

Dear Drs. Armitage and Buckley,

On behalf of my co-authors – Drs. Boffetta, Adami, Cole and Mandel – I am pleased to report that our critical review of the recent epidemiological literature on TCDD and human cancer risks was accepted for publication in Critical Reviews in Toxicology and, according to the Editor in Chief, is expected to be available on-line by end of March (see message below).

In the mean time, I have attached a copy of the accepted manuscript for EPA's review and consideration. Please note in the message below the conditions under which I have been allowed to share this with you. [\[Note from the SAB Staff Office: the published version of this article is now available at http://informahealthcare.com/doi/abs/10.3109/10408444.2011.560141\]](http://informahealthcare.com/doi/abs/10.3109/10408444.2011.560141)

Thank you for your kind consideration, and please do not hesitate to contact me with any questions or if you require additional information.

Sincerely yours,

Ken

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Principal and Director of Epidemiology  
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**Comments from Kenneth A. Mundt to the EPA Science Advisory Board  
Dioxin Review Panel  
3/3/11**

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1 **TCDD and cancer: A critical review of epidemiologic studies**

2

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Abstract

We reviewed the epidemiologic studies on exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and cancer risk, published since the last full-scale review made by the International Agency for Research on Cancer Monographs program in 1997. The update of a cohort of US herbicide producers generated negative results overall; the internal analysis provided evidence of an increased ‘all cancer’ risk in the highest exposure category, with a statistically significant exposure-response association in some of the many analyses performed. The update of a similar Dutch cohort did not confirm the previously observed association with TCDD exposure. The updated surveillance of the Seveso population provided evidence of increased all cancer mortality 15-20 years after exposure among those living in the most contaminated area but might also reflect random variation, as overall excesses in the most recent follow-up were not observed. Corresponding data on cancer incidence offer little support to the mortality results. Updated results from cohort studies of Vietnam veterans potentially exposed to TCDD did not consistently suggest an increased risk of cancer. Results of additional, smaller studies of other occupational groups potentially exposed to TCDD, and of community-based case-control studies did not provide consistent evidence of an increased cancer risk. In conclusion, recent epidemiological evidence falls far short of conclusively demonstrating a causal link between TCDD exposure and cancer risk in humans. The emphasis on results for overall cancer risk - rather than risk for specific neoplasms - is not justified on epidemiologic grounds and is not a reason for ignoring the weaknesses of the available evidence.

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## Introduction

2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is carcinogenic in experimental animals, but has not been conclusively proven to cause cancer in humans. Indeed, evidence for an effect in humans has remained controversial, because exposure to TCDD is widespread, but almost invariably occurs at very low doses, with TCDD as a contaminant, typically as part of complex mixtures of chlorinated compounds, several of which are also suspected to be carcinogenic. Such exposure circumstances represent a challenge to epidemiology, because of methodological issues such as limited power to detect small risks, exposure misclassification and residual confounding.

As with other important known or suspected environmental carcinogens, emphasis on the carcinogenic effect of TCDD rests mainly on exposure-response modeling and possible health (and in particular carcinogenic) effects at low levels of exposure. Such effects are generally not observable with epidemiologic methods. Instead, they are often estimated based on low-dose extrapolation models. However, in the absence of empirical data, such extrapolations depend heavily on assumptions regarding the exposure-response relationship at the lowest levels of exposure. Despite their lack of direct relevance to the possible effects at low doses, epidemiologic studies of TCDD and cancer are important because of the need to determine if the agent is carcinogenic to humans exposed to high doses. The question of whether the epidemiologic evidence demonstrates carcinogenicity of TCDD in humans (hazard identification) remains central for risk assessment, and for regulatory decisions.

A number of national and international agencies have reviewed the evidence from epidemiologic studies of TCDD and cancer [e.g., EPA, 2003; NAS, 2006; WHO, 1998; WHO, 2002]. In this review, we refer primarily to the reviews conducted by the International Agency for Research on Cancer (IARC) within its Monographs program [IARC, 1977; 1987; 1997; Baan et al., 2009].

*IARC reviews of carcinogenicity of TCDD in humans*

1 The last full-scale IARC Monographs review, completed in 1997, led to a conclusion of limited  
2 evidence of carcinogenicity in humans [IARC, 1997]. In this review the emphasis was on a  
3 small increase in overall cancer risk among humans following high exposure to TCDD, and on  
4 exposure-response associations. The overall evaluation in IARC Group 1 (established human  
5 carcinogen) was based on mechanistic considerations on the role of the Ah receptor in TCDD-  
6 related carcinogenesis in both humans and animals. The same mechanism was used to justify  
7 emphasis on the risk of all cancers combined rather than specific cancer sites.

8  
9 The IARC evaluation was criticized by Cole and colleagues [2003] who stressed the lack of an  
10 overall increase in cancer risk in humans exposed to TCDD, the inconsistent selection of highly  
11 exposed groups in the IARC evaluation, and the weak evidence that the Ah receptor mediates  
12 multi-organ carcinogenicity. Cole and colleagues also briefly reviewed the data published after  
13 the IARC 1997 review, stressing that no additional evidence had been reported to alter their  
14 conclusions. Conversely, another review, authored by some members of the 1997 IARC panel,  
15 argued that the data reported after 1997 supported the IARC conclusions [Steenland et al., 2004].  
16 The conclusions by Steenland and colleagues were based on positive exposure–response  
17 analyses in the US cohort, the evidence of excesses of some cancers in the Seveso accident  
18 cohort, and mechanistic data regarding the role of the Ah receptor in TCDD carcinogenicity.

19  
20 In 2009 IARC reviewed the carcinogenicity of TCDD as part of a systematic re-assessment of all  
21 agents classified in Group 1 and classified the evidence of carcinogenicity in humans as  
22 sufficient, based on increased risk of all cancers combined [Baan et al., 2009]. Details of this  
23 latter evaluation, based on a more cursory review of the available data than regular IARC  
24 Monographs, have not yet been reported, and a comprehensive review of recent epidemiologic  
25 data is not available.

## 26 27 *Aims*

28  
29 We provide a detailed review of the epidemiologic studies on cancer risk among individuals  
30 exposed to TCDD. With the exceptions of multiple myeloma and breast cancer, for which recent  
31 comprehensive reviews are not available, we do not review in detail results published before

1 1997 because they are extensively reviewed and readily available in the IARC Monograph,  
2 which provided a comprehensive summary of the evidence available at that time [IARC, 1997].  
3 We also do not address the adequacy of experimental and mechanistic data to support the  
4 hypothesis of a central role of Ah receptor activation in TCDD-related carcinogenesis in humans  
5 and in experimental systems (although we address the use of these data to justify the  
6 interpretation of epidemiologic studies), nor do we review low-dose extrapolations and risk  
7 assessment models for TCDD.

## 8 9 Methods

### 10 11 *Selection of studies*

12  
13 The most informative populations for which exposure to TCDD is convincingly documented or  
14 highly probable include occupational groups involved in the production or use of herbicides  
15 potentially contaminated by TCDD (particularly 2,4,5-T), other industrial processes entailing  
16 potential exposure to TCDD (e.g., trichlorophenol [TCP] manufacture), as well as populations  
17 exposed to potentially contaminated intermediates or herbicides via industrial accidents and war-  
18 related circumstances.

19  
20 We also considered community-based studies in which exposure to TCDD (mainly from  
21 occupational sources) has been assessed using different approaches, including self-reports, job-  
22 exposure matrices, and expert evaluations. In general, these studies are less informative than  
23 those based on occupational or accidental exposures because exposures were lower, of shorter  
24 duration, and subject to more misclassification. Nevertheless, these studies are included in the  
25 review for sake of completeness.

26  
27 We do not review studies of workers exposed to herbicides not contaminated by TCDD (e.g.,  
28 2,4-D), to agents contaminated by PCDDs without TCDD (e.g., pentachlorophenol [PCP]  
29 [Demers et al., 2006]), and to unspecified combinations of pesticides and herbicides (e.g., studies  
30 of farmers or pesticide applicators [e.g., Fleming et al., 1999; Swaen et al., 2004]). Nor do we  
31 include studies of populations potentially exposed to TCDD, but without detailed exposure

1 information (e.g., pulp and paper workers [McLean et al., 2006], waste incinerator workers  
2 [Leem et al., 2003], fishermen [Mikoczy and Rilander, 2009]), and Vietnam Veterans without  
3 information on TCDD exposure [Leavy et al., 2006]. Because of the abundance of studies with  
4 individual-level exposure and outcome assessment, we do not include ecologic studies in which  
5 such information is lacking (e.g., [Zambon et al., 2007; Poulstrup et al., 2004; Fukuda et al.,  
6 2003; Read et al., 2007; Viel et al., 2008a; Viel et al., 2008b]).

7  
8 We identified the relevant literature from the IARC 1997 Monograph [IARC, 1997] and PubMed  
9 searches for subsequent publications. We used keywords such as 'dioxin,' 'TCDD,' 'pesticides,'  
10 'cancer' and 'neoplasms' (as well as specific cancers). We also checked references in recent  
11 reviews. We also included a few studies published after the 2009 IARC review.

### 12 13 *Results subsequent to the IARC 1997 review*

14  
15 We aimed to identify subgroups at highest exposure. One such population comprises exposed  
16 individuals who developed chloracne, a dermatologic condition caused by high TCDD exposure.  
17 Although it is unclear whether mechanisms leading to chloracne (e.g., genetic susceptibility) are  
18 also relevant to carcinogenesis, there is little doubt that chloracne patients experienced heavy  
19 exposure. In addition, several studies analyzed duration of exposure to TCDD, time since first  
20 exposure, and some quantitative or semi-quantitative indices of exposure. These data were  
21 reviewed in detail because they help testing the hypothesis of a causal association between  
22 TCDD exposure and cancer risk. The 1997 IARC review identified four groups at highest  
23 exposure (see below), and emphasized the importance of the results in these groups [IARC,  
24 1997; Steenland et al., 2004]. Wherever possible, we identified new results relevant to the  
25 high-exposure groups.

26  
27 When the same population was studied both before and after the 1997 IARC review, we  
28 evaluated the specific contribution of the extended follow-up. Whenever possible, we subtracted  
29 the number of observed and expected cancer deaths (or cases) of the early report from the  
30 updated report; however, when this was not possible, we showed results of the two reports side  
31 by side.

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*Outcomes*

The evaluation by IARC of the carcinogenicity of TCDD is unique because more emphasis is given to all cancers combined (hereafter referred to as 'all cancer') than to specific cancers. We assume that the results for all cancer do not refer to individual cancer sites. The emphasis on all cancer has been justified by the role of activation of the Ah receptor by TCDD as an unspecific mechanism of cancer promotion in humans as well as experimental systems [Gasiewicz et al., 2008; Schwarz and Appel, 2005]. This mechanistic interpretation of epidemiologic results has, however, been criticized [Cole et al., 2003]. In the IARC evaluations evidence of a causal association with TCDD exposure was considered strongest for lung cancer, non-Hodgkin lymphoma (NHL), and soft-tissue sarcoma (STS) [Baan et al., 2009]. Hence, we systematically reviewed the results for these neoplasms. In addition, we reviewed in detail the studies on prostate cancer among Vietnam veterans potentially exposed to TCDD-contaminated herbicides, as well as studies on breast cancer and multiple myeloma, because these cancers have been specifically discussed in previous reviews as possible evidence of dioxin's human carcinogenicity [Brody et al., 2007; Alexander et al., 2007].

Relatively few measurements are available on levels of exposure of the populations included in the relevant epidemiologic studies. For some of these populations, TCDD was measured in blood samples, usually several years after cessation of exposure. We present selected results in Figure 1, together with the estimated levels at the time of exposure. As a comparison, typical blood levels of TCDD in adults without known sources of exposure fall in the range of 1-10 ppt [IARC, 1997].

Review of epidemiologic studies

*Manufacture of herbicides potentially contaminated with TCDD*

Cancer risk has been extensively studied among workers employed in manufacturing of herbicides potentially contaminated with TCDD (mainly 2,4,5-T, TCP and PCP). These studies

1 differ according to inclusion criteria, follow-up periods, exposure assessment, overlaps, and  
2 other characteristics, which complicates comparisons as well as synthesis of evidence across  
3 studies. The most comprehensive publication [Kogevinas et al., 1997] combines data from three  
4 studies also reported separately: 12 plants from the United States [Fingerhut et al., 1991], 4  
5 plants from Germany [Becher et al., 1996], and 16 plants from Austria, Denmark, Finland, Italy,  
6 the Netherlands, New Zealand, Sweden and the United Kingdom [Saracci et al., 1991]. A  
7 German cohort exposed through an accident [Ott and Zober, 1996] is the only relevant study not  
8 included in the combined international analysis.

9  
10 Most informative of all these studies – involving the highest and best documented exposure to  
11 TCDD – are the 12-plant cohort from the United States, the 4-plant cohort from Germany, the  
12 accident cohort from Germany and the cohort from the Netherlands [IARC, 1997; Steenland et  
13 al., 2004]. Since the 1997 IARC Monograph, updated results have been reported for the US  
14 cohort [Steenland et al., 1999; 2001], two subsets of workers in one of the US plants exposed to  
15 either TCP/2,4,5-T [Collins et al., 2009a (AJE)] or PCP [Collins et al., 2009b (JOEM)], the  
16 Dutch cohort [Hooiveld et al., 1998; Boers et al., 2010] and the New Zealand cohort [t Mannelje  
17 et al., 2005 and McBride et al., 2009]<sup>1</sup>.

18  
19 Update of the multicenter US cohort

20  
21 As Cole and colleagues [2003] have stated, the update of the US study [Steenland et al., 1999;  
22 Steenland et al., 2001] provided no evidence of excess cancer mortality in the whole cohort of  
23 5,172 workers, beyond what was reported in the first follow-up [Fingerhut et al., 1991] (Table 1).  
24 Steenland and colleagues also analyzed mortality in a subcohort of 608 workers with chloracne  
25 (see below), and the results of several analyses based on estimated exposure to TCDD of 3,538  
26 workers. In the 1999 article, the results of the main exposure-response analysis (on unlagged  
27 cumulative exposure score based on internal comparisons) showed a non-significant increase in

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<sup>1</sup> Additional papers published shortly after the 1997 IARC Monograph on the 4-plant German cohort [Becher et al., 1998; Flesch-Janys et al., 1998], and the Danish cohort [Lynge et al., 1998] were based on the same data included in the multicenter study [Kogevinas et al., 1997], and therefore are not reviewed in detail here.

1 risk of all cancer mortality among the workers in the two highest categories of cumulative  
2 exposure, while there was no gradient in risk across the five categories of lower exposure (Figure  
3 2). Because this cohort experienced a small excess mortality from cancer (all cancer  
4 standardized mortality ratio [SMR] 1.13; 95% confidence interval [CI] 1.02, 1.25, essentially  
5 reflecting results of the first follow-up) the SMR in the category of highest cumulative exposure  
6 is statistically significant (SMR 1.60; 95% CI 1.15-1.82).

7  
8 Authors of the update also analyzed cumulative exposure, log-cumulative exposure, average  
9 exposure and applied various lag times (no lag, 5, 10, 15 and 20 years). A cumulative exposure  
10 lagged 15 years, showed a statistically significant association (Figure 3 summarizes the results  
11 based on cumulative serum TCDD level; similar results were obtained for cumulative exposure  
12 score). Mortality from lung cancer was neither increased in the first nor in the updated follow-up  
13 (overall SMR 1.06; 95% CI 0.88, 1.26; Table 1); however, an exposure-response association was  
14 observed in the analysis by log-cumulative exposure score lagged 15 years (p-value for trend  
15 0.03). The excess of NHL and STS mortality in the first follow-up were not confirmed in the  
16 extended follow-up (Table 1): no results have been reported on exposure-response analyses for  
17 these neoplasms. The 2001 article was based on the same population as the 1999 article, but the  
18 results are slightly different and not directly comparable, because the analysis was based on a  
19 different exposure index (cumulative TCDD exposure) and different exposure categories.

#### 20 21 Update of the Midland cohort

22  
23 The updated mortality of two groups of workers in one of the factories of the multicenter US  
24 study located in Midland, MI, was reported separately [Collins et al., 2009a; Collins et al.,  
25 2009b]<sup>2</sup>. The first group of 1,615 workers were exposed to TCDD in the manufacture of TCP or  
26 2,4,5-T from 1948 to 1982 [Collins et al., 2009a (AJE)]. No excess in mortality from all cancer  
27 was observed. Mortality from lung cancer was reduced (SMR 0.7; 95% 0.5, 0.9). The SMR for  
28 NHL was 1.3 (95% CI 0.6, 2.5). Excess mortality was observed for leukemia (SMR 1.9; 95% CI

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<sup>2</sup> An additional report of mortality among the workers in this factory has been published [Bodner et al., 2003].

1 1.0, 3.2; 13 deaths) and STS (SMR 4.1; 95% CI 1.1, 10.5; 4 deaths). The only neoplasm showing  
2 an increased mortality according to estimated TCDD exposure was STS. The second group of  
3 773 workers was involved in the manufacture of PCP [Collins et al., 2009b (JOEM)]. No excess  
4 mortality from all cancer or lung cancer was observed. NHL mortality was increased, based on 8  
5 deaths (SMR 2.4; 95% CI 1.0, 4.7). One death from STS was observed (SMR 2.2; 95% CI 0.0,  
6 12.1). Similar results were obtained when 196 workers with TCP exposure (and included in the  
7 TCP sub-cohort) were excluded.

#### 8 9 Update of the Dutch cohort

10  
11 The Dutch study comprised workers in two factories included in the multicenter IARC study  
12 [Saracci et al., 1991; Kogevinas et al., 1997] Both factories included groups of workers exposed  
13 and unexposed to TCDD. In the most recent publication, relative risks (RR) were calculated by  
14 comparing the mortality in the two groups. A comparison of the results with the previous results  
15 for factory A [Hooiveld et al., 1998] is possible (Table 2); however, in factory B, only 4 deaths  
16 occurred in the first follow-up among exposed workers, and 5 among unexposed workers  
17 [Kogevinas et al., 1992], making a comparison with the updated results difficult.

18  
19 In factory A, the excess risk among exposed workers reported in the early publication [Hooiveld  
20 et al., 1998] was not confirmed in the recent update [Boers et al., 2010]. As mentioned above,  
21 factory A workers were among the groups considered at high TCDD exposure identified in the  
22 IARC 1997 review [IARC, 1997; Steenland et al., 2004]. In a subset of 140 workers in factory  
23 A, employed during an accident resulting in high TCDD exposure, the RR of all cancer was 1.56  
24 (95% CI 0.86, 2.80) compared to the unexposed. No exposure-response gradient was observed  
25 in an analysis on modeled TCDD exposure [Hooiveld et al., 1998]. In a recent follow-up of  
26 factory B, the RR was 1.54 (95% CI 1.00, 2.37) for all cancer mortality, and 1.22 (95% CI 0.56,  
27 2.66) for lung cancer [Boers et al., 2010]. The reason for the important difference in results  
28 between the two reports of mortality among factory A workers (e.g., between the two reports the  
29 number of observed cancer deaths increased 1.6-fold in the unexposed and more than 4-fold in  
30 the exposed; Table 2) is unclear.

31

1 Update of the New Zealand cohort

2

3 The follow-up of a cohort of pesticide manufacturers from New Zealand, included in the IARC  
4 multicenter study [Saracci et al., 1991; Kogevinas et al., 1992; Kogevinas et al., 1997], has been  
5 updated twice since the 1997 IARC Monograph. 't Mannetje updated the cohort through 2000.  
6 The results (Table 3) show a small excess in all cancer mortality compared to the national rate  
7 over time, and increased lung cancer mortality. Duration of employment was not associated with  
8 cancer mortality ['t Mannetje et al., 2005]. McBride et al. (2009) expanded and further updated  
9 this cohort of New Zealand TCP and 2,4,5-T manufacturers. A total of 1599 workers (versus  
10 813 in the previous update) employed between 1969 and 1988 were followed through the end of  
11 2004. Among 1134 exposed workers, the SMR for all cancer mortality was 1.1, (95% CI 0.9,  
12 1.4). The SMR for NHL was 1.6 (95% CI 0.3, 4.7), whereas the lung cancer SMR was 0.8 (95%  
13 CI: 0.4 –1.5). No significant trends with exposure levels were reported [McBride et al., 2009].

14

15

16 Herbicide manufacturers - conclusions

17

18 The results of studies of manufacturers of herbicides potentially contaminated with TCDD,  
19 reported since the 1997 IARC Monograph review, provide weak additional evidence of an  
20 increased all cancer risk among exposed workers. As already noted [Cole et al., 2003], the  
21 update of the US cohort study produced negative results overall; the internal analysis provided  
22 evidence of an increased risk in the category at highest exposure, with a statistically significant  
23 exposure-response association in some of the many analyses performed. Update of the Dutch  
24 cohort did not confirm the association with TCDD exposure previously observed in one factory,  
25 and resulted in a small excess risk in the other factory. The other two studies of workers at high  
26 TCDD exposure (4-plant German cohort and German accident cohort) have not been updated.

27

28 *Application of herbicides potentially contaminated with TCDD*

29

30 The IARC multicenter study included four cohorts of herbicide sprayers from Australia, Canada,  
31 New Zealand and United Kingdom [Saracci et al., 1991; Kogevinas et al., 1992; Kogevinas et

1 al., 1997]. The cohort from New Zealand was independently updated in parallel to the cohort of  
2 manufacturers (see above) [t Mannetje et al., 2005 and McBride et al., 2009]. No excess  
3 mortality from all cancer, lung cancer, or NHL was observed either in the original follow-up of  
4 this cohort or in the two updated reports.

5  
6 In Sweden, 15 foremen, 139 male lumberjacks and 103 female lumberjacks exposed to 2,4,5-T  
7 were followed from 1958 to 1992 [Thörn et al., 2000]. The standardized incidence ratio (SIR)  
8 for all cancer was 2.74 (95% CI 1.00, 5.96) for foremen, 0.72 (95% CI 0.37, 1.25) for male  
9 lumberjacks and 0.82 (95% CI 0.42-1.44) for female lumberjacks. Results for individual cancers  
10 were sparse; two cases of NHL occurred among lumberjacks vs. 0.85 expected.

11  
12 Overall, the studies of herbicide applicators published after 1997 do not support the hypothesis  
13 of an association between indicators of TCDD exposure and cancer risk.

#### 14 15 *Seveso industrial accident*

16  
17 In the population exposed to TCDD as a result of the 1976 accident in the TCP production plant  
18 in Seveso, Italy, updates of cancer mortality (to 2001) and incidence (to 1996), have been  
19 recently reported [Pesatori et al., 2009; Consonni et al., 2008]<sup>3</sup>. This population was divided  
20 among those living in zone A (N=723, median serum TCDD level in 1976, 447.0 ppt), zone B  
21 (N=4821, median serum TCDD 94.0 ppt) and zone R (N=31,643, median TCDD level 48.0 ppt).  
22 Neither study reported an excess of all cancers (SMR 0.69 and 1.03) among residents in any zone  
23 including zone A, the one with highest soil contamination. However, comparison of results of  
24 the mortality report [Consonni et al., 2008] along with the publications available at the time of  
25 the 1997 IARC review [Bertazzi et al., 1996] suggests an excess mortality from all cancer, lung  
26 cancer, and NHL over time, but not STS (no deaths in zones A and B) (Table 4). This apparent  
27 increase reflects a return of observed cases from a slight deficit originally reported to the  
28 expected number. Mortality from multiple myeloma was increased among zone A residents (4  
29 deaths at the latest follow-up, SMR 4.34).

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<sup>3</sup> Additional reports based on follow-up of cancer incidence to 1991 and mortality to 1996 [Bertazzi et al., 2001; Pesatori et al., 2003] are not reviewed in detail.

1  
2 Similarly, neither of the two reports on cancer incidence [Pesatori et al., 2009; Bertazzi et al.,  
3 1993] demonstrated any excess risk of all cancers (or lung cancers) in any zone in either time  
4 period. Between the two time periods there was a small increase in all cancer and lung cancer in  
5 zone A residents (Table 5). This apparent increase largely offsets deficits reported in the earlier  
6 report [Bertazzi et al., 1993]. All cancer incidence was below expectation at the previous follow-  
7 up, but close to expectation at the new follow-up, based on 30 additional observed vs. 25.7  
8 expected cases. For lung cancer there were 5 observed and 3.5 expected cases between the two  
9 study periods. Results on time since accident [Consonni 2008] are broadly consistent with the  
10 results shown in Table 4 and 5 (because most of the 'difference' in Tables 4 and 5 is the results of  
11 the follow-up 15 years after the accident), although the numbers are not identical. The excess in  
12 all cancer mortality is apparent only 20+ years after the accident, i.e., after 1996, the year the  
13 most recent cancer incidence follow-up ended. However the excess mortality from lung cancer  
14 and NHL is apparent also 15-19 years after the accident, without a corresponding increase in the  
15 incidence of these two neoplasms suggesting some inconsistencies between the mortality and the  
16 incidence results. For example, misclassification on death certificates may contribute to an  
17 excess of mortality not supported by a parallel increase in incidence. Etiologically, the incident  
18 cases therefore might provide more valid results.

19  
20 In conclusion, updated surveillance of the Seveso population shows increased all cancer  
21 mortality 15-20 years after exposure among those living in the most contaminated area.  
22 However, this might reflect random variation, because no excess was observed in the most recent  
23 follow-up. Corresponding data on cancer incidence, limited by a shorter duration of follow-up,  
24 offer little support to the mortality results. The number of expected events in the highly  
25 contaminated area remains too small to allow conclusions for specific cancer sites.

26  
27 *Vietnam veterans, with emphasis on risk of prostate cancer*

28 Akhtar and colleagues [2004] investigated cancer incidence and mortality between 1950 and  
29 2000 among 1189 US Air Force veterans who handled Agent Orange, a mixture of herbicides

1 contaminated with TCDD (the Ranch Hand [RH] operation)<sup>4</sup>. Among RH veterans, the SIR for  
2 all cancer was 1.08 (95% CI 0.91, 1.26) and the SMR was 0.68 (95% CI 0.50, 0.91)<sup>5</sup>. The SIR  
3 for lung cancer and lymphopietic neoplasms were not increased. As shown in Table 6, these  
4 results agree with early reports of this cohort, including those available at the time of the 1997  
5 IARC review [Ketchum et al., 1996].

6  
7 The new analysis [Akhtar et al., 2004], revealed an excess incidence of prostate cancer (SIR  
8 1.46; 95% CI 1.04, 2.00) and melanoma (SIR 2.33; 95% CI 1.40, 3.65) among white RH  
9 veterans. However, the incidence of prostate cancer was also increased in a group of 1776  
10 veterans who did not handle Agent Orange (SIR 1.62; 95% CI 1.23, 2.10) as well as veterans  
11 who spent no more than two years in Vietnam. Among the 82% of cohort members who had  
12 serum TCDD measured between 1987 and 1997 there was no evidence of a TCDD exposure-  
13 response relation for all cancer, melanoma, or prostate cancer. Subsequent analyses showed a  
14 RR of 1.0 (95% CI 0.8-1.4) for cancer mortality among RH veterans compared to veterans who  
15 were deployed in units in Southeast Asia not using Agent Orange [Ketchum and Michalek,  
16 2005].

17  
18 A re-analysis was conducted of serum dioxin among the 1482 veterans who did not handle Agent  
19 Orange used as comparison group in the main analyses of the RH study. This analysis suggested  
20 a relation between increasing serum TCDD level and risk of all cancer and melanoma, but not  
21 respiratory or prostate cancer; the risk of prostate cancer, on the other hand, was positively  
22 associated with duration of service in Southeast Asia [Pavuk et al., 2005]. Analysis of prostate  
23 cancer incidence up to 2003 revealed no association with TCDD exposure [Pavuk et al., 2006].  
24 Interpretation of cancer risk among RH Veterans is complicated by the lack of clear  
25 correspondence of the study populations, as well as the shift from an internal comparison of air  
26 force pilots with and without Agent Orange exposure in the early publications to a comparison of  
27 these thoroughly surveyed pilots to the general population in the later publications.

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<sup>4</sup> An additional report based on cancer mortality to 1993 [Michalek et al., 1998] is not reviewed in detail.

<sup>5</sup> These results were derived by summing up observed and expected deaths in White and non-White veterans reported in the original publication.

1  
2 Cypel and Kang [2010] updated to 2005 the analysis by Dalager and Kang [1997] of cancer  
3 incidence and mortality of a group of 2872 Army Chemical Corps (ACC) Vietnam veterans.  
4 ACC units were responsible for handling and spraying herbicides, including Agent Orange,  
5 around the perimeters of military base camps. At the time of the 1997 IARC Monograph review  
6 only an early report of mortality among 894 ACC veterans was available, with 6 observed cancer  
7 deaths vs. 6.6 expected [Thomas and Kang, 1990]. In the whole group of ACC Vietnam  
8 veterans, the SMR for all cancer, based on national mortality rates, was 1.13 (95% CI 0.95, 1.33,  
9 142 deaths), that of respiratory cancer was 1.35 (95% CI 1.03, 1.73, 60 deaths). The  
10 corresponding SMRs were not increased in a comparison group of 2737 non-Vietnam veterans.  
11 The only other outcome category with increased mortality in both groups of veterans was a  
12 miscellaneous group, mainly comprising malignant neoplasms from undefined organs. Results  
13 for NHL were not reported separately, but mortality from lymphoheamatopoietic cancers was  
14 lower than expected (SMR 0.46, 95% CI 0.17, 0.99, 6 deaths). Mortality from non-malignant  
15 respiratory diseases was increased. When a subgroup of 662 Vietnam veterans who reported in  
16 1999-2000 having sprayed herbicides was compared to 811 Vietnam veterans without such  
17 exposure, the RR was 1.00 for all cancer (95% CI 0.53, 1.90), and 1.35 (95% CI 0.53, 3.43) for  
18 respiratory cancer.

19  
20 Chamie and colleagues [2008] studied 13,144 Vietnam veterans from California whose Agent  
21 Orange exposure status was self-reported. Incidence of prostate cancer was ascertained from  
22 1998 to 2006, between 27 and 44 years following exposure. The total number of identified  
23 prostate cancers was 239 among 6,214 exposed and 124 among 6,930 non-exposed veterans  
24 yielding a Cox proportional hazard ratio of 2.87 (95% CI 2.31-3.57). The association was even  
25 stronger for high Gleason grade and for metastatic disease. These results are of potential  
26 concern. Limitations of this study include ambiguities with regards to the reported design and  
27 analysis of the study, increased surveillance of exposed veterans, re-classification of exposure  
28 status at prostate cancer diagnosis, self-report of exposure status after diagnosis, inconsistencies  
29 in tables and results as well as unclear standardization of Gleason scores and clinical staging.

30

1 A case-control study conducted at the Department of Veterans Affairs Medical Center included  
2 47 prostate cancer cases identified from medical record and 142 hospital controls [Giri et al.,  
3 2004]. Agent Orange exposure, based on self-reports from medical records, was reported by 11  
4 cases and 17 controls (OR 2.06, 95% CI 0.81, 5.23). It is unclear whether this information was  
5 collected before or after diagnosis.

6  
7 A prevalence study was conducted among 400 Vietnam veterans referred for prostate biopsy  
8 [Zafar and Terris, 2001]. Thirty-two veterans who reported Agent Orange exposure were  
9 compared to a sample of 96 unexposed veterans. Prostate cancer was detected in 13 exposed and  
10 33 unexposed veterans (p-value for the difference in proportion was 0.15). No association was  
11 found between Agent Orange exposure and disease differentiation or age at diagnosis.

12  
13 In conclusion, cohort studies of Vietnam veterans potentially exposed to TCDD as a contaminant  
14 of herbicides do not suggest an increased risk of all cancer, lung cancer, or NHL. Recent  
15 analyses of RH veterans showed an increased risk of prostate cancer and melanoma, two  
16 neoplasms whose incidence is sensitive to diagnostic intensity. Out of three case-control studies  
17 of prostate cancer among Vietnam veterans, no association was found in the only study with  
18 exposure assessment before diagnosis, which would avoid recall bias. The detection of prostate  
19 cancer strongly depends on the intensity of medical surveillance, and in particular testing with  
20 prostate-specific antigen (PSA). Intensive PSA screening results in the detection of a large  
21 number of early neoplastic lesions of uncertain clinical significance. Differences in prostate  
22 cancer incidence between populations can merely reflect differences in screening practices. In  
23 only one study [Chamie et al., 2008] was severity of prostate cancer taken into consideration.  
24 Studies on prostate cancer mortality, which avoid the potential problem of detection bias, do not  
25 indicate an increased risk of prostate cancer among TCDD-exposed workers: in the pooled  
26 international analysis of cohorts of herbicide manufacturers and sprayers the SMR for prostate  
27 cancer was 1.11 (95% CI 0.81, 1.50) for workers exposed to TCDD and 1.10 (95% CI 0.71,  
28 1.62) for workers not exposed to TCDD [Kogevinas et al., 1997].

29  
30 *Community-based case-control studies of NHL and STS*

31

1 A number of community-based case-control studies included in the 1997 IARC review [IARC,  
2 1997] addressed the risk of NHL, STS and other neoplasms. Exposure to TCDD was based on  
3 either self-reports or classification of occupational data. Since the 1997 IARC Monograph,  
4 various community-based studies of NHL and STS have been reported.

5  
6 A study of 207 cases of Hodgkin lymphoma, NHL and chronic lymphocytic leukemia and 180  
7 population controls was conducted in a rice growing area in Italy, in which phenoxyacetic  
8 herbicides, including 2,4,5-T were widely used in the fields [Fontana et al., 1998]. The OR for  
9 NHL for employment in rice growing was 1.1 (95% CI 0.1, 19) in men and 1.9 (95% CI 0.6, 6.0)  
10 in women. No corresponding results were reported for the other two neoplasms included in the  
11 study.

12  
13 In a study of 110 cases with STS and 227 patients with appendicitis as controls from 16 hospitals  
14 in Finland, the concentration of 17 PCDD/Fs was measured in subcutaneous fat samples  
15 [Tuomisto et al., 2004]. The risk of STS was lower in subjects with TCDD level (expressed  
16 either as WHO-TEQ or 2,3,7,8-TCDD) above the lowest quintile, although no exposure-response  
17 was observed. The OR in the highest vs. lowest quintile was 0.65 (95% CI 0.22, 1.95) for WHO-  
18 TEQ and 0.53 (95% CI 0.20, 1.43) for 2,3,7,8-TCDD.

19  
20 In a study of NHL in four areas of the US including 1321 cases and 1057 population controls,  
21 total dioxin, analyzed in plasma samples from a subset of 100 cases and 100 controls was not  
22 associated with NHL risk (OR for 0.01 mol/g lipid 1.002; 95% CI 0.999, 1.005); the  
23 corresponding OR for dioxin TEQ was 1.94 (95% CI 0.94, 4.00) [De Roos et al., 2005].

24  
25 Overall, community-based studies reported after the 1997 IARC review do not support the  
26 hypothesis of an association between TCDD exposure and risk of NHL or STS.

### 27 28 *TCDD exposure and risk of multiple myeloma*

29  
30 Incidence of, or mortality from multiple myeloma among populations exposed to TCDD have  
31 been reported in eight studies published after the IARC 1997 Monographs [IARC, 1997]. In four

1 of them (Dutch pesticide manufacturers, [Boers et al., 2010], New Zealand pesticide sprayers [t  
2 Mannelje et al., 2005], Swedish forestry workers [Thörn et al., 2000], and RH Vietnam Veterans  
3 [Akhtar et al., 2004]) no incident cases or deaths were observed, with less than one expected in  
4 each of the studies. The results of the other four studies (US pesticide manufacturers [Steenland  
5 et al., 1999], Seveso residents [Consonni et al., 2008], and two of the New Zealand pesticide  
6 manufacturers [t Mannelje et al., 2005 and McBride et al., 2009]) are summarized in Table 7.  
7 Statistically significant excess mortality from multiple myeloma was observed among employees  
8 in the first, but not the second of the updated New Zealand pesticide manufacturers cohort, as  
9 well as among residents in Seveso zone A. The reduced number of multiple myeloma cases  
10 (from 3 to 2) in the New Zealand group suggests that one of the cases originally classified as a  
11 multiple myeloma was subsequently reclassified, although this is not clear from the paper.  
12 Although results suggest an increased risk of multiple myeloma among people exposed to TCDD  
13 (at least for the cohorts of US pesticide manufacturers and Seveso zone A residents, the results  
14 have become stronger in the most recent publications), cautious interpretation is warranted due to  
15 the lack of detailed results from studies with no cases observed, and the possibility of selective  
16 reporting of positive results, all of which are based on small numbers of cases. A recent review  
17 of the epidemiology of multiple myeloma reached similar conclusions [Alexander et al., 2007].  
18

#### 19 *TCDD exposure and risk of breast cancer*

20  
21 The risk of breast cancer from exposure to TCDD has been reviewed in detail by several authors  
22 [Laden and Hunter, 1998; Calle et al., 2002; Brody et al., 2007] as well as IARC [IARC, 1997]  
23 with no consistent evidence of an increased risk. In particular, no excess breast cancer incidence  
24 or mortality was observed in the population-based studies of Seveso residents (Table 8) [Bertazzi  
25 et al., 1993; Bertazzi et al., 1996; Consonni et al., 2008]. An independent study was conducted  
26 in a cohort of 981 women living in zones A and B, with serum samples collected during 1976-  
27 1981 [Warner et al., 2002]. During 1996-1998 these women were asked whether they had been  
28 diagnosed with cancer, and self-reported cases were validated against pathology and medical  
29 records. The median serum TCDD of 15 cases of breast cancer (71.8 ppt) was higher than that of  
30 the study population (55.1 ppt). The hazard ratio for 10-fold increase in serum TCDD level was

1 2.1 (95% CI 1.0, 4.6). Limitations of this study include back-extrapolation of serum TCDD level  
2 for many participants, and the lack of multivariate adjustment for potential confounders.

3  
4 A study of 30,454 wives of farmers from Iowa and North Carolina enrolled in 1993-1997 in the  
5 Agriculture Health Study (AHS) and followed up to 2000 identified 309 cases of breast cancer  
6 [Engel et al., 2005]. Detailed information on the use of 50 pesticides by the women and their  
7 husbands was obtained at enrollment via questionnaire. Less than 1% of cases and 0.7% of non-  
8 cases ever used 2,4,5-T, the herbicide most likely contaminated by TCDD (no risk estimate  
9 available). The RR for use of 2,4,5-T by husbands of women who did not use pesticides was 1.3  
10 (95% CI 0.9, 1.9).

11  
12 Because occupational cohorts of TCDD-exposed workers included few women, results on breast  
13 cancer were limited by small numbers. Community-based case-control studies of breast cancer  
14 were limited by imprecise exposure assessment and low prevalence of exposure to dioxin above  
15 background [Adami et al., 1995; Calle et al., 2002]. Two studies comparing TCDD level in  
16 breast adipose tissue among women with cancer and benign disease reported no statistically  
17 significant difference [Hardell et al., 1996; Reynolds et al., 2005]. In a recent study of 104 male  
18 breast cancers and 1901 community controls from eight European countries the OR for estimated  
19 occupational exposure to PCB and dioxin below the median was 0.9 (95% CI 0.3, 2.6), that for  
20 exposure above the median was 1.6 (95% CI 0.7, 3.7) [Villeneuve et al., 2010].

21  
22 Overall, the evidence linking TCDD exposure to breast cancer risk is inconclusive at present: a  
23 conclusion that is consistent with previous reviews [Adami et al., 1995; Calle et al., 2002].

#### 24 25 *Studies of chloracne patients*

26  
27 Groups of individuals who developed chloracne following high TCDD exposure have been  
28 studied in the cohorts of US (N=608), German (N=113), and Dutch herbicide manufacturers  
29 (N=29), as well as Seveso residents (N=182). Among US chloracne patients, 73 cancer deaths  
30 occurred (SMR 1.25; 95% CI 0.98, 1.57), including 30 from lung cancer (SMR 1.45; 95% CI  
31 0.98, 2.07), 6 from lymphohematopoietic neoplasms (SMR 1.13; 95% CI 0.41, 2.46) and 3 from

1 STS (SMR 11.32; 95% CI 2.33, 33.10) [Steenland et al., 1999]. Among 113 German chloracne  
2 patients, 18 cancer deaths were observed 20 or more years since first exposure (SMR 1.90; 95%  
3 CI 1.13, 3.00), including 6 from digestive cancers (SMR 1.83; 95% CI 0.67, 3.98) and 7 from  
4 respiratory cancers (SMR 2.42; 95% CI 0.97, 4.99) [Ott and Zober, 1996]. Cancer risk was  
5 higher among patients with moderate chloracne than among those with severe disease. No  
6 cancer deaths or cases were identified among Seveso chloracne patients [Consonni et al., 2008;  
7 Pesatori et al., 2009]. The number of expected cases or deaths was not provided, but it is likely  
8 to be low because of the young age of these patients [Baccarelli et al., 2005]. No cancer deaths  
9 were reported among Dutch chloracne patients [Hooiveld et al., 1998].

## 11 Discussion

13 We compared the current evidence of cancer risk among individuals exposed to TCDD with the  
14 results available at the time of the 1997 IARC Monograph. Since 1997, the strongest evidence  
15 for a carcinogenic effect comes from the exposure-response re-analysis of all cancer mortality  
16 among herbicide manufacturing cohort, in which an association was apparent at high doses, or  
17 when lagging of exposure was applied [Steenland et al., 1999; Steenland et al., 2001]. Supportive  
18 evidence comes also from the updated mortality follow-up of the Seveso population [Consonni et  
19 al., 2008]. In contrast, however, other results published since 1997 - including the main SMR  
20 analysis of the US herbicide manufacturing cohort [Steenland et al., 1999], the updated mortality  
21 analysis of one of the largest plants included in the US cohort [Collins et al., 2008a; Collins et  
22 al., 2008b], the cancer incidence follow-up of the Seveso population [Pesatori et al., 2009], the  
23 update of the Dutch cohort of herbicide manufacturers [Boers et al., 2010], and the studies of  
24 Vietnam veterans [Akhtar et al., 2004; Cypel and Kang, 2010] - do not support an association  
25 between TCDD exposure and cancer risk.

27 Among the four studies with highest TCDD exposure, given the greatest weight in the 1997  
28 IARC review [IARC, 1997], updated results were reported for the US multicenter cohort  
29 [Steenland et al., 1999; Steenland et al., 2001] and the Dutch cohort [Boers et al., 2010]. While  
30 the US cohort added evidence in favor of an association between TCDD exposure and cancer  
31 risk, the Dutch cohort add evidence against it. While the hypothesis that TCDD is a human

1 carcinogen is plausible based on experimental evidence, in our opinion the weak and  
2 contradictory evidence from epidemiologic studies does not support a causal association.

3  
4 With respect to results for individual neoplasms, the updated mortality analysis of the Seveso  
5 population suggested an increased risk of lung cancer [Consonni et al., 2008], which was not  
6 confirmed in the update of any other study. As for NHL, the updates of the mortality analyses of  
7 Seveso population [Consonni et al., 2008] and New Zealand herbicide sprayers suggested an  
8 increased risk, which was not confirmed in the updates of the US multicenter study [Steenland et  
9 al., 1999], the Dutch study [Boers et al., 2010], or the Ranch Hand study [Akhtar et al., 2004].  
10 An increased mortality from STS was suggested in the updated mortality analysis of the Midland  
11 cohort [Collins et al., 2008a], but not in the analysis of the larger US multicenter cohort  
12 [Steenland et al., 1999] or in the other studies.

13  
14 Because human and experimental studies on TCDD and cancer risk have continued for more  
15 than 40 years, this area of research is heavily charged with political and emotional issues. In  
16 such circumstances, specific types of bias might occur, in addition to those affecting  
17 epidemiologic studies in general. These include publication, diagnostic and reporting biases.  
18 Selective reporting of 'positive' results is plausible because of the great concern that TCDD is an  
19 environmental carcinogen. As has been shown [Boffetta et al., 2008], early studies on NHL risk  
20 might have been subject to publication bias. To assess publication bias by identifying  
21 unpublished studies is difficult. In the case of TCDD and cancer there is at least one such  
22 example: a case-control study of STS and NHL conducted in the 1990s in Ho Chi Min City,  
23 Vietnam, of possible association with Agent Orange exposure during the Vietnam War  
24 [Kramarova et al., 1998]. To the best of our knowledge no results have been reported.  
25 Furthermore, apart from the findings on breast cancer mentioned above [Engel et al., 2005], and  
26 a brief mention of null results in a study of prostate cancer [Alavanja et al., 2003], to our  
27 knowledge no results on TCDD-contaminated pesticides have been reported from the AHS, the  
28 most extensive study of agricultural exposures and cancer conducted to date.

29

1 Bias might also arise because several of the cohorts have been subject to intensive medical  
2 surveillance, possibly resulting in over-diagnosis as compared to the unexposed populations used  
3 for comparison. This potential form of bias would be particularly relevant for neoplasms whose  
4 detection is highly dependent on diagnostic intensity (e.g., melanoma, and thyroid and prostate  
5 cancer [Adami, 2010]), and for neoplasms suspected to be linked to dioxin exposure, which are  
6 subject to diagnostic uncertainties, such as STS and NHL, as has been suggested for pleural  
7 mesothelioma in cohorts exposed to asbestos [Siemiatycki 1998]. However, no direct evidence  
8 is available in favor of, or against, this form of bias.

9  
10 Two of the most informative studies (US herbicide manufacturers and Seveso residents) suggest  
11 an association with all cancer only after a latency of 15 or 20 years [Steenland et al., 1999;  
12 Steenland et al., 2001; Consonni et al., 2008; Pesatori et al., 2009]. The authors interpret these  
13 studies as supporting a causal association between TCDD and cancer risk. TCDD exerts its  
14 carcinogenic effect in experimental systems through the Ah receptor, which activates cell  
15 proliferation [Safe, 2001]. This mechanism has been invoked to explain an unspecific action on  
16 risk of all cancer [Mandal 2005; Walker 2007]. However, a long latency between exposure and  
17 cancer is a hallmark of agents acting through DNA damage. Cheng and colleagues [2006] have  
18 proposed to solve the apparent inconsistency by assuming that cell proliferating activity of  
19 TCDD should be sustained for a long follow-up. Hence, individuals with less than 10 or 15  
20 years since first exposure would not have acquired a sufficiently long exposure. However,  
21 known carcinogens acting via other late-stage mechanisms (e.g., hormones) do not support this  
22 notion.

23  
24 A more fundamental challenge in the evaluation of TCDD as a human carcinogen is the  
25 emphasis on risk of all cancer rather than specific neoplasms or a specific subset of neoplasms.  
26 As already explained in a previous review [Cole et al., 2003], we have not found convincing  
27 evidence for a central role of the Ah receptor in dioxin-related carcinogenesis. Hence, the  
28 ubiquitous presence of the Ah receptor should not guide the interpretation of the epidemiologic  
29 evidence we have summarized above. Indeed, a non organ-specific carcinogenicity of TCDD  
30 would represent a unique feature in cancer epidemiology. Known non-genotoxic carcinogenic

1 agents, including those acting through pathways present in all organs and tissues (e.g.,  
2 overweight/obesity [WCRF, 2007]), target only one or a few specific organs.

3  
4 An increase in all cancer risk has not been clearly shown in animal carcinogenicity tests. The  
5 reader is referred to previous reviews [IARC, 1997; EPA, 2003; Knerr 2006] and results of  
6 recent studies [NTP, 2006]. TCDD causes specific tumors in mice (hepatocellular carcinoma,  
7 skin tumors, and lymphoma in multiple studies, as well as thyroid and lung tumors in single  
8 studies), rats (hepatocellular carcinoma, cholangiocarcinoma, and lung and oral cavity tumors in  
9 multiple studies, as well as tumors of the thyroid, skin, and uterus in single studies), and hamster  
10 (skin tumors in multiple studies). TCDD is therefore classified as an experimental carcinogen  
11 [IARC, 1997; EPA, 2003; Baan et al., 2009]; however, these evaluations are based on the  
12 evidence of increased incidence of groups of specific tumors (and in particular those commonly  
13 occurring in mice and rats), and not on all-cancer incidence in experimental animals.

14  
15 Consistency of results is a key criterion for assessing causality. Shifting the emphasis from  
16 specific cancers to all cancer allows for the possibility that different types of cancer-specific  
17 biases affecting various studies (e.g., residual confounding by different risk factors) would  
18 generate an apparently consistent increase in all cancer risk. Protection from bias should  
19 therefore be subject to more stringent scrutiny when evaluating an epidemiological hypothesis  
20 that some risk factor causes all cancers.

21  
22 In addition, the hypothesis of an increase in all cancer risk would not dispense with the  
23 requirement that cancer-specific results have to be consistent across studies, especially in the  
24 case of more common cancers, such as lung cancer, for which random fluctuation can hardly be  
25 invoked as cause for the lack of consistency. For none of the specific neoplasms is there a  
26 consistent pattern showing an increased risk in populations exposed to TCDD.

27  
28 In some of the epidemiologic studies, an exposure-response is suggested, in the absence of an  
29 overall increase in cancer risk. In these circumstances, the apparent trend arises from a  
30 comparison of exposure categories with SMRs distributed below and above the null value of 1.0.  
31 One example is lung cancer mortality in the cohort of US chemical workers: the overall SMR

1 was 1.06 (95% CI 0.88, 1.26), and the p-value of test for trend in an internal analysis by  
2 cumulative exposure score (log-transformed and lagged 15 years) was 0.03 [Steenland 1999]. In  
3 this analysis, the SMR of three of the seven exposure categories was below 1.0.

4  
5 A further problem in the interpretation of the epidemiologic studies of TCDD exposure and  
6 cancer risk arises from the fact that mortality was used as outcome measure in several of them.  
7 In addition to possible differential misclassification of causes of death between exposed and  
8 unexposed subjects, there are other issues, including confounding by different quality of  
9 treatment among exposed and unexposed due to different access to health care. Another problem  
10 in population-based studies such as the cohort of Seveso residents is that mortality analysis is not  
11 incidence based. Hence, there is a contribution to the mortality from cases that were already  
12 prevalent at the time of exposure. Conversely, when occupational cohorts are compared with the  
13 general population a healthy worker effect is quite likely due to a lower prevalence of existing  
14 cancer among those who are occupationally active.

15  
16 In conclusion, the carcinogenicity of TCDD may be plausible on the basis of animal experiments  
17 conducted at high doses, but the epidemiological evidence falls far short from conclusively  
18 demonstrating such a relationship in humans. In the case of complex data such as the  
19 epidemiologic studies on TCDD exposure and cancer risk, it is important to consider all the  
20 evidence, and not just selected components which might support one particular hypothesis. The  
21 use of mechanistic data to link experimental and human results is justified when there is a  
22 specific and strong correspondence between the different systems such as presence of the same  
23 DNA damages and mutations in the same cancer-related genes in both human tumors,  
24 experimental animals and in-vitro systems, as in the case of benzo-a-pyrene, alterations in *TP53*  
25 gene, and lung cancer [IARC, 2010]. The exercise becomes questionable, however, when  
26 weaker data are used and inconsistencies are ignored. Furthermore, TCDD is a likely example of  
27 how epidemiologic studies in a controversial area might be particularly susceptible to multiple  
28 types of bias. These considerations support our conclusion that the epidemiological evidence of  
29 carcinogenicity of TCDD in humans is not "sufficient" and remains "limited."

30  
31

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2

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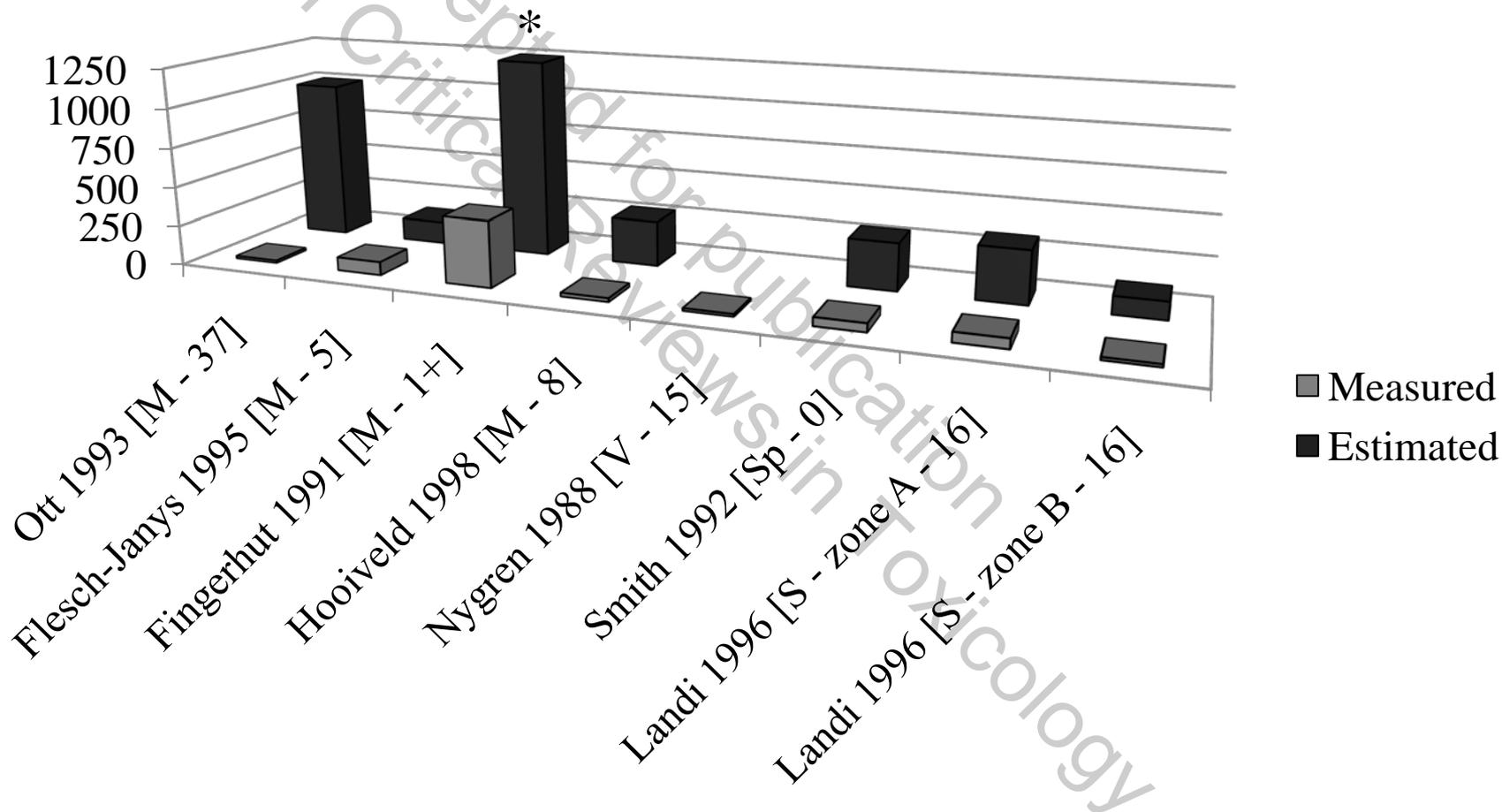
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25

Figure 1. Measured and estimated blood dioxin level (ppt) in selected studies



\* 2,000 ppt. In square brackets, type of population (M, pesticide manufacturers; V, Vietnam Veterans, Sp, pesticide sprayers, S, Seveso) and average years between measured and estimated level

Figure 2. Relative risk of all cancer mortality in the US cohort, by categories of cumulative dioxin exposure

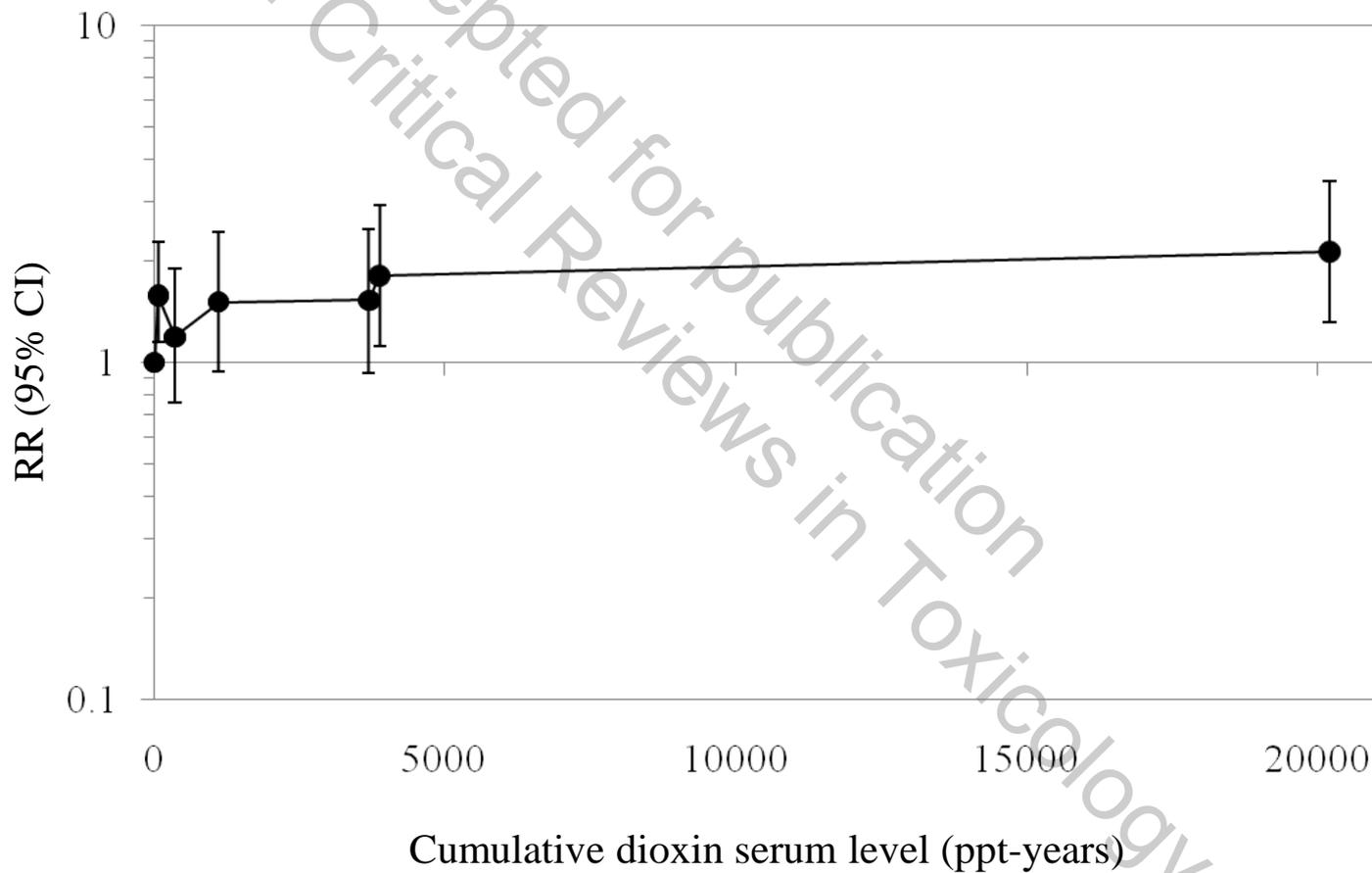


Figure 3. Relative risk of all cancer mortality in the US cohort, by categories of cumulative dioxin serum level, lagged 15 years

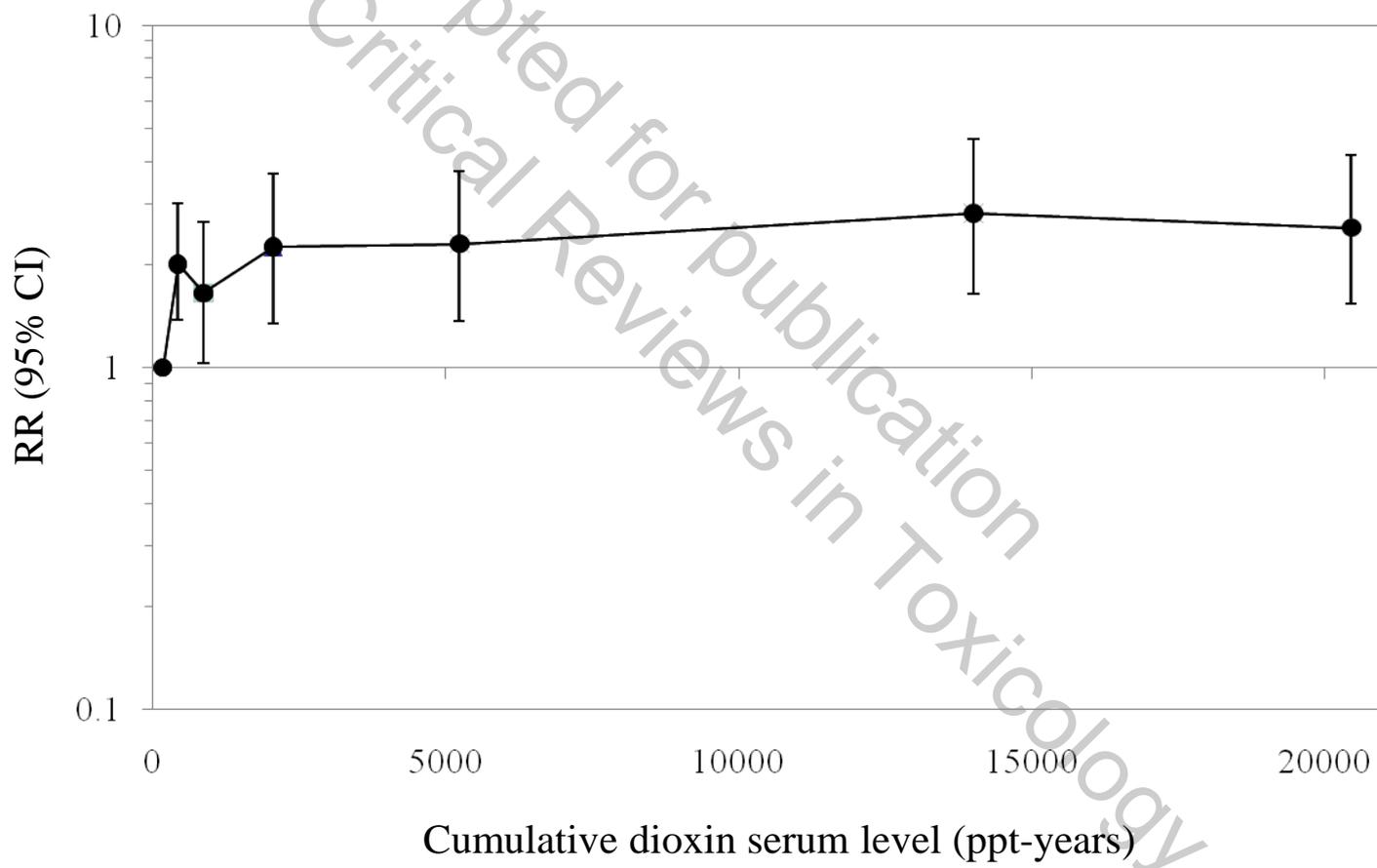


Table 1. Comparison of results of the first and the second follow-up of US pesticide manufacturing workers (modified from Cole et al., 2003).

Publication	Follow-up	All cancers		Lung cancer		NHL		STS	
		O/E	SMR	O/E	SMR	O/E	SMR	O/E	SMR
Fingerhut et al., 1991	1942-1987	265/229.9	1.15	89/80.1	1.11	10/7.3	1.37	4/1.2	3.38
Steenland et al., 1999	1942-1993	377/333.6	1.13	125/117.9	1.06	12/10.9	1.10	4/1.7	2.32
Difference		<i>112/103.7</i>	<i>1.08</i>	<i>36/37.8</i>	<i>0.95</i>	<i>2/3.6</i>	<i>0.56</i>	<i>0/0.5</i>	<i>0</i>

O, observed deaths; E, expected deaths; SMR, standardized mortality ratio, NHL, non-Hodgkin lymphoma; STS, soft-tissue sarcoma  
 Figures in italics were derived from raw data reported in the papers

Table 2. Comparison of results of the first and the second publication of pesticide manufacturing workers from the Netherlands (factory A).

Publication	Follow-up	N workers E/U	All cancers		Lung cancer		NHL	
			N E/U	RR	N E/U	RR	N E/U	RR
Hooiveld et al., 1998	1955-1991	549/482	51/7	4.1	14/1	6.5	3/1	1.7
Boers et al., 2010	1955-2006	539/482	81/31	1.31	20/7	1.15	4/3	0.92

E, exposed; U, unexposed, N, number of cases; RR, relative risk, NHL, non-Hodgkin lymphoma

Table 3. Comparison of results of the first and the second follow-up of pesticide manufacturing workers from New Zealand.

Publication	Follow-up	N workers	All cancers		Lung cancer		NHL	
			O/E	SMR	O/E	SMR	O/E	SMR
Kogevinas et al., 1992	1969-1987	782	15/11.99	1.25	2/3.56	0.56	0/0.32	0
't Mannetje et al., 2005	1969-2000	813	43/34.6	1.24	12/8.8	1.37	1/1.1	0.87
Difference			<i>28/22.6</i>	<i>1.24</i>	<i>10/5.2</i>	<i>1.92</i>	<i>1/0.8</i>	<i>1.25</i>
McBride et al., 2009	1969-2004	1134	196/196	1.0	61/55.5	1.1	3/1.9	1.6
Difference			<i>181/184</i>	<i>1.0</i>	<i>59/51.9</i>	<i>1.1</i>	<i>3/1.6</i>	<i>1.9</i>

O, observed deaths; E, expected deaths; SMR, standardized mortality ratio, NHL, non-Hodgkin lymphoma  
 Figures in italics were derived from raw data reported in the papers

Table 4. Comparison of results of the last and next-to-last follow-up of residents in Seveso - cancer mortality

Publication	Follow-up	All cancers		Lung cancer		NHL	
		O/E	SMR	O/E	SMR	O/E	SMR
Zone A							
Bertazzi et al., 1996	1976-1991	<i>16/23.3</i>	<i>0.69</i>	<i>4/4.5</i>	<i>0.89</i>	<i>0/0.2</i>	<i>0</i>
Consonni et al., 2008	1976-2001	42/40.8	1.03	11/8.7	1.26	3/0.9	3.35
Difference		<i>26/17.4</i>	<i>1.49</i>	<i>7/4.2</i>	<i>1.65</i>	<i>3/0.7</i>	<i>4.44</i>
Zone B							
Bertazzi et al., 1996	1976-1991	<i>152/147.9</i>	<i>1.03</i>	<i>36/31.7</i>	<i>1.14</i>	<i>2/2.5</i>	<i>0.79</i>
Consonni et al., 2008	1976-2001	244/265.2	0.92	62/55.9	1.11	7/5.7	1.23
Difference		<i>92/117.3</i>	<i>0.78</i>	<i>26/24.2</i>	<i>1.07</i>	<i>5/3.2</i>	<i>1.58</i>
Zone R							
Bertazzi et al., 1996	1976-1991	<i>1008/1120.0</i>	<i>0.90</i>	<i>205/224.6</i>	<i>0.91</i>	<i>18/18.0</i>	<i>1.00</i>
Consonni et al., 2008	1976-2001	1848/1905.2	0.97	383/390.8	0.98	40/40.4	0.99
Difference		<i>840/785.2</i>	<i>1.07</i>	<i>178/166.3</i>	<i>1.07</i>	<i>22/22.4</i>	<i>0.98</i>

O, observed deaths; E, expected deaths; SMR, standardized mortality ratio, NHL, non-Hodgkin lymphoma  
 Figures in italics were derived from raw data reported in the papers

Table 5. Comparison of results of the last and next-to-last follow-up of residents in Seveso - cancer incidence

Publication	Follow-up	All cancers		Lung cancer		NHL	
		O/E	SIR	O/E	SIR	O/E	SIR
Zone A							
Bertazzi et al., 1993	1977-1986	<i>14/17.0</i>	0.82	<i>2/2.7</i>	0.74	<i>0/0.4</i>	0
Pesatori et al., 2009	1977-1996	44/42.7	1.03	7/6.3	1.12	1/1.3	0.80
Difference		<i>30/25.7</i>	1.17	<i>5/3.5</i>	1.41	<i>1/0.9</i>	1.18
Zone B							
Bertazzi et al., 1993	1977-1986	<i>112/114.1</i>	0.98	<i>18/17.8</i>	1.01	<i>4/2.4</i>	1.65
Pesatori et al., 2009	1977-1996	270/270.0	1.00	37/38.5	0.96	12/7.9	1.51
Difference		<i>158/155.9</i>	1.01	<i>19/20.8</i>	0.91	<i>8/5.5</i>	1.47
Zone R							
Bertazzi et al., 1993	1977-1986	<i>765/850.0</i>	0.90	<i>112/130.7</i>	0.86	<i>22/17.6</i>	1.25
Pesatori et al., 2009	1977-1996	1808/1883.3	0.96	280/269.2	1.04	49/54.4	0.90
Difference		<i>1043/1033.3</i>	1.01	<i>168/138.6</i>	1.21	<i>27/36.9</i>	0.73

O, observed cases; E, expected cases; SIR, standardized incidence ratio, NHL, non-Hodgkin lymphoma  
 Figures in italics were derived from raw data reported in the paper

Table 6. Comparison of results of last and next-to-last follow-up of Ranch Hand veterans - cancer mortality

	N	Follow-up	All cancers		Lung cancer		NHL	
			O/E	SMR	O/E	SMR	O/E	SMR
Ketchum et al., 1996	1261	1966-1993	30/33.3	0.90	12/13.0	0.92	1/0.7	1.43
Akhtar et al., 2004	1061*	1966-2000	45/61.7	0.73	21/24.1**	0.87	6/6.3***	0.95

O, observed deaths; E, expected deaths; SMR, standardized mortality ratio, NHL, non-Hodgkin lymphoma

\* Whites only; \*\* respiratory cancer; \*\*\* lymphohematopoietic neoplasms

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Table 7. Relative risk of multiple myeloma mortality in selected studies of populations exposed to dioxin - Results reported before and after the 1997 IARC Monograph [IARC, 1997]

Population	Publication before the 1997 IARC Monograph			Publication after the 1997 IARC Monograph				
	Reference	O	SMR	95% CI	Reference	O	SMR	95% CI
US pesticide mft	Fingerhut 1991	5	1.6	0.5, 3.9	Steenland 1999	10	2.07	0.99, 3.80
NZ pesticide mft	Kogevinas 1992	1	6.25	0.16, 34.8	't Mannetje 2005	3	5.51	1.14, 16.1
					McBride 2009**	2	2.2	0.2, 8.1
Seveso, Zone A	Bertazzi 1996*	0	0	<i>0, 18.4</i>	Consonni 2008***	2	4.34	1.07, 17.5
Seveso, Zone B	Bertazzi 1996*	5	3.3	<i>1.1, 7.7</i>	Consonni 2008***	5	1.68	0.69, 4.10

O, observed deaths; mft, manufacturers; SMR, standardized mortality ratio; CI, confidence interval

\* Similar results in the cancer incidence analysis [Bertazzi 1993]

\*\* Unclear why the expanded and updated cohort [Mc Bride et al., 2009] has one less case of the earlier cohort ['t Mannetje et al., 2005]

\*\*\* Similar results in the cancer incidence analysis [Pesatori 2009]

Figures in italics were derived from raw data reported in the paper

Table 8. Risk of female breast cancer among residents in Seveso

	Incidence*			Mortality**		
	O	SIR	95% CI	O	SMR	95% CI
Zone A	8	1.43	0.71, 2.87	2	0.60	0.15, 2.41
Zone B	30	0.85	0.59, 1.22	13	0.65	0.37, 1.12
Zone R	249	1.00	0.88, 1.15	133	0.87	0.73, 1.05

O, observed cases/deaths; SIR, standardized incidence ratio, SMR, standardized mortality ratio; CI, confidence interval

\* Follow-up 1977-96 [Pesatori et al., 2009]

\*\* Follow-up 1976-2001 [Consonni et al., 2008]