

Invited Commentary: How Do the Seveso Findings Affect Conclusions Concerning TCDD as a Human Carcinogen?

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Dioxin, specifically 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), is a chemical with remarkable persistence in humans and a half-life of about 5–10 years. It is also noteworthy that a recent International Agency for Research on Cancer (IARC) monograph classified TCDD as a group 1 human carcinogen, in spite of the conclusion by the Working Group involved that there was only “limited evidence” of carcinogenicity in epidemiologic studies (1). The key epidemiologic evidence came from four industrial cohort studies (2–5), each of which included confirmation of exposure for some workers with measurements of the concentrations of TCDD in their blood or fat samples. Overall increases in mortality from all cancers combined were reported for each of these cohorts, but no particular cancer sites were prominent. This IARC monograph stated that the “lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution” (1, p. 337).

In making the overall evaluation that TCDD is carcinogenic to humans, the Working Group considered the following supportive evidence:

- (i) 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor;
- (ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals;
- (iii) TCDD tissue concentrations were similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays (1, p. 343).

The decision to classify TCDD as a group 1 carcinogen was based on a clause in the evaluation criteria stating the following: “Exceptionally, an agent may be classified in this category when the evidence in humans is less than sufficient, but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of

carcinogenicity” (1, p. 26). Whether the supportive evidence related to tissue concentrations and a receptor site, presented by the Working Group, is judged adequate to invoke this exception depends, at least in part, on how strictly one adheres to a literal interpretation of “relevant mechanism.” A liberal interpretation cognizant of the probable underlying sentiment must take into consideration that we do not know the complete mechanisms involved in any cause of human cancer.

Be that as it may, unprecedented decisions such as this one warrant careful scrutiny. In particular, they should be reexamined in light of new information when it becomes available. The Seveso, Italy, population experienced well-documented exposure to TCDD resulting from an industrial accident in which TCDD was released and dispersed to surrounding residential areas. Unlike the industrial cohorts that included only men, studies of the Seveso population also have the potential to yield important information concerning the effects of TCDD in women and children. When the IARC Working Group met, it was noted that follow-up of the Seveso residents was shorter than in the industrial cohort studies. Indeed, the follow-up period was then a maximum of 15 years, which is inadequate for considering the usually long latency between causal exposures and increases in cancer incidence. However, the time from the first exposure to the follow-up reported in this issue of the *Journal* extended to 20 years and therefore included sufficient latency to address at least early cancer findings (6). Furthermore, the Bertazzi et al. study has some excellent features, including virtually complete follow-up for those who continued to reside in the exposed area and about 99 percent follow-up for those moving out of the area during the follow-up period. The cohort also included documented exposure based on blood samples taken from some residents soon after the industrial accident occurred. Another valuable feature is that the authors provided extensive tables of results according to zone of residence in relation to the industrial plant in which the accident occurred, as well as findings separated into latency time windows.

Before considering the Seveso results (6), and to help put them in perspective, we abstracted some of the industrial cohort study findings on which the IARC Working Group based their conclusions. The all-cancer standardized mortality ratio calculated by the Working Group for the combined cohorts was 1.4, with a narrow confidence interval of 1.2 to 1.6. Some will interpret a standardized mortality ratio of 1.4 as low compared with what is often reported for specific sites for known human carcinogens. It is, but a combined all-

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Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. From the School of Public Health, University of California, Berkeley, Berkeley, CA.

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cancer standardized mortality ratio as high as this is not often found in cohorts with occupational exposure to known human carcinogens. More importantly, it is certainly not to be expected that four separate cohort studies selected solely on the basis of their documented very high exposures to a particular chemical agent would all report the increases in combined all-cancer standardized mortality ratios shown in table 1.

What do the new Seveso results (6) show? Perhaps with so much data in so many tables, there is a little bit of something for everybody. Regarding all-cancer mortality, we might focus on the results for the combined zone A and zone B exposed population, since the numbers in zone A—with the highest exposure—are too small to consider on their own. We abstracted the results for the latency time window of 15–20 years, the only one with sufficient latency to warrant consideration (table 1). At first glance, it appears that the findings for men add to and support the conclusions concerning the industrial cohort studies. The standardized mortality ratio is 1.3 (95 percent confidence interval (CI): 1.0, 1.7) for Seveso men compared with 1.4 (95 percent CI: 1.2, 1.6) for the four industrial cohorts. Of course, the lack of an increase in overall cancer mortality among women (standardized mortality ratio = 0.8, 95 percent CI: 0.6, 1.2) could be attributed to chance or to male susceptibility to the carcinogenicity of TCDD, perhaps involving synergy with a cofactor such as cigarette smoking.

There are two key problems with the interpretation that the overall male cancer mortality findings from Seveso support the findings from the industrial cohort studies. The first is that the exposures to TCDD are not comparable. In table 2, we present information concerning TCDD concentrations found in members of the industrial cohorts back-calculated to the time that the exposures occurred, based on half-life estimates. In addition, we took the data from tables 1 and 2 of the Bertazzi et al. paper (6) and also calculated a population-weighted average estimate for zone A and zone B combined. Our table 2 shows that, whereas each industrial cohort includes workers with TCDD concentrations of more than 1,000 ng/kg (lipid adjusted), the weighted average for the two highest exposure zones in Seveso is only 136 ng/kg. On the basis of the industrial cohort studies, one therefore would not expect to find detectable increases in all-cancer mortality in the Seveso cohort for any latency. Hence, we do not think that the results add to or detract from the findings reported for the industrial cohorts.

A second problem with interpreting the findings concerning all-cancer male mortality in the Seveso cohort involves smoking-related causes of death. Along with all-cancer mortality, lung cancer mortality was increased among men for the 15–20-year latency period in zones A and B combined (respiratory cancer, standardized mortality ratio = 1.4, 95 percent CI: 0.9, 2.2). In itself, this finding is not important since the same was found to be true for the industrial cohorts. For the four industrial cohorts, the pooled standardized mortality ratio for lung cancer was 1.4 (95 percent CI: 1.1, 1.7) (1). However, the 15–20-year latency findings for the Seveso cohort also include standardized mortality ratios of 1.3 (95 percent CI: 0.8, 2.3) for myocardial infarction and 1.7 (95 percent CI: 0.9, 3.1) for chronic respiratory disease. The authors

(6) discuss these findings, but the combination of relatively low dioxin exposures plus increases in all major smoking-related causes of death for the 15–20-year latency time window do not seem to support attributing the overall increase in cancer mortality to TCDD.

There are many other interesting results in this important paper concerning the Seveso cohort (6). The increase in diabetes mortality among women is of particular interest in light of findings in previous studies suggesting that TCDD may

TABLE 1. Standardized mortality ratios for all cancers combined in the major industrial cohort studies assessed by IARC* and results reported for zones A and B of the Seveso, Italy, cohort with 15–20 years of latency from exposure

Study (reference no.)	Observed no.	SMR*	95% CI*
Combined US cohorts (2)†	114	1.5	1.2, 1.8
BASF Corporation cohort, Germany (3)†	18	1.9	1.1, 3.0
Chlorophenol plant, Germany (4)†	105	1.3	1.0, 1.5
Chlorophenol plants, the Netherlands (5)†	51	1.5	1.1, 1.9
Above 4 cohorts combined†	288	1.4	1.2, 1.6
Seveso men, zones A + B 15–20 years after exposure (6)	58	1.3	1.0, 1.7
Seveso women, zones A + B 15–20 years after exposure (6)	25	0.8	0.6, 1.2

* IARC, International Agency for Research on Cancer; SMR, standardized mortality ratio; CI, confidence interval.

† Refer to table 38 in reference 1.

TABLE 2. Comparison of TCDD* blood lipid concentrations reported in the major industrial cohort studies compared with the highest Seveso, Italy, population exposures

Study (reference no.)	Concentration estimated to time of the last exposure (ng TCDD/kg)
Combined US cohorts (2)	3,600 (mean)†
BASF Corporation cohort, Germany (3)	1,000–2,400†
Chlorophenol plant, Germany (4, 7)	345–3,890†
Chlorophenol plants, the Netherlands (5)	1,842 (mean)†
Seveso men and women, zones A + B combined	136 (weighted mean)
Background TCDD concentration of the general population (1)	2–3

* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

† Highest-exposed subcohorts.

increase the risk of diabetes (e.g., Henriksen et al. (8)). However, as the authors note, the Seveso evidence comes from death certificate data alone and must be interpreted with caution. Findings concerning Hodgkin's disease, non-Hodgkin's lymphoma, and soft tissue sarcoma will constitute a topic for widespread discussion and no doubt disagreement regarding their interpretation. We are indebted to Bertazzi et al. for the excellent follow-up they are achieving in this important cohort study and for presenting the results in a manner that allows detailed assessment of its results. Continued follow-up is definitely warranted, and we look forward to a few years from now, when we can also consider a 20–25-year latency window from the time that the industrial accident occurred.

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Bertazzi et al. Respond to Smith and Lopipero

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We thank Smith and Lopipero for their invited commentary (1), which we found appropriate and useful for interpreting the latest Seveso, Italy, findings (2). Human exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is widespread (3). Epidemiologic studies are essential to assessing the risk linked to the environmental contamination, and consistency in the findings enhances confidence in their results.

It is not surprising that, on average, exposure to TCDD in Seveso was lower than in occupational cohorts. In the former case, the chemical release was limited in time, and its content eventually was diluted over an extended outdoor area (4). Still, the average TCDD blood concentration in the Seveso population was two orders of magnitude higher than the reported background environmental level (1). Thus, the finding of increased cancer mortality cannot be considered totally unexpected. An increase in all-cancer and lung cancer mortality, consistent with what was observed in occupational cohorts, was found in men in zones A and B after 15 years. Smith and Lopipero (1) suggest that smoking might be the actual explanation. This is a possibility, and we intend to further explore smoking habits in our index and referent populations.

However, if the increased risk was due to smoking, one would expect high rate ratios for the whole study period, not only 15–20 years since dioxin exposure. With regard to concomitant potentially smoking-related findings, several other studies linked increased cardiovascular mortality to dioxin exposure, sometimes with a dose-related pattern (5–7) and use of internal reference groups (6, 7), thus leaving little room for confounding arguments. In addition, other smoking-related cancers (e.g., larynx, esophagus, pancreas, and bladder) were not elevated in Seveso males after 15 years (2). To be a confounder, smoking should be distributed unevenly among zones. Independent surveys assessed

smoking habits in 1986–1987 in random samples of the population of Desio (352 subjects), one of the cities affected by the Seveso accident, and in the population in a nearby district outside the study area (466 subjects), quite similar to our reference population. Distribution of the subjects by smoking category in the two samples was as follows: never smokers, 76 (22 percent) in Desio versus 104 (22 percent) in the outside area; former smokers, 107 (30 percent) versus 154 (33 percent); current smokers of <10 cigarettes/day, 30 (9 percent) versus 38 (8 percent); current smokers of 10–20 cigarettes/day, 99 (28 percent) versus 134 (29 percent); and current smokers of >20 cigarettes/day, 40 (11 percent) versus 36 (8 percent) (8). This, although limited, set of data suggests that geographic variation in smoking habits might be negligible across subareas in the region including the accidentally contaminated territory.

Although we admit that with so many data “there is a little bit of something for everybody” (1, p. 1046), results for lymphatic and hemopoietic neoplasms clearly do stand out. The pattern suggests a systematic difference in mortality from these causes between the TCDD-exposed and the local reference population. Cancer incidence data for the first postaccident period support these findings (9). The non-Hodgkin’s lymphoma increase became significant after 15 years (five observed; rate ratio = 2.8, 95 percent confidence interval: 1.1, 7.0). An increased occurrence of non-Hodgkin’s lymphoma also has been observed in occupational cohorts (6, 10, 11).

On the basis of our interpretation, the 20-year mortality results do show that the Seveso population experienced, consistent with other exposed populations, a modest excess of all-cancer and respiratory cancer mortality long after initial exposure and a moderately increased occurrence of lymphatic and hematopoietic cancer. This pattern is different from what might have been expected on the basis of animal experiments. A limited number of persons probably had extremely high levels of exposure, and susceptibility factors might also have played a role.

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Abbreviation: TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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