ChemRisk
A Division of McLaren/Hart

Stroudwater Crossing
1685 Congress Street
Portland, ME 04102
(207) 774-0012
FAX (207) 774-8263

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Mr. Robert K. Sells, APR
Bob Sells PR Associates
5905 Forest Place/ Suite 208
P.O. Box 250116
Little Rock, Arkansas 72225

Dear Mr. Sells:

At Dr. Keenan's request, I am enclosing the following materials pertaining to the Banbury Conference:

- Carlo Report
- Birnbaum Memorandum
- Summary by van der Heijden
- Summary by Scheuplein
- Summary by Gallo
- Chlorine Institute Press Release (Draft)

If we can be of any further assistance, feel free to contact either Russ Keenan or myself.

Sincerely,

Ellen S. Ebert
Associate Toxicologist

DIOXIN AND HUMAN HEALTH

Prepared by George Carlo, PhD, JD, an epidemiologist at State University of New York (SUNY) at Buffalo School of Medicine and chairman of the Health and Environmental Sciences Group, Washington, D.C.

Scientists have been studying the potential health effects of dioxin since the 1960s. Although dioxin has been shown to cause disease in animals, data from human studies collected over the last 30 years have failed to demonstrate a cause-and-effect relationship between exposure to dioxin and a variety of diseases, including cancer. This disparity in results has led many scientists and public health officials to question the value of using data from animal studies to assess human risk from dioxin exposure. And, as data from human studies have evolved, the weight of the scientific evidence strongly suggests that dioxin at very low levels does not constitute a significant health risk to humans.[Kimbrough, 1990]

An international scientific conference aimed at developing a consensus on the hazards of dioxin in the environment was held Oct. 22-24, 1990, at the Banbury Conference Center of Cold Spring Harbor Laboratory, Long Island, N.Y. It reinforced the notion that dioxin is much less toxic to humans than originally believed, and that low dioxin levels found in the environment are not harmful to humans. Conference organizers were Dr. Michael A. Gallo, UMDNJ-Robert Wood Johnson Medical School, Piscataway, N.J.; Dr. Robert Scheuplein of the U.S. Food and Drug Administration, and Dr. C.A. van der Heijden of the National Institute of Public Health and Environmental Hygiene in the Netherlands. Conference proceedings are in development.

Dioxin: A class comprising many compounds

Dioxin is a generic term used to refer to a class of chemicals comprising 210 different compounds. Of those, 75 are known as dioxins and 135 are related compounds known as dibenzofurans. While there is general agreement among scientists that most have no adverse effects, the health effects of some, particularly 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), have been studied closely over the past decade. Indeed, most of the scientific data available on the health effects of dioxin are from studies of TCDD.

Dioxin was first identified in 1957 as an unavoidable, spontaneously formed product of the manufacture of 2,4,5-trichlorophenol (2,4,5-TCP), which is used in making hexachlorophene (an antibacterial) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). 2,4,5-T is an herbicide and ingredient in Agent Orange, a defoliant which was used during the Vietnam War. Since then, it has been learned that dioxin is formed primarily through incomplete combustion, as occurs in the burning of leaded gasoline, solid wastes and domestic trash.[redacted, 1986] Dioxin also is formed during such processes as barbecuing, bleaching paper pulp and burning wood.[redacted, 1986]

Dioxin in the environment

Dioxin usually settles in soil, to which it binds tightly. Dioxin does not move from soil into plants, nor does it migrate.[Reggiani, 1981; Fehrley, 1986] Because dioxin is not water soluble, it

adheres to the solid material in water and usually is removed during filtration.

Because it is a non-volatile compound, dioxin does not vaporize. Therefore, it is found in air only when bound to particulate matter. The levels of dioxin on particulate matter are so low as to be undetectable.

Human exposure to dioxin

Most humans are exposed to very low levels of dioxin in the environment through absorption, ingestion and respiration. As a result of this low-level background exposure (measured in the range of parts per trillion to parts per quadrillion), most individuals living in industrialized countries have low dioxin levels (ranging from non-detectable levels to 30 parts per trillion) in their fat tissues.[Patterson, 1986a, 1986b] (One part per trillion is equivalent to one second in 32,000 years; one part per quadrillion can be thought of as one second in 32 million years.) Such exposure has not been associated with adverse human health effects. [Patterson, 1986a, 1986b] Humans also have been exposed to dioxin at higher levels, primarily through long-term occupational exposure to herbicides, accidents occurring during industrial production, and following improper disposal of contaminated industrial waste. It is from such incidents that scientists have been able to study whether dioxin adversely affects human health.

Effects on animals

Studies conducted over the past two decades have affirmed dioxin's teratogenic effects in animals, and further delineated its cancer-causing role in certain laboratory animals. In animals, dioxin also has been shown to cause changes in blood chemistry, liver damage, skin disorders, lung lesions, weight loss and death.[Kociba, 1976; McConnell, 1984; Goldstein, 1982]

Differential effects among species

Dioxin's toxicity in animals varies greatly, not only among species, but even among subspecies.[Van Miller, 1976] Guinea pigs, for example, are approximately 3,000 times more susceptible than hamsters to a single dioxin dose (3,000 micrograms per kilogram of body weight).[Kimbrough, 1990]

Different strains of mice also experience different effects following exposure to dioxin.[Poland, 1976] One explanation for the variation in toxicity observed among species and subspecies is that animals have different metabolic processes. Thus, each species may clear dioxin from the body at a rate that is different from other species.[Kimbrough, 1990] Some of the biologic and toxic effects of dioxin occur as a result of the binding of dioxin to a specific receptor on cells, a process known as receptor-mediated toxicity.[Cohen, 1979; Poland, 1976] Variations in the structure of this receptor among different species may explain why some species are more susceptible than others to dioxin. Scientific evidence also suggests that there is a threshold level

below which no toxic or carcinogenic effects of dioxin occur.[Universities Associated for Research and Education in Pathology] That this threshold may differ among species also may explain why susceptibility to dioxin varies among species.

Epidemiologic studies fail to link low-level human exposure with disease

Several international scientific organizations have reviewed the extensive literature -- included among more than 17,000 published studies of animals and humans -- on the potential health effects of dioxin. Those reviews, convened by such bodies as the American Medical Association, the American Association for the Advancement of Science and the Universities Associated for Research and Education in Pathology, indicate that humans are far less susceptible to the toxic effects of dioxin than laboratory animals.

For example, low-level exposure to dioxin, such as that occurring in the environment (levels in the range of parts per trillion to parts per quadrillion), has not been shown to cause adverse health effects in humans, including cancer or reproductive effects.[Purchase, 1988]

High-level exposure to dioxin

In numerous reviews of the scientific literature, the only human health effect that has been shown unequivocally to result from exposure to high levels of dioxin is chloracne.[Universities Associated

for Research and Education in Pathology, 1988 Chloracne is a serious skin eruption that is generally reversible, but can cause scarring. It occurs only when dioxin exposure is in the range of parts per million or higher (one million times higher than background exposure, which is in the range of parts per trillion to parts per quadrillion). One part per million is equal to one inch in 16 miles.

No other adverse health effects, including cancer, have been manifested in individuals exposed to high levels of dioxin, as can result from long-term occupational exposure or chemical plant accidents.[Cook, 1988] (Long-term occupational exposure is defined as exposure in the workplace occurring over more than five years.) An in-depth review of the scientific literature by the Universities Associated for Research and Education in Pathology did not demonstrate reproductive effects or increased cancer risk among men exposed occupationally to dioxin.[Universities Associated for Research and Education in Pathology, 1988]

These findings are based on numerous incidents of high-level dioxin exposure throughout the world, including industrial accidents in West Germany, the United Kingdom, Italy, and the United States (Michigan and West Virginia), and use of contaminated waste oil in Missouri. Although hundreds of cases of chloracne -- a clinical marker of very high-level exposure to dioxin -- have been recorded following these incidents, long-term surveillance of those exposed has shown no increased incidence of cancer, chronic liver disease, immune disease, cardiovascular disease, or early mortality.

For example, of the 121 workers who developed chloracne following the West Virginia incident, no excess in total mortality or in deaths due to malignant neoplasms or diseases of the circulatory system was observed after 30 years of follow-up.[Cook, 1990] And although Michigan chemical workers exposed to dioxin experienced an outbreak of chloracne, they showed no overall excess mortality or incidence of cancer.[Cook, 1990]

Only one study, conducted a number of years ago, has suggested a possible association between dioxin-induced chloracne and cancer, but the study is methodologically problematic.[Fisher, 1990] In that study, exposure to other, potentially harmful chemicals was not taken into account, nor was exposure to other variables that might have affected outcome. Most importantly, an increase in cancer (beyond expected rates) was also found among individuals <u>not exposed</u> to dioxin, calling into question the validity of the findings. The authors concluded that "our findings suggest that a small hazard may have been caused by the heavy exposure in the 1953 accident, but they do not prove it."[Fisher, 1990]

In addition to data from chemical plant accidents, numerous epidemiological studies have analyzed long-term occupational exposure to dioxin through use of herbicides (e.g., forestry workers, farmers, and U.S. Air Force personnel who sprayed Agent Orange in Vietnam). The evidence indicates that long-term occupational exposure also does not increase the incidence of cancer.[Cook, 1990] The Universities Associated for Research and

Education in Pathology stated that: "Taken collectively, the available human studies do not demonstrate an increased risk of cancer from exposure to dioxin."[Universities Associated for Research and Education in Pathology, ...] And, the American Medical Association's Advisory Panel on Toxic Substances found no convincing evidence that herbicides containing dioxin are mutagenic, carcinogenic, or teratogenic in humans.[Meijer, 1991]

A 20-year health assessment of 995 U.S. Air Force veterans who were exposed occupationally to dioxin-containing herbicides during flight operations and maintenance of aircraft and spray equipment in Vietnam (Operation Ranch Hand) showed no excess morbidity or mortality from high-level exposure.[Wolfe, 1990] No differences in reported health problems, liver function, cardiovascular or immune profiles, chloracne, melanoma, or systemic cancer at any site were observed between Ranch Hands and a control group of 1,299 Air Force veterans not exposed to the herbicide. Ranch Hands were found to have more basal cell carcinomas (an easily treatable and curable skin cancer) than controls. However, there is no scientific basis to link dioxin exposure with this particular type of cancer.

Although some studies purport to show an association between exposure to dioxin and cancer in humans, those studies have been widely criticized and not widely accepted by the scientific community. Soft tissue sarcoma, for example, became a focus of concern when one investigator hypothesized that dioxin was associated with an increased incidence of this rare type of

cancer, which can affect the muscles, fat tissues, blood vessels, nerves, and tendons and other connective tissues.[Merrell, 1979] The methodology used in those studies, in which interviewers were not blinded and were told to look for exposure, has been called into question by numerous investigators, including the United Kingdom Government Advisory Committee on Pesticides and the Universities Associated for Research and Education in Pathology. Sir Richard Doll, an eminent British epidemiologist, claimed that the methodology of these studies was so flawed that they should not be considered in the literature.[Young, 1988] More recently, studies have consistently shown no significant association between soft tissue sarcoma and exposure to dioxin-containing herbicides, thus refuting the hypothesis that dioxin causes soft-tissue carcinoma.[Fingerhut, 1984; Wiklund, 1984a; Wiklund, 1984b; Smith, 1983; Smith, 1983; Woods, 1987]

In contrast to findings from animal studies, no human deaths have been attributed to dioxin, despite numerous incidents in which tens of thousands of people have been exposed to high levels of dioxin (parts per million or higher) as a result of industrial accidents.[Mohrbacher, 1986]

Models used to interpret dioxin's action

Two types of data can be used to determine the potential human health effects of a particular substance: animal toxicology data and human epidemiology data. Until the mid-1980s, scientists had access only to animal toxicology data for use in assessing potential human risks associated with dioxin. During