do not allow conclusions to be drawn regarding immunotoxic effects of environmental chemicals, the authors of the Wingspread work session concluded that the risk of exposure to known immunomodulators is sufficient to warrant regulatory approaches that would limit exposure.[4]

REFERENCES:

1) Anisman H, Baines MG, Berczi I, et al. 1996 Can Med Assoc J. 155:867-874
2) Krzystyniak K, et al. 1995. Environ Health Perspect 103(Suppl 9):17-22
3) Luster MI, Rosenthal GJ. 1993. Environ Health Perspect 100:219-236
4) Colborn T. 1996. Environ Health Perspect 104(Suppl 4):807-808
5) Ross P, De Swart R, Addison R, et al. 1996. Toxicol 112:157-169
6) Grasman KA, et al. 1996. Environ Health Perspect 104(4):829-842
7) Holladay SD, Luster MI. 1996. Environ Health Perspect 104(4):809-813
8) Tryphonas H. 1996. Environ Health Perspect 103(Suppl 9):35-46
9) Weisglas-Kuperus N, et al. 1995. Pediatr Res 38:404-410
10) Kerkvliet N. 1995. Environ Health Perspect 103(Suppl 9):47-53
11) Svensson B-G, et al. 1994. Int Arch Occup Environ Health 65:351-358
12) Hagmar L, Hallberg T, Leja M et al. 1995. Toxicol Lett 77:335-342
13) Stiller-Winkler R, Idel H, Leng G, et al. 1996. J Clin Epidemiol 49:527-534
14) Hadnagy W, Stiller-Winkler R, Idel H. 1996. Toxicol Lett 77:147-153
15) Snyder CA, Udasin I, et al. 1996. Arch Environ Health 51:26-28
16) Undeger U, Basaran N, Campinar H, Kansu E. 1006. Toxicol 109:167-172
17) Szczeklik A, et al. 1994. Environ Health Perspect 102:302-304
18) Kstsksys S, Yuvrdoy N, Burgaz S et al. 1996. Hum Exp Toxicol 15:56-58
19) Faustini A, et al. 1996. Occup Environ Med 53:583-585
20) Tanigawa G, et al. 1996. Int Arch Occup Environ Health 69:69-72
21) Colosio C, et al. 1996. Arch Environ Health 51:445-451
22) Thomas PT. 1995. Environ Health Perspect 103(Suppl 9):55-61