Chloracne: How relevant is it to dioxin poisoning?

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Introduction

A goal in environmental public health is the establishment of a linkage between exposure to environmental chemicals and adverse health outcomes. In order to assess this linkage, it is necessary to accurately assess exposure. Epidemiologists have traditionally used information gleaned from questionnaires, environmental measurements, and biological measurements (biomonitoring) for assessing human exposure to environmental chemicals.[1] Each of these instruments provides needed information. For example, questionnaires provide information for determining the route of exposure and for estimating the duration, frequency, and time since last contact with the environmental medium containing the chemical. Environmental measurements provide concentrations of the chemical in various media with which people may have contact. Thus, taken together questionnaire data and environmental measurements provide the information for developing exposure indices, which are useful for classifying the exposure status of individuals or groups of people. Environmental measurements are also useful for determining which of three possible main routes- ingestion, inhalation, and dermal contact- are the most likely exposure routes and thus are very useful in mitigating potential exposures. However, in examining the public health continuum, the further towards the effect that we can assess exposure, the more relevant that exposure assessment is for health study purposes. Thus, ideally, we would like to assess exposure to an environmental chemical by measuring that chemical in its target organ; however, for various reasons this is generally not possible. Therefore, we work "backwards" from the target organ dose and measure the internal dose in a selected biological matrix. For assessing exposure to dioxins and other lipophilic, persistent chemicals, blood measurements are generally considered the gold standard for use as "biomarkers of exposure." Other biological matrices, such as adipose tissue and breast milk, have also been used for biomonitoring purposes for these chemicals. Although concentrations of persistent chemicals are higher on a whole weight basis in these higher fat containing matrices, blood and its components (serum, plasma) are generally used because of their accessibility. Thus, the blood concentration of dioxin and similar chemicals is the exposure biomarker of choice for classifying exposure to these chemicals. But because biomarker measurements are expensive, we need other biomarkers of exposure to dioxin-like chemicals can be used.

Biomarkers of Exposure

Two properties that a biomarker of exposure should possess are sensitivity and specificity. The actual measurements of dioxin-like chemicals in blood by gas chromatography- high resolution mass spectrometry with isotope dilution is very sensitive (both in an analytical and epidemiological context; i.e., able to quantify the chemical at low concentrations) and also very specific (to measure the chemical of choice and not others- thus minimize false positives) for determining the concentration of a given chemical in the blood sample taken at that time. For determining what the blood concentration may have been at some former time we need to model the data which requires information on the exposure, such as time since last exposure, as well as pharmacokinetic information for that chemical in the population of interest.[2] Thus, in environmental public health the most accurate means of classifying human exposure to dioxin is the measurement of dioxin in blood and its components.

In environmental public health studies we generally deal with low level chronic exposures. Exposures in an occupational setting to chemicals like dioxin have generally involved higher concentrations. Still higher exposure concentrations have resulted from accidental or intentional poisonings. Certainly, dioxin and dioxin-like chemicals have been implicated in each of these exposure scenarios. Following exposures, different adverse health outcomes as well as no adverse health outcomes have been reported. However, the hallmark biomarker of effect following potential exposure to dioxin is "chloracne," which is characterized by persistent, prominent comedones, pale- yellow keratin cysts, and inflamed papules that generally are distributed at the malar crescents, post-auricular spaces, ears, neck, and scrotum. Lesions may clear within a few months or last over 15 years, and a chronic form of the disease may persist up to 30 years.[3] Although chloracne is in itself an adverse health outcome, certainly there is concern that exposure to dioxin-like chemicals may result in more severe outcomes so the question can be asked, "Can chloracne

also be used as a biomarker of exposure to dioxin?"

Properties of the chloracne biomarker

This question should be examined in terms of specificity and sensitivity. In addressing specificity, if one assumes that chloracne can be assessed accurately, then the question becomes, "What other chemicals can produce chloracne?" Although several lists have been compiled, it is clear that several polyhalogenated (primarily polychlorinated) aromatic chemicals are those of least debate. These include polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), polyhalogenatednaphthalenes, and the contaminants of 3,4-dichloroaniline herbicides: 3,3',4,4'-tetrachloroazobenzene and 3,3',4,4'-tetrachloroazoxybenzene.[4] Therefore, chloracne is not a specific indicator of dioxin exposure. The next questions of course are, "Is chloracne specific to planar aromatic halogen containing chemicals?" and, "Is binding to the Ah receptor necessary for this effect?" The answer to the first question is that certainly these are the chemicals with the highest association with chloracne. It would be of interest among the PCBs, if exposure to those and only those with dioxin-like activity, cause chloracne. This could readily be checked by applying those compounds to species of monkeys, rabbits, and hairless mice that produce the characteristic skin lesions. The second question is related to the first. If only those chemicals that bind to the Ah receptor produce chloracne, this would be an indication, but not proof, that binding to the Ah receptor is needed for chloracne formation.

To address sensitivity to the formation of chloracne following exposure to dioxin, we have to examine the literature. Chloracne has been observed following occupational exposures to dioxin in plants producing chlorophenols in the U.S., such as Midland, MI, Nitro, WV, and Southwestern IL; Great Britain; the former Czechoslovakia; Germany; Russia; and China.[5-12] In the German plant workers, at the time of the diagnosis, all chloracne cases had estimated adipose tissue levels greater than 200 pg/g lipid of 2,3,7,8-TCDD and greater than 2000 pg/g lipid of HCDD isomers. However, there was not a clear association between internal dose and the development of chloracne. The authors suggested where adipose tissue concentrations were relatively low but the former workers exhibited chloracne, this may be due to their having been exposed primarily by the dermal route and thus the levels of dioxins at the target site (skin) were sufficient to cause chloracne. In Chinese workers using a similar production process to the German process, the chloracne group had blood levels of dioxin I-TEQ ranging from 1170 to 22,300 pg/g and in the exposed, without chloracne group ranging from 420 to 660 pg/g. The authors concluded that the level needed to develop chloracne ranged between 650 and 1,250 pg/g lipid basis. In the Russian workers, the authors reported no correlation between reported chloracne status in 1965 to 1967 and TCDD or WHO-TEQ blood levels in 1992. In the U.S., the CDC's National Institute for Occupational Safety and Health conducted a cross-sectional medical study to examine the long-term health effects of occupational exposure to 2,3,7,8-TCDD; they reported a statistically significant odds ratio for chloracne of 2.3 (95% CI 1,1, 4.3) in the highest stratum of serum TCDD.[13] A follow-up study of the Midland, MI chlorophenol workers, with and without chloracne, was recently completed and the article is pending publication. Chloracne has also been reported among three laboratory workers exposed to pure 2,3,7,8-TCDD.[14] In addition to these workers, chloracne has been reported in workers performing cleanup activities after the 1953 BASF trichlorophenol reactor incident. In the early 1990s blood samples were taken and TCDD concentrations were measured and then back-calculated to estimate levels in 1953. The mean TCDD concentrations were 38 for no chloracne subgroup, 420 for moderate chloracne subgroup, and 1000 for the severe chloracne subgroup.[15]

In the Seveso, Italy residential setting Mocarelli et al. described chloracne in 10 people from Zone A who had 2,3,7,8-TCDD levels ranging from 820 to 56,000 pg/g in serum taken within 1 year of the 1976 reactor release; however, they also reported levels ranging from 1770 to 10,400 pg/g in Zone A residents who did not develop chloracne.[16] With the exception of one 16 year old person with chloracne, all of the chloracne cases were in those younger than 11 years of age. Those who did not exhibit chloracne were adults. In 1996, blood samples were taken from 101 Seveso chloracne cases and 211 non-chloracne people from the same area. Elevated plasma TCDD was associated with chloracne and chloracne risk was higher in people younger than 8 years of age in 1976. People with light hair color had higher relative odds of chloracne.[17]

Related Chemicals

Another class of chemicals with dioxin-like activity is the polychlorinated dibenzofurans (PCDFs). Mass poisonings from ingestion of PCB/PCDF contaminated rice oil led to mass poisonings in Japan in 1968 and in central Taiwan in 1979 (Yusho and Yucheng, respectively). In both incidents chloracne was widely reported. For example, 17% of the

Yucheng exposed subjects reported symptoms compatible with chloracne.[18]

Heavy Exposure

More recently, in a potential poisoning incident involving two people in Austria, the person with blood TCDD levels of 144,000 pg/g developed severe generalized chloracne whereas the person with 26,000 pg/g had only mild facial lesions; six months later the levels had decreased to 80,900 and 16,100 pg/g, respectively. In the two samples of pooled cyst contents, also taken six months later from the more highly exposed person, the TCDD levels were 34,400 and 18,600 pg/g lipid.[19] Another more recent incident in the Ukraine the victim presented with severe facial lesions and had a TCDD blood level of 100,000 pg/g.[20] So the question remains, is chloracne relevant to dioxin poisoning. What we can say with a high degree of certainty is that based on the approximate 4000 known cases of chloracne the presence of chloracne indicates exposures to a fairly short list of chemicals (specificity) that lead to high internal doses but the absence of chloracne does not imply the absence of such exposures; also, low level exposures probably do not lead to chloracne (lack of sensitivity). This then points to susceptibility and perhaps the exposure pathway. Some people because of their genetic make-up and age may be more susceptible for developing chloracne following similar exposures than others. The exposure route may be important. Because the target organ for chloracne is the skin, the dermal route may produce chloracne at lower exposure concentrations than inhalation or ingestion. Another factor could include the delivery of the dose- one time acute dose versus low level chronic dose. So, in conclusion, we can say that if chloracne is present in a potential poisoning victim, certainly this would point strongly towards high level exposure to a dioxin-like chemical(s) but in the absence of chloracne, such exposures still may have occurred. Therefore, the ultimate biomarker of exposure from both a specificity and sensitivity standpoint to dioxin-like chemicals is the measurement of those chemicals in an appropriate biological sample by an “approved” laboratory.

References

1. Needham L.L., Özkaynak H., Whyatt R., Barr D.B., Wang R. and Naeher L. (in press.) *Environ Health Perspect* doi:10.1289/ehp.7613.

2. Aylward L.L., Brunet R.C., Carrier G., Hays S.M., Needham L.L., Patterson D.G. Jr., Gerthoux P.M., Brambilla P. and Mocarelli P. (2005) *J Exposure Ana Environ Epidemiol* 15:51-65.

3. Suskind R.R. and Hertzberg V.S. (1984) *J Am Med Assoc.* 251: 2372-2380.

4. Scarisbrick D.A. and Martin J.V. (1981) *J Soc Occup Med* 31: 158-163.

5. Bond G.G., McLaren E.A., Brenner F.E. and Cook R.R. (1989) *J Occup Med.* 31: 771-774.

6. Moses M., Lilis R., Crow K.D., Thornton J., Fischbein A., Anderson H.A. and Selikoff I.J. (1984) *Am J Ind Med.* 5: 161-182.

7. O’Malley M.A., Carpenter A.V., Sweeney M.H., Fingerhut M.A., Marlow D.A., Halperin W.E. and Mathias C.G. (1990) *Am J Ind Med.* 17: 411-421.

8. May G. (1973) *Br J Ind Med.* 30: 276-283.

9. Peclová D., Fenclová Z., Dlasková Z., Urban P., Luká š E., Procházka B., Rappe C., Preiss J., Kocan A., Vejlupková J. (2001) *Arch Environ Health.* 56: 493-500.

10. Beck H., Eckart K., Mathar W. and Wittkowski R. (1989) *Chemosphere* 18: 507-516.

11. Ryan J.J. and Schecter A. (2000) *J Occup Environ Med.* 42: 861-870.

12. Coenraads P.J., Olie K. and Tang N.J. (1999) *Br J Dermatol.* 141: 694-697.

13. Sweeney M.H., Calvert G.M., Egeland G.A., Fingerhut M.A., Halperin W.E. and Piacitelli L.A. (1998)

*TeratogCarcinogMutag.*17: 241-247.

14. Oliver R.M. (1975) *Br J Ind Med.* 32: 49-53.

15. Ott M.G., Messerer P. and Zober A. (1993) *Int Arch OccEnvHea* 65: 1-8

16. Mocarelli P., Needham L.L., Marocchi A., Petterson D.G., Jr., Brambilla P., Gerthoux P.M., Meazza L. And Carreri V. (1991) *J Toxicol Environ Health.* 32: 357-366.

17. Baccarelli A., Pesatori A.C., Consonni D., Mocarelli P., Patterson D.G., Caporaso N.E., Bertazzi P.A. and Landi M.T. (2005) *Br J Dermatol.* 152: 459-465.

18. Guo Y.L., Yu M., Hsu C. and Rogan W.J. (1999) *Environ Health Perspect.* 107: 715-719.

19. Geusau A., Abraham K., Geissler K., Sator M.O., Stingl G. and Tschachler E. (2001) *Environ Health Perspec.* 109: 865-869.

20. BBC News World Edition, Thursday, 25 November 2004.