NATIONAL TOXICOLOGY PROGRAM
FACT SHEET
Headquartered at the National Institute of Environmental Health Sciences • NIH • DHHS

DIOXINS MIXTURES RESEARCH

Year 2006

Humans are constantly exposed to dioxins through their diet. Dioxins are persistent and once exposure occurs, these compounds remain in human tissues, particularly fatty tissues, for extended time periods. Basic information about dioxins is available from the National Institute of Environmental Health Sciences (NIEHS) web site: *http://www.niehs.nih.gov/oc/factsheets/dioxin.htm*

Both the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) have concluded that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most potent dioxin, is a known human carcinogen. The detailed biochemical pathway that leads to cancer is not understood completely, but scientists are confident that the first step in one pathway leading to cancer takes place when TCDD binds to an intracellular protein known as the AhR (aryl hydrocarbon receptor). When that happens, the AhR can then bind to DNA and alter the expression of certain genes, changing the level of specific proteins and enzymes in the cells. The resulting cellular imbalance then initiates cancer.

In addition to TCDD, many other chemicals including polyhalogenated aromatic hydrocarbons bind to the AhR, for example, some polychlorinated biphenyls and polychlorinated dibenzofurans. Public health officials around the world are concerned about the combined effects of multiple chemicals that work this way, and how health standards can be adjusted to take into account that people are always exposed to mixtures of dioxin-like compounds, not just one at a time.

To address this problem, most agencies assume they can just add -- an assumption called 'additivity' -- exposures for the different chemicals, adjusting for the fact that some dioxin-like compounds are more toxic than others. The standard method used to estimate toxicity of mixtures of dioxin-like compounds is based upon "Toxic Equivalency Factors" or TEFs.

A TEF approach ranks the toxicity of a dioxin-like compound relative to the most powerful dioxin TCDD. Tests of individual dioxin-like compounds are conducted to establish the potency of each compared to TCDD. Then, that relative potency is used to adjust each compound's contribution to the toxicity of a mixture of the compounds. For example, it would take 20 units of a dioxin-like compound 1/10 as powerful as TCDD to produce toxicity equivalent to one unit of TCDD. To estimate the overall toxicity of a mixture, the contaminants' weighted contributions are then added together. This calculation assumes that the effects are additive; however, this is not necessarily true as contaminants might enhance or interfere with one another's effects.

NTP TEF Studies

To test this assumption, the NTP carried out a series of studies in which rodents were exposed to either a single dioxin-like compound or mixtures of them for up to two years and then evaluated for toxicity and carcinogenicity relative to TCDD. Analysis of data from one group of completed studies confirms the assumption that the effects of the dioxin-like compounds in mixtures are additive. The number of cancer cases in the rats exposed to the mixture could be predicted accurately by adding the concentration of each compound, adjusted for its potency relative to TCDD using TEFs.

ADDRESS P.O. Box 12233, Maildrop A3-01, Research Triangle Park, NC 27709-2233 *WEB SITE* http://ntp.niehs.nih.gov/
NTP LIAISON & SCIENTIFIC REVIEW OFFICE 919-541-0530 *E-MAIL* liaison@starbase.niehs.nih.gov

A second series of studies is being conducted to determine whether co-exposure of TCDD or dioxin-like compounds with non-dioxin-like compounds, which also bind the AhR, affects TEF values. As part of this effort, the NTP recently completed studies to evaluate the chronic toxicity and carcinogenicity of polychlorinated biphenyl and their binary mixtures. Studies are also ongoing that examine the chronic toxicity of other compounds with weak dioxin-like activity to which humans are exposed. The compounds include polychlorinated naphthalenes, tetrachloroazobenzene, hexachlorobenzene, and indole-3-carbinol.

For further information contact:
Dr. Nigel Walker, NIEHS, P.O. Box 12233, MD D4-01, Research Triangle Park, North Carolina 27709; Phone: 919/541-0530; E-mail: liaison@starbase.niehs.nih.gov