Reconciling Old and New Findings on Dioxin

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Whether dioxin, or more specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has caused cancer in humans has been the subject of many epidemiology studies. A recent review concluded that the findings of these studies were not consistent, although the evidence was considered "weak to strong" for non-Hodgkin's lymphoma and too inconsistent for soft tissue sarcomas.[1] More recently, however, two studies have been published that report consistent findings indicative of dioxin carcinogenicity. These two studies are an update, by Zober *et al*,[2] of a study of workers exposed as a result of a 1953 accidental release of dioxin in Germany, and the National Institute for Occupational Safety and Health (NIOSH) Dioxin Registry study by Fingerhut *et al*.[3] We will consider how these new studies add to our knowledge of the potential dioxin health effects.

In 1977, a case report appeared, followed by a related case-control study in 1979, that suggested a connection between herbicide exposure and soft tissue sarcoma.[4,5] Dioxin can be a contaminant in some herbicides. This finding appeared to receive some support from three occupational studies[6-8] that reported a total of four soft tissue sarcomas, a relatively rare tumor, among small groups of workers exposed to relatively high levels of dioxin. These findings, as well as public concerns, motivated the formation of the NIOSH Dioxin Registry.

After these early findings, however, the potential causal relation between dioxin and soft tissue sarcoma was questioned in two separate areas. First, the earlier reported association was not replicated in later studies,[9] and two of the original four soft tissue sarcoma deaths were not confirmed on review of the pathology reports.[10] Thus, the general view of these findings shifted, and the evidence for a causal relation between dioxin and soft tissue sarcoma was considered "suggestive but unproven."[11]

Other cancer sites have occasionally been reported to be associated with phenoxy herbicides or dioxin exposure.[12] These sites include Hodgkin's disease, non-Hodgkin's lymphoma, and stomach cancer. As with soft tissue sarcoma, however, these associations were not consistent across studies, and so these sites were not recognized as related to exposure.[1]

Recently, however, two studies have been published that show elevated mortality for total cancers in occupational subcohorts with long latency. Zober *et al*,[2] in updating an earlier study of workers exposed from an accidental release, determined exposure from proximity to the accident. One hundred fourteen cases of chloracne, a condition related to significant exposure to dioxin as well as to other substances, and 13 cases of erythema (that is, suggestive of chloracne) were observed among the 247 persons in the study. There were 67 deaths in this study; however, for 11 of these decedents, death certificates could not be located, and clinical reports were used to ascertain cause of death. It is unknown what impact this case-finding procedure had on the final results, since rates for the general population comparison group were ascertained from death certificate information only. In addition, the impact of including nonchloracne (that is, erythema) with chloracne cases is not reported.

In the Zober *et al* study, mortality rates were evaluated for four groups of potentially exposed persons: (1) 69 workers, all of whom had chloracne, identified from a plant list; (2) 84 workers involved in protective operations and demolition of the building after the accident; (3) 94 persons from several sources known to be involved in the accident; and (4) 127 persons from the previous three groups with chloracne or erythema. No mortality excesses were observed among group 1 or group 3. Group 2 had a significant excess in the category of "other and unspecified cancers." Group 4 had no significant excesses for any cause of death, but persons with 20 or more years of latency had a significant excess for all cancers combined [standardized mortality ratio (SMR), = 2.0, 95% confidence

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interval (CI) = 1.1-3.4]. From these data, Zober *et al* conclude: "our results do not appear to support a strong association between cancer mortality and dioxin, but they do suggest that some hazard may have been produced."[2]

In the second recent study, Fingerhut *et al*[3] included 5,172 workers from 12 U.S. manufacturing plants that produced chemicals potentially contaminated with dioxin. Dioxin exposure was assumed on the basis of proximity to a process. Overall, none of the *a priori* hypothesized cancers (for example, soft tissue sarcoma, stomach cancer, and non-Hodgkin's lymphoma) was significantly elevated. In a subcohort of 1,520 workers with 1 or more years of exposure and 20 years of latency, there was a statistically significant SMR for unconfirmed soft tissue sarcoma (SMR = 9.2, 95% CI = 1.9-27.0), respiratory cancer (SMR = 1.4, 95% CI = 1.0-1.9), and all cancers combined (SMR = 1.5, 95% CI = 1.2-1.8). Mortality for all cancers combined (SMR = 1.2, 95% CI = 1.0-1.3) was also elevated for the entire study population. From these data, Fingerhut *et al* conclude: "the increased mortality, especially in the subcohort with one year or more of exposure, is consistent with the status of dioxin as a carcinogen."[3]

Because of these recent studies, some have concluded that dioxin is more likely a carcinogen than not and that the weight of evidence has contributed to the "weakening of the position of those who believe that low levels of dioxin are entirely safe for humans."[13] We believe, however, that any such strengthening of the conclusion regarding dioxin carcinogenicity is premature and not fully supported by the data. Four issues need to be resolved.

The first issue is that the recent studies focus attention on a new group of cancers not previously reported. The only exception might be the finding in the Fingerhut *et al* study of a soft tissue sarcoma excess in a subcohort of workers, but this reported excess is difficult to interpret because: (1) upon pathologic review, two of the four deaths were found not to be soft tissue sarcoma[10]; (2) no new soft tissue sarcoma deaths were found, although 10 additional plants were studied (that is, all four deaths were known from prior published studies[6-8] of two plants); and (3) at least one of the reported deaths has been coded by three different nosologists to a non-soft tissue sarcoma category,[6] indicating variability in nosologic decision making for this cause of death. Furthermore, there were no soft tissue sarcoma deaths reported in the Zober *et al* study. The substantial variability in both diagnosis and nosology coding indicates that there may be no unbiased way to compare worker and general population death rates for soft tissue sarcoma. The comparison of exposed and unexposed workers at the studied plants may be the only viable approach for assessing the possible relation between dioxin and soft tissue sarcoma.

The second issue is that the findings are not concentrated in specific cancer sites and instead relate to all cancers combined. Such findings are not consistent with the patterns reported for known occupational carcinogens. Furthermore, the Fingerhut *et al* study found no trend in risk with increasing exposure or duration of exposure to dioxin (as shown in Table 4 of the Fingerhut *et al* report[3]), and the pattern of risk was not indicative of an occupational carcinogen (that is, the largest risk was not found in the highest exposure/longest latency strata), although the risk, as measured with the SMR, did increase with latency alone. Additionally, the primary findings were unexpected at the beginning of the study. Therefore, these new findings should be viewed cautiously as warranting further analysis and awaiting replication from other epidemiologic investigations, but not as direct evidence of causality.

The third issue is that the findings of Zober *et al* and Fingerhut *et al* are each internally inconsistent. That is, each study is a mixture of previously studied workers and new data, and the old and new results differ. Characterized in this way, each study can be evaluated for internal consistency.

The Zober *et al* study is in large part an update of a previous study[14] in which three stomach cancers were reported (expected = 0.5, SMR = 5.8, 95% CI = 1.2-16.9). Although the populations were slightly different between studies, Zober *et al* found no additional stomach cancers during 12 additional years of follow-up (expected = 0.5, SMR = 0.0, 95% CI = 0.0-7.4) but only reported combined results for the total follow-up period (SMR = 3.0, 95% CI 0.6-8.7). Two conclusions are possible from contrasting the old and new data: the stomach cancer findings from the original study were not confirmed by further follow-up, or the maximum induction period for dioxin-related stomach cancer passed prior to the additional follow-up period. Assessment of results from other dioxin populations with similar time since exposure does not show elevated stomach cancer rates,[15-17] supporting the former conclusion.

The Fingerhut *et al* study is a combination of previously published data[4,7,15-17] from two plants and data from 10 additional plants that were not studied previously. The former plants include 49% (2,544 workers) of the total study population, and the dioxin-related

manufacturing periods and the subsequent follow-up periods overlap substantially, with the 10 additional plants providing a comparable basis for contrasting the findings.[12] Although the data were not reported separately for the 10 newly studied plants, this separation can be approximated (Table 1). The two plants formerly studied show no remarkable cancer patterns with the exception of the previously reported findings for soft tissue sarcoma. This finding was, in part, the basis for the NIOSH Dioxin Registry. Findings from the 10 newly studied plants show no cases of soft tissue sarcoma (SMR = 0), although the expected number of deaths is almost the same as for the previously studied plants (0.6 *vs* 0.7). Thus, the previously reported finding for soft tissue sarcoma was not confirmed in a very similar study among a second exposed worker population. A second possible explanation is that the period since exposure for workers differs between studies despite the overlap of manufacturing activities and follow-up periods between studies; but that seems unlikely. It is also noteworthy that stomach cancer mortality was not elevated in either subgroup—findings inconsistent with those in the original study of the Zober *et al* cohort.

Other findings from the 10 additional plants indicate an excess of all cancers combined and a borderline excess of lung cancer—findings not evident in the two plants previously studied. These "new" findings should be viewed as internally inconsistent and provide a rationale for evaluating potential confounding factors as noted in the remainder of this paper.

The fourth issue is that the interpretation of the findings is obscured by the potential influence of important confounding factors such as: (1) other occupational exposures, (2) smoking, and (3) failure to control for regional variation in the general population cancer mortality.

As Fingerhut *et al* point out, duration of dioxin exposure was correlated with duration of time employed in these plants. The two Monsanto plants included in the study have been studied with respect to various substances other than dioxin; other exposures in these plants could be important confounders in subgroups of workers. The same may also be true for the other plants. The relative nonspecificity of the reported cancer findings in this study and in the Zober *et al* study are consistent with exposures to a variety of substances, but this issue has not been addressed in detail by the authors. While both the Fingerhut *et al* and the Zober *et al* studies assumed that non-dioxin exposures were not important confounders, our experience with two plants in the Fingerhut *et al* study

TABLE 1. Comparison of Observed Deaths (Obs), Expected Deaths (Exp), and Standardized Mortality Ratios (SMR) with Confidence Intervals (CI) of Old Results (Two Plants Previously Studied) with New Results (Ten Plants not Previously Studied) from the Fingerhut *et al* Study[12]

	SMR Obs/Exp* (95% CI)†	
Site of Cancer (ICD9 Code)	Old Results‡	New Results‡
All cancers (140–208)	1.06 140/132.6 (0.89–1.25)	1.28 125/97.3 (1.07–1.53)
Non-Hodgkin's lymphoma (200, 202)	1.67 7/4.2 (0.67–3.45)	0.96 3/3.1 (0.20–2.81)
Soft tissue sarcoma (171)	6.15 4§/0.7 (1.66–15.76)	0.00 0/0.6 (0.0–6.71)
Hodgkin's disease (201)	1.33 2/1.5 (0.16–4.82)	1.00 1/1.0 (0.03–5.57)
Stomach (151)	1.24 7/5.7 (0.50–2.55)	0.68 3/4.0 (0.15–2.18)
Liver (155, 156)	0.68 2/2.9 (0.08–2.47)	1.76 4/2.3 (0.48–4.51)
Lung (162)	0.93 43/46.3 (0.67–1.25)	1.36 46/33.8 (1.00–1.82)

* Estimated from Table 6 of Fingerhut *et al*.[12]
† Confidence intervals using Byar approximation for 5 or more deaths and the Fisher exact method for fewer than 5 deaths.[20]
‡ The Monsanto plant appears in studies 6 and 7, and the Dow plant appears in studies 15–17.
§ Only two of these cases were confirmed as soft tissue sarcoma on pathologic review.

suggests otherwise. For example, in one of our plants, a subgroup of the dioxin cohort had exposure to 4-aminobiphenyl, a potent bladder carcinogen,[18] which was discontinued in 1955 after it was discovered to be a carcinogen. The excess of bladder cancer reported by Zack and Gaffey[7] in a subset of the NIOSH cohort illustrates the effect of 4-aminobiphenyl. Aromatic amines were also produced in the plant studied by Zober *et al*, and several bladder cancers were attributed to such exposure.[2] The bladder cancer attributable to 4-aminobiphenyl contributes to the total cancer excess observed in the Fingerhut *et al* study.

A second example of a potential confounding exposure is indicated by the mesothelioma deaths present in both the Fingerhut *et al* study (two deaths) and the Zober *et al* study (one death). These deaths indicate

TABLE 2. Observed Deaths and Standardized Mortality Ratios (SMR) by Plant for Lung Cancers and All Cancers Combined*

Plant Code	Lung Cancer		All Cancers Combined	
	Observed	SMR	Observed	SMR
1	7	0.72	32	1.15
2	1	1.55	2	1.11
3	4	1.07	10	0.87
4	3	1.01	7	0.75
5	3	1.66	7	1.41
6	2	1.04	7	1.29
7	3	2.38	3	0.86
8	15	1.44	35	1.18
9	28	0.78	105	1.02
10	13	2.14	30	1.81
11	5	2.39	11	1.93
12	5	1.25	16	1.41
Total	89	1.11	265	1.15

* Source: Fingerhut *et al.*[12]

the potential for asbestos exposure among one or more of the workforces in the study and could be contributing to the lung cancer findings in these studies.[19] The possibility that these and other occupational factors may be affecting the reported findings is suggested by the wide variation in the SMRs for lung cancer and all cancers combined for the 12 plants in the Fingerhut *et al* study[12] (Table 2). For lung cancer and all cancers, the SMRs range from 0.7 to 2.4 and from 0.8 to 1.9, respectively. Although sampling variation is a possible explanation for the wide range of SMRs, it would be useful to assess the potential confounding at the plants with high SMRs.

Smoking is another confounder whose impact has likely been underestimated, at least in the Fingerhut *et al* study. This underestimation takes on added importance because smoking is a strong risk factor for lung cancer that has a synergistic effect with asbestos exposure.[19] To assess the potential confounding effect of smoking, Fingerhut *et al* used estimates of smoking prevalence for the cohort in 1965 based on a survey of workers alive at two of the 12 plants in 1987. Smokers would be underreported in this cross-sectional survey since nonsmokers would be overrepresented among surviving workers.

Additionally, smoking prevalence in 1965 may underreport the smoking prevalence over the subsequent study period (that is, 1965–1987), compared with the general U.S. population, since the cohort is comprised predominantly of blue collar workers who may take longer than the general population to quit smoking.[20] These two factors suggest an underestimate of the true confounding effect of smoking on lung cancer in the study. The general pattern of elevated SMR for smoking-related cancers in both studies supports a potential confounding effect due to smoking.

An additional important factor could be the failure in both studies to account adequately for geographical variation in mortality rates by comparing worker mortality with national rates. Because of known regional variations, it is more appropriate to use regional comparison populations.[21,22] Cancer SMRs in the range of the present study can diminish substantially when regional comparisons over the total study time frame are used.[21,22] For the two Monsanto plants, using regional comparison rates reduces the SMR 24% and 28% for lung cancer and 11% and 20% for all cancers combined. Hence, geographical variation is often significant and may obscure the estimation of cancer risk.

In summary, the recent dioxin studies report important new information relevant to potential effects of dioxin, but the inconsistency of results with previous findings makes causal inference difficult. The recent findings that have been emphasized were not those expected on the basis of earlier studies, were not related to dioxin exposure, and were of such small magnitude that bias should be a critical concern. Further studies of these populations could evaluate the potential confounding factors mentioned above to clarify the potential cancer risk from dioxin or other exposures.

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Old and New Reflections on Dioxin

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What is "old" and what is "new"? As with most things epidemiologic, it depends on your definition.

The paper by Collins *et al*[1] claims that a recent study[2] of dioxin-exposed workers by the National Institute for Occupational Safety and Health (NIOSH) is a mixture of "old" (that is, previously studied) and "new" findings, which are internally inconsistent. We present the historical context in which the NIOSH study was conducted to point out the erroneous assumptions of Collins *et al* regarding "old" and "new." We also explore the question of how to evaluate "consistency" in an epidemiologic study.

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This study was initiated in 1978 by NIOSH to include all (5,172) chemical workers in the United States who had work records verifying assignment to the production of 2,4,5-trichlorophenoxyacetic acid or its precursor 2,4,5-trichlorophenol, both contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), commonly referred to as dioxin.[2] By 1978, toxicity and teratogenic and carcinogenic effects had been seen in animals, but only limited epidemiologic investigations had been conducted.[3] The NIOSH study was initiated because of the animal data and out of concern about potential effects on the Vietnam veterans exposed to Agent Orange, which contained dioxin, and the workers who produced the products contaminated with dioxin.

All of the Monsanto and Dow studies cited by Collins *et al*[1] as "previously published" were actually published after the 1978 initiation of the NIOSH study. Table 1 lists key aspects of four studies of Monsanto and Dow workers published in the early 1980s.[4–7] Since most of the workers fit the NIOSH protocol definitions and were included in the NIOSH

study, these four studies should be viewed as small subsets of the large NIOSH study of all U.S. workers, with the vital status of the workers updated through 1987. Table 1 shows that the total of 444 workers identified in the four early Monsanto and Dow studies constitute 17% of the 2,544 dioxin-exposed workers identified by NIOSH at the Monsanto and Dow plants and less than 9% of the 5,172 workers in the full NIOSH study of 12 U.S. plants. This number is well below the 49% cited by Collins *et al*,[1] who erroneously suggest that the large Dow cohort studied in the *late* 1980s[8–10] is independent of the NIOSH study. That cohort was actually the NIOSH cohort of Dow workers identified for the NIOSH study by NIOSH researchers with the active collaboration of Dow epidemiologists (Table 1). The Dow researchers, however, published several mortality analyses of this cohort[8–10] before publication of the full NIOSH study.[2] Consequently, since Monsanto and Dow published studies of fewer than 20% of the workers exposed to dioxin at the two plants, we cannot agree with the premise of Collins *et al* that "the Fingerhut *et al* [NIOSH] study is a combination of previously published data. . . from two plants and data from 10 additional plants that were not studied previously."

A more substantive issue regarding the re-analysis of published studies is raised by consideration of the paper by Collins *et al*.[1] What is an appropriate epidemiologic rationale for splitting a multiplant study conducted from a single protocol to look for internal consistency? What is the definition of "internal consistency"? Collins *et al* appear to be seeking similar cause-specific standardized mortality ratios (SMRs) in the various plants. We suggest that this standard is not appropriate in the absence of thoughtful consideration about age distributions, levels (or duration) of exposure, latency (time since first exposure), and power.

In our study,[2] as in other multiplant studies, there are a number of reasons why one might not expect to find similar SMRs across plants. For example, all workers at two of the 12 plants in the NIOSH study had been first exposed less than 20 years earlier, so cancers may not have had time to develop. Several plants had only about 100 exposed workers, leading to few deaths, limited statistical power, and unstable numbers. We found that the excess cancer was concentrated in workers with more than 1 year of exposure. Thus, at two plants, where most workers were exposed for less than 1 year, the overall risk would be lower than at the plants where workers were exposed for many years. The intensity of exposure also differed at the plants. The NIOSH study utilized years of assignment to

TABLE 1. Comparison of Studies by Dow, Monsanto, and National Institute for Occupational Safety and Health (NIOSH) of Workers Exposed to Dioxin-Contaminated Products at Two U.S. Plants

Plant	Reference	Measure of Exposure*	Study End Date	Total Workers	Total Deaths	Type of Study†	All Cancers‡			Lung Cancer			Soft Tissue Sarcoma		
							Obs	Exp	Risk Ratio	Obs	Exp	Risk Ratio	Obs	Exp	Risk Ratio
Monsanto, Nitro, WV	Zack[4]	Chloracne, TCP accident	1978	121	32	SMR	9	9.04	100	5	2.85	175	1§	?	?
Monsanto, Nitro, WV	Zack[5]	2,4,5-T	1977	58	58	PMR	9	10.94	82	6	3.78	159	1	?	?
Monsanto (NIOSH), Nitro, WV	Fingerhut[16]	TCDD (TCP and 2,4,5-T)	1987	452	121	SMR	35	29.6	118	15	10.4	144	2§	0.13	1,516‖
Dow, Midland, MI	Cook[6]	Chloracne, TCP	1978	61	4	SMR	3	1.6	188	0			1	?	?
Dow, Midland, MI	Ott[7]	2,4,5-T	1976	204	11	SMR	1	3.6	28	1	?	?	0		
Dow (NIOSH), Midland, MI	Fingerhut[16¶]	TCDD (TCP and 2,4,5-T)	1987	2,092	427	SMR	105	102.5	102	28	35.6	78	2	0.5	394

* TCP, 2,4,5-trichlorophenol; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin).
† SMR, standardized mortality ratio; PMR, proportional mortality ratio.
‡ Obs, observed; Exp, expected.
§ The cause of death was coded by Monsanto as International Classification of Diseases (ICD) 173.9 (cancer of skin). It was coded by NIOSH as ICD 171 (soft tissue sarcoma). The death certificate says "malignant fibrous histiocytoma of soft tissue origin."
¶ The cohort of Dow workers identified for the NIOSH study was also analyzed by Cook,[6] Ott,[7] and Bond[10] with fewer years of vital status follow-up.
‖ $P < 0.05$.

dioxin-contaminated processes as a measure of cumulative exposure for all workers. We are currently developing an industrial hygiene-based exposure matrix to estimate relative exposures of the workers in the cohort. The planned re-analysis of the cohort will further examine the question of exposure-response, using an internal comparison.

Collins *et al*[1] expressed concern that the "recent [NIOSH[2] and Zober *et al*[11]] studies focus attention on a new group of cancers not previously reported." We agree that our finding of an excess of total cancers was unexpected, since it is unusual in studies of chemical workers. Earlier studies of dioxin-exposed animals, however, are consistent with our finding in that they have found tumors in a number of organs.[12,13] The Zober study of German workers, although small and limited in its assessment of exposure, reported a similar finding of excess total cancers in a subgroup with chloracne who had been exposed 20 or more years earlier.[11]

The history of soft tissue sarcoma studies described by Collins *et al* requires clarification. Although a case report about soft tissue sarcoma[14] was published before the NIOSH study was initiated in 1978, all of the other epidemiologic studies of soft tissue sarcoma in various countries were conducted during the period when the NIOSH study of dioxin-exposed U.S. production workers was under way. Thus, the claim of Collins *et al*[1] is incorrect that the 1978 initiation of the NIOSH study was motivated by the soft tissue sarcomas reported in the Swedish case-control studies and the U.S. occupational cohorts of the 1980s.

The difficulties of studying soft tissue sarcoma from death certificates have been described, including the problem of misclassification of cause of death[2,15,16] The NIOSH mortality analysis[2] included four deaths identified from death certificates as soft tissue sarcoma deaths. Based on tissue review, two of these were found not to have died of soft tissue sarcoma. Misclassification in the opposite direction also occurred. Two other men in the NIOSH cohort of Monsanto workers died of soft tissue sarcoma, based upon medical records and tissue review. They were not counted as soft tissue sarcoma deaths in our study, however, because soft tissue sarcoma was not listed on their death certificates.[2,16] Misclassification is also known to occur in the coding of death certificates for the U.S. population.[17] Thus, the usual practice is to conduct the cohort analysis using the data on the death certificate, without attempting any correction for misclassification, and to add a discussion if additional information is known about the deaths in the cohort.

What is truly "old" in the paper by Collins *et al* is the listing of possible confounders in the NIOSH study. All of these were discussed in some detail by Fingerhut *et al*.[2,16] Collins *et al*[1] have omitted several balancing considerations presented in these papers. For example, they point out that we used a smoking survey conducted at two plants to estimate the possible influence of smoking on the observed lung cancer excess in the entire cohort of 12 plants. This survey indicated little difference in smoking between these two plants and the U.S. referent population. In drawing our conclusions, we also considered other factors, including an evaluation of mortality from other diseases known to be associated with smoking. We found that mortality from nonmalignant respiratory disease was lower than expected (15 deaths, SMR 96, 95% CI 54–158) in the subcohort with over 1 year of exposure and more than 20 years of latency. This is the subcohort in which the excess respiratory cancer was found (43 deaths, SMR 142, 95% CI 103–192). Additionally, the subcohort with over 20 years of latency, but with less than 1 year of exposure, did not have an excess of respiratory cancer (19 deaths, SMR 103, 95% CI 62–161). Consequently, it did not seem to us that smoking would have fully accounted for the respiratory cancer excess in the subcohort with long exposure.

Collins *et al*[1] suggest that regional rates should have been used in the NIOSH study. The choice of comparison rates, always a judgment call, has to address the limitations in the use of local rates, such as the instability of small numbers, the question of whether the workers actually live within the region, the problem that some cohorts may influence the local rates, and the locations of the 12 plants in 10 states across the country. Because of the limitations of local rates, we chose to use national rates, as did the authors of the Dow and Monsanto studies listed in Table 1.[4–10]

One new suggestion can be drawn from the Collins *et al* paper[1], namely, that future epidemiologic mortality studies compare workers exposed to dioxin-contaminated products with unexposed workers at the same plant. Studies with internal comparisons would indeed be helpful, particularly if exposure to dioxin-contaminated chemicals is carefully characterized. Internal comparisons at the plants could address several potential confounders not fully addressed in the NIOSH multiplant study of mortality.

In summary, we differ with the views of Collins *et al*.[1] We consider the NIOSH study to be a "new" study, which followed a single protocol to identify all workers in the United States assigned to the manufacture of products contaminated with dioxin. The study

utilized standard epidemiologic methods and found an overall 15% excess of all cancers, which was more pronounced (46% excess) in a subcohort with more than 1 year of exposure and over 20 years of latency. In this subcohort, a 42% excess of respiratory cancer and a ninefold excess of soft tissue sarcoma were also found. Although the NIOSH study could not completely exclude the possible contribution of other occupational carcinogens or smoking, we conclude that the results are consistent with TCDD being a carcinogen.

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