Dioxins and Furans: Epidemiologic Assessment of Cancer Risks and Other Human Health Effects

Heiko Becher[1] and Dieter Flesch-Janys[2]

[1]German Cancer Research Center, Division of Epidemiology, Heidelberg, Germany; [2]Hamburg State Department of Work, Health and Social Affairs, Hamburg, Germany

Within the last two decades tremendous efforts have been made to uncover the potential risks to human health associated with exposure to polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF), especially for the general population exposed at background levels. Very few other chemicals have been investigated as intensively as these substances, in particular, the most toxic congener within this group, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Public concern with regard to the potential adverse health effects of this chemical, especially the risk for cancer, was generated by the accident in Seveso, Italy, in 1976. Other major environmental or occupational exposures have also occurred, for example, in accidents in chemical factories such as the BASF in Germany in 1953 and during the Vietnam war.

Risk assessment for dioxins is an interdisciplinary effort. It is self-evident that disentangling this puzzle requires the integration of research results from various scientific disciplines such as toxicology, molecular biology, biochemistry, medicine, and epidemiology. Epidemiology plays a central role, as there are a number of dioxin-exposed human cohorts worldwide. These have received much attention by scientists, public health professionals, and most importantly by the general population, as dioxins and furans are ubiquituous substances and every human is exposed to them to a greater or lesser degree.

The present volume of the *Environmental Health Perspectives Supplements* presents contributions to the International Symposium on Dioxins and Furans: Epidemiologic Assessment of Cancer Risk and Other Human Health Effects held 7–8 November 1996 at the German Cancer Research Center in Heidelberg, Germany. The meeting was part of a scientific project on Risk Assessment for Dioxins Using Epidemiological Data, which was funded by the Federal Office for the Environment in Germany. The main objectives of the meeting were *a*) to present new data from epidemiologic studies with regard to several end points such as cancer, cardiovascular diseases, and immunologic and other biochemical effects, focusing on populations with high exposure to PCDD/PCDF; *b*) to give an overview on the extent, distribution, and modifying factors of the exposure in different populations; and *c*) to elucidate the consistencies and inconsistencies between the epidemiologic studies and to relate the epidemiologic findings to the available knowledge from animal and *in vitro* studies.

Several contributions to the present volume deal with the question of the potential carcinogenic effects of dioxins, especially TCDD, and we briefly describe these in the order in which they appear. Bertazzi and colleagues (*1*) give an overview of the studies on the Seveso population exposed during the accident in 1976. Calvert and colleagues (*2*) present new results on cardiovascular diseases in a cross-sectional morbidity study of workers, guided by the U.S. National Institute for Occupational Safety and Health (NIOSH). Vena and colleagues (*3*) report the latest results on noncancer mortality from a large international cohort organized by the International Agency of Research on Cancer (IARC) in Lyon, France, including some 27,000 workers from cohorts occupationally exposed to phenoxy herbicides and chlorophenols and their contaminants. The paper by Flesch-Janys and colleagues (*4*) presents a quantitative approach to estimate the extent of PCDD/PCDF exposure in an occupationally exposed German cohort based on blood levels and presents an analysis of the relationship of this quantitative exposure indicator to cancer risk. It is followed by a paper by Becher and colleagues (*5*) in which, based on the same study, an analysis of the dose–response relationship for both TCDD and toxicity equivalents TEQ (weighted sum of dioxins and furans) exposure and total cancer mortality is presented and an estimate of a unit risk is given. The result of a case–control study on non-Hodgkin's lymphoma and exposure to Agent Orange in Vietnam is presented by Kramerova and colleagues (*6*). Thereafter, Hardell and colleagues (*7*) describe the findings of a case–control study on the relation of non-Hodgkin's lymphoma and levels of specific polychlorinated biphenyl congeners and chlordanes in adipose tissue. Lynge (*8*) reports on the cancer incidence in Danish workers exposed to phenoxy herbicides.

Several data sets indicate that the immune system may be a sensitive target for the action of TCDD. Jung and colleagues (*9*) describe the results of a study on morphological and functional parameters of the immune system in workers highly exposed to PCDD/PCDF. Triebig and colleagues (*10*) present data on the exposure of workers to dioxins and furans in a thermal metal recycling plant and its effects on liver function, lipid metabolism, and thyroid parameters. Ernst and colleagues (*11*) describe a comparative analysis of certain immune cell functions in workers with and without exposure to TCDD.

Dioxins and furans are contaminants of different industrial processes. Because of their persistence in the environment and their accumulation in the food chain, human exposure is ubiquitous. Von

This paper is based on a presentation at the International Symposium on Dioxins and Furans: Epidemiologic Assessment of Cancer Risks and Other Human Health Effects held 7–8 November 1996 in Heidelberg, Germany. Manuscript received at *EHP* 17 July 1997; accepted 12 January 1998.

Address correspondence to H. Becher, German Cancer Research Center, Division of Epidemiology, Heidelberg, Germany.

Abbreviations used: IARC, International Agency for Research on Cancer; NIOSH, U.S. National Institute for Occupational Safety and Health; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Manikowsky and colleagues (*12*) report on a study investigating the PCDD/PCDF blood levels among children in German day care centers in which wood was treated with pentachlorophenol and lindane. Menzel and colleagues (*13*) investigated occupational exposures to PCDD/PCDFs by thermal oxygen cutting, welding, and soldering of metals. Päpke (*14*) gives an overview of the amount of PCDD/PCDF detected in biologic samples in different populations, explains factors that influence these levels, and gives data on the time trends. Messerer and colleagues (*15*) report new measurements from production workers at the BASF plant in Germany exposed long term to phenoxy herbicides. Schecter (*16*) reviews the use of congener-specific human tissue measurements as sensitive and specific biomarkers of exposure to PCDD/PCDF in human health studies.

In the paper by Tomaseth and Salvan (*17*) a model for the kinetics of TCDD for risk assessment using the data of the large mortality study of the NIOSH is developed. To round up, McGregor and colleagues (*18*) give an outline of the new evaluation of TCDD by the IARC according to which TCDD is now in group 1 (the substance is carcinogenic to humans). Finally, Grassman and colleagues (*19*) describe the use of animal models for predicting human response to dioxins.

In a final discussion of the available epidemiological knowledge as accumulated until this meeting, almost all participants agreed that TCDD can be considered a human carcinogen. This viewpoint was confirmed by the IARC evaluation which took place 3 months later in February 1997. The more challenging task, however, is a quantitative assessment of cancer risks. Although few participants believe that it is unwise to present quantitative risk estimates in the presence of large uncertainties in the quantitative exposure assessment, most discussants favor presenting those estimates, together with the appropriate caveats, accomplished with information on the degree of uncertainty. Fortunately, in many countries the background exposure of PCDD/PCDFs seems to be decreasing, but health hazards associated with dioxin exposure may remain for further decades because of the slow elimination from the environment and the long latency period for chronic diseases such as cancer. The results presented in this issue indicate that the magnitude of cancer risk may not be as large as initially apprehended.

REFERENCES AND NOTES

1. Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori AC. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ Health Perspect 106(Suppl 2):625–633 (1998).
2. Calvert GM, Wall DK, Haring Sweeney M, Fingerhut MA. Evaluation of cardiovascular outcomes among U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Environ Health Perspect 106(Suppl 2):635–643 (1998).
3. Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T et al. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environ Health Perspect 106(Suppl 2):645–653 (1998).
4. Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. Environ Health Perspect 106(Suppl 2):655–662 (1998).
5. Becher H, Steindorf K, Flesch-Janys D. Quantitative cancer risk assessment for dioxins using an occupational cohort. Environ Health Perspect 106(Suppl 2):663–670 (1998).
6. Kramárová K, Kogevinas M, Anh CT, Cau HD, Dai LC, Stellman SD, Parkin DM. Exposure to Agent Orange and occurrence of soft-tissue sarcomas or non-Hodgkin lymphomas: an ongoing study in Vietnam. Environ Health Perspect 106(Suppl 2):671–678 (1998).
7. Hardell L, Lindström G, van Bavel B, Fredrikson M, Liljegren G. Some aspects of the etiology of non-Hodgkin's lymphoma. Environ Health Perspect 106(Suppl 2):679–681 (1998).
8. Lynge E. Cancer incidence in Danish phenoxy herbicide workers, 1947–1993. Environ Health Perspect 106(Suppl 2):683–688 (1998).
9. Jung D, Berg PA, Edler L, Ehrenthal W, Fenner D, Flesch-Janys D, Huber C, Klein R, Koitka C, Lucier G et al. Immunologic findings in workers formerly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and its congeners. Environ Health Perspect 106(Suppl 2):689–695 (1998).
10. Triebig G, Werle E, Päpke O, Heim G, Broding C, Ludwig H. Effects of dioxins and furans on liver enzymes, lipid parameters, and thyroid hormones in former thermal metal recycling workers. Environ Health Perspect 106(Suppl 2):697–700 (1998).
11. Ernst M, Flesch-Janys D, Morgenstern I, Manz A. Immune cell functions in industrial workers after exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: dissociation of antigen-specific T-cell responses in cultures of diluted whole blood and of isolated peripheral blood mononuclear cells. Environ Health Perspect 106(Suppl 2):701–705 (1998).
12. von Manikowsky S, Sagunski H, Päpke O, Fabig K-R, Neus H, Schümann H, Spannhake K, Karmaus W, Osius N, Zier B. PCDD/PCDF indoor exposure in day-care centers and PCDD/PCDF blood concentrations of female employees. Environ Health Perspect 106(Suppl 2):707–714 (1998).
13. Menzel HM, Bolm-Audorff U, Turcer E, Bienfait HG, Albracht G, Walter D, Emmel C, Knecht U, Päpke O. Occupational exposure to dioxins by thermal oxygen cutting, welding, and soldering of metals. Environ Health Perspect 106(Suppl 2):715–722 (1998).
14. Päpke O. PCDD/PCDF: human background data for Germany, a 10-year experience. Environ Health Perspect 106(Suppl 2):723–731 (1998).
15. Messerer P, Zober A, Becher H. Blood lipid concentrations of dioxins and furans in a sample of BASF employees included in the IARC registry of workers exposed to phenoxy acid herbicides and/or chlorophenols. Environ Health Perspect 106(Suppl 2):733–735 (1998).
16. Schecter A. Commentary: A selective historical review of congener-specific human tissue measurements as sensitive and specific biomarkers of exposure to dioxins and related compounds. Environ Health Perspect 106(Suppl 2):737–742 (1998).
17. Thomaseth K, Salvan A. Estimation of occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin using a minimal physiologic toxicokinetic model. Environ Health Perspect 106(Suppl 2):743–753 (1998).
18. McGregor DB, Partensky C, Wilbourn J, Rice JM. An IARC evaluation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis. Environ Health Perspect 106(Suppl 2):755–760 (1998).
19. Grassman JA, Masten SA, Walker NJ, Lucier GW. Animal models of human response to dioxins. Environ Health Perspect 106(Suppl 2):761–775 (1998).