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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	384

* 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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