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October 5, 1994

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Dear Sirs:

Please send me Volumes I, II, and III of the dioxin reassessment.

Thank you.

Sincerely,

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SUBJECT: EPA's 9/13/94 Final Draft, Dioxin Reassessment SEP 15 1994

FROM: Cate Jenkins

Attached are key portions of EPA's September 13, 1994 final draft of the dioxin reassessment that relate to all cancers at all sites combined, including lung cancer. Other health effects are also evaluated in the document. If you want a full copy of this 2000 page EPA document, ask for Volumes I, II, and III of the dioxin reassessment by calling or writing to:

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It is important to understand that the EPA reassessment addresses "all cancers combined," a standard epidemiological category of cancers that reflects a general carcinogenic effect on all organs of the body. For example, a cancer-causing agent could act by compromising the immune system, leading to all types of cancers. A cancer-causing agent could affect some aspect of the hormone system, causing cancers to occur throughout the body. A cancer could act as a promoter, greatly enhancing any carcinogenic action of other substances already present in the body, also leading to cancers throughout the body.

For unidentified reasons, the National Academy of Sciences (NAS) declined to address this valid, scientifically recognized, and always utilized epidemiological category of "all cancers combined" when it performed its preliminary review of Agent Orange on behalf of the Department of Veterans' Affairs. The NAS did include a description of the category "all cancers combined" in the section that discussed specific cancer categories, such as "soft tissue sarcomas," and "non-Hodgkin's lymphoma." Mysteriously, however, the NAS did not include a conclusion section relating to the "all cancers combined" category, as it did for other cancer categories. It appears that NAS was deliberately overlooking its responsibility to evaluate "all cancers combined."

The EPA did evaluate the "all cancers combined" category. The EPA evaluation does not contradict the NAS evaluation in this regard, since the NAS did no evaluation of "all cancers combined." The EPA June, 1994 final draft (released September 13) of Chapter 7, Epidemiology/Human Data (Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds, Volume II of III) states the following:

CONCLUSIONS

Of all the cancers examined in both the case-control and follow-up studies, STS [soft tissue sarcoma] provides the greater evidence of an association with TCDD relative to other sites...[p. 7-73]

The evidence for lung cancer and TCDD exposure comes from the three recent cohort follow-up studies... All three studies showed increased risks of borderline statistical significance of about 40% to 100% in their highly exposed groups and low risks in their less exposed groups. In addition to the above studies, the report of a significantly increased lung cancer risk in male victims of the Japanese rice oil poisoning accident ... is also suggestive of a TCDD-like effect...[p. 7-75]

While no one tissue site can account for this observed increase, lung cancer is also increased in four of these [studies]. Although these data suggest a hypothesis of "general carcinogenicity" consistent with a tumor promoter effect or immune suppression, it must be kept in mind that no single agent has ever been determined to cause an overall cancer response by the epidemiologic method. Although many carcinogens have been shown to increase the risk at sever sites, the magnitude of the risk has differed with respect to each site. One would not expect to see the same magnitude of increase in risk at every site affected from exposure to a carcinogen. [p. 7-76]

> In conclusion, although there are uncertainties associated with the epidemiologic evidence that could have influence risk estimates, the overall weight of evidence from the epidemiologic studies suggests that the generally increased risk of cancer is more than likely due to exposure to TCDD. [p. 7-77]

(Note that the EPA document mentions increased lung cancer rates as being one of those cancers responsible for the increased risks in the "all cancers combined" category.)

The final summary document, Risk Characterization, Chapter 9 (Vol. III of II), dated august, 1994, released September 13, further emphasizes the conclusion that dioxin is a probable or likely carcinogen, causing cancer at many different organs in the body, including the lung:

> What emerges from an analysis of the epidemiology data is a view of dioxin-like compounds as potentially multisite carcinogens in more highly exposed human population that have been studies, consisting primarily of adult males. ... [p. 9-41]

An explanation of the level of evidence expressed by phrase "more than likely due to exposure to TCDD" is needed for a correlation to the degree of proof required a court of law or for a typical compensation determination before the Department of Veterans' Affairs, or the Department of Labor,. Attached is the August, 1994 draft of an EPA document, *Draft Revisions to the Guidelines for Carcinogen Risk Assessment.* This document explains the "likely" language as follows:

> *"Likely" or "Known"*
>
> These descriptors are appropriate when the evidence provides a reasonable assurance of carcinogenic potential for human beings and supports proceeding with the risk assessment. "Likely" is the descriptive term generally used. "Known" is used when the weight of evidence gives especially high assurance ... [p. 36]

Thus, EPA's use of the term "likely" correlates with the required level of proof of causation for typical compensation cases, meaning that the probability of is more likely than not. There are few carcinogens which qualify for the "known" category. However, compensation has been granted for many carcinogens categorized only as "likely." The Department of Veterans' Affairs awarded compensation for those veterans with soft tissue sarcoma and non-Hodgkin's lymphoma, even though these cancers are only classified as "likely" carcinogens. "Likely" carcinogens, with supporting human data, are the equivalent of the older EPA classification "B1." Before this reassessment, EPA classified dioxin as "B2" based on animal evidence.

Although the EPA dioxin reassessment is not complete, the key statements in the final drafts discussed above are expected to remain substantially the same. Even before the release of the September 13 drafts, EPA had already held several formal public hearings, convened expert panels, and sought and gained formal review and input from the public and scientists on many drafts of the reassessment. The reassessment will now be forwarded to EPA's Science Advisory Board (SAB) for acceptance or rejection. This final review may take many months, or even a year, but the scientific conclusions in the final draft EPA documents is unlikely to change.

In my opinion, veterans should be entitled to compensation for any type of cancer if it is associated with Agent Orange, as soon as this EPA document is finalized. The same goes for the conclusions by EPA on the other health effects, which in several cases directly contradict the NAS conclusions. The EPA document has more scientific credibility than the NAS report or the NAS system in general for evaluating health effects on behalf of veterans.

United States Environmental Protection Agency | Office of Research and Development Washington DC 20460 | EPA/600/BP-92/001b June 1994 External Review Draft

EPA

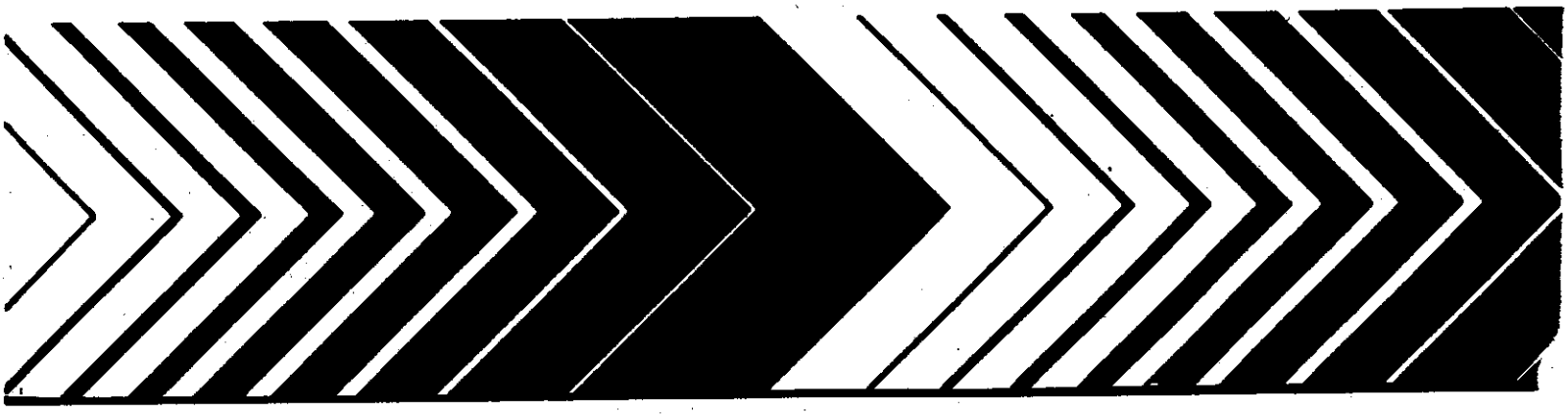
Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds

Review Draft (Do Not Cite or Quote)

Volume II of III

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds

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animals has been well documented." Deaths from chronic liver diseases and cirrhosis are also elevated but not significantly.

An outbreak of illness similar to Yusho was reported among some 2,000 persons in the Taichung and Changhwa provinces of Taiwan in March 1979. The illness consisted of chloracne, hyperpigmentation, and meibomian gland dilatation. In October 1979, the illness was found to be the result of the ingestion of cooking oil contaminated with PCBs and PCDFs. Chen et al. (1980) reported on the blood PCB levels of 66 victims for which gas chromatograms had been prepared. Basically, blood concentration residues ranged from 11 ppb to 720 ppb in these patients. The mean value was 49 ppb; most values were under 100 ppb. In only two instances were the concentrations greater, at 120 ppb and 720 ppb. The authors reported that the higher value of 720 ppb occurred in a patient who had difficulty metabolizing and excreting PCB components. They also maintain that blood PCB levels of these patients are "much higher" than those of 72 Japanese Yusho patients (Koda and Masuda, 1975). Koda and Masuda reported the mean PCB value in Yusho patients was 5.9 ppb with a standard deviation of 4.5 ppb in 1973 and 1974. Chen et al. (1980) maintained that this difference is due to a lengthy time lapse from the exposure to PCB in Yusho patients before measurements were taken compared with a much shorter time lapse in Yu-Cheng patients. Furthermore, the patients of Yu-Cheng consumed a larger proportion of higher-chlorinated PCBs compared with those of Yusho and, as a result, the substance will be retained longer in the body, according to the authors. Ten years have now passed. Researchers should take a close look at this cohort now that the latent period has almost been achieved for liver cancer in order to confirm or deny that an excess liver cancer risk is present in these patients.

7.9. CONCLUSIONS

Of all the cancers examined in both the case-control and follow-up studies, STS provides the greater evidence of an association with TCDD relative to other sites. The original reports by Hardell, Sandstrom, and Eriksson of an association between STS and exposures involving TCDD-contaminated phenoxy herbicides have stood up to extensive criticism and a great deal of subsequent research. The degree of risk, as estimated in later

studies by Hardell's research group, does not appear to be as great as originally suggested, but an association with TCDD exposure is strengthened by tissue measurements of 2,3,7,8-TCDD in potentially exposed groups.

It is also possible that the herbicides, phenoxyacetic acid, and/or chlorophenols may exert a confounding effect. The results of the recent Lynge (1993) study suggest that TCDD-free phenoxyherbicides and/or chlorophenols may by themselves increase the risk of STS. Eriksson et al. (1990) further suggested that the higher-chlorinated dioxin isomers may also be carcinogenic.

Not every study that has looked for an association between TCDD exposure and soft tissue sarcoma risk has found one, but several studies of sound design and adequate size have done so to a greater or lesser extent. The results from the important cohort study by Fingerhut et al. (1991) of 5,000 chemical production and processing workers exposed to TCDD are corroborative, as are those from the second 5 years of follow-up of the persons exposed to TCDD in Seveso (Bertazzi et al., 1989a, b). The large IARC Registry cohort study also suggested an association between STS and phenoxy herbicide exposure, but the TCDD exposure component was less certain. The first New Zealand sarcoma study (Smith et al., 1983, 1984) also appeared to produce positive results when the analysis, presented above, was restricted to farmers to minimize bias. These results were produced by independent investigators using substantially different research methods and studying populations exposed under conditions much different from those in the studies by Hardell and colleagues, with TCDD exposure being the common link.

Moreover, no persuasive case has been made that the entirety of the association in these studies is real and not due to selection bias, differential exposure misclassification, confounding, or chance.

The evidence on malignant lymphomas in connection with TCDD exposure has not been substantiated, but recent evidence suggests an association between NHL and exposure to the herbicide 2,4-D (Zahm and Blair, 1992), which may contain dioxins other than 2,3,7,8-TCDD. The evidence from two large industrial cohort studies (Fingerhut et al., 1991; Saracci et al., 1991), and from the Seveso population suggest little if any evidence of increased risk. The limited evidence on TCDD exposure that can be extracted from the

extensive case-control studies on NHL by the National Cancer Institute (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) also does not indicate a consistent and pronounced increase in risk. It would be interesting to see results restricted to farmers from the New Zealand study of NHL. At the present time, however, the existing studies do not present even a minimally consistent picture of increased risks of malignant lymphoma among persons most probably exposed to TCDD.

The evidence for lung cancer and TCDD exposure comes from the three recent cohort follow-up studies (Fingerhut et al., 1991; Manz et al., 1991; Zober et al., 1990), all of which provided good TCDD exposure surrogates and some actual TCDD serum level samples. All three studies showed increased risks of borderline statistical significance of about 40% to 100% in their highly exposed groups and low risks in their less exposed groups. In addition to the above studies, the report of a significantly increased lung cancer risk in male victims of the Japanese rice oil poisoning accident (Kuratsune, 1988) is also suggestive of a TCDD-like effect (see discussion of animal carcinogenicity in Chapter 6). While confounding or synergism by tobacco smoke cannot be excluded, the limited analyses conducted suggest that smoking cannot explain the entire increase and that the association is real.

It must be remembered that the confounding influence of other occupational chemicals and presence of asbestos in the workplace could have added to the observed lung cancer cases in these studies and helped to increase the lung cancer risk calculated for these studies.

The evidence for an association with stomach cancer is less than that for lung cancer. While the high exposure/long duration cohorts in both the Fingerhut and Manz studies suggest increased risks of at least 40%, the estimates are based on too few deaths for any conclusions to be made. There are no case-control studies relating to TCDD exposure and either lung or stomach cancer because the cancers are too common with too many potential causes. Further research is needed.

While males comprise all the case-control studies and the bulk of the cohort study analyses, animal and mechanism studies suggest that males and females might respond differently to TCDD, which reduces estrogen levels in reproductive tissues and reduces estrogen-receptor binding in rat and mouse liver. These antiestrogenic effects are thought to

be responsible for decreased tumor incidences seen in the mammary gland, uterus, and pituitary of TCDD-treated female rats and may also be responsible for increased liver cancer seen in female but not male rats (see Sections 6.4.1 and 6.5.4) although in the Japanese rice oil poisonings, the reverse was the case. These female rat liver tumors may be ovary-dependent, while at the same time the ovaries appear to protect against TCDD-mediated tumor promotion in the rat lung (see Section 6.4.2). Thus, these complex mechanisms might very well affect human carcinogenicity in males and females differently. The only reported female cohort with good TCDD exposure surrogate information was that of Manz et al. (1991), which had a borderline statistically significant increase in breast cancer. While Saracci et al. (1991) did report reduced female breast and genital organ cancer mortality, this was based on few observed deaths and chlorophenoxy herbicide, rather than TCDD exposures. Bertazzi et al. (1993) reported a deficit of breast cancer and endometrial cancer in women living in geographical areas around Seveso contaminated by dioxin. Although Kogevinas et al. (1993) saw an increase in cancer incidence among female workers most likely exposed to TCDD, no increase in breast cancer was observed in her small cohort. In sum, TCDD cancer experience for women may differ from that of men but currently there are few results.

Other TCDD-related hormonal effects, including immune suppression, may result in multiorgan sensitivity and may contribute to the overall increased mortality from all malignancies combined seen in all four cohort production worker subcohorts with higher estimated TCDD exposures (Fingerhut et al., 1991; Manz et al., 1991; Zober et al., 1990; Saracci et al., 1991; Kogevinas et al., 1993). These increased relative risks, while not large (10% to 70%) are consistent and are either statistically significant or of borderline significance. While no one tissue site can account for this observed increase, lung cancer is also increased in four of these. Although these data suggest a hypothesis of "general carcinogenicity" consistent with a tumor promotor effect or immune suppression, it must be kept in mind that no single agent has ever been determined to cause an overall cancer response by the epidemiologic method. Although many carcinogens have been shown to increase the risk at several sites, the magnitude of the risk has differed with respect to each

site. One would not expect to see the same magnitude of increase in risk at every site affected from exposure to a carcinogen.

In conclusion, although there are uncertainties associated with the epidemiologic evidence that could have influenced risk estimates, the overall weight of evidence from the epidemiologic studies suggests that the generally increased risk of cancer is more than likely due to exposure to TCDD. The consistency of this finding in the four major cohort studies is corroborated by animal studies that show TCDD to be a multisite, multisex, and multispecies carcinogen.