CHAPTER 7. EPIDEMIOLOGY/HUMAN DATA
PART A: CANCER EFFECTS

7.1. INTRODUCTION

Animal bioassay data provide substantial presumptive evidence of the human carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (see Chapter 6), but confirmation must come from well-designed human studies. TCDD is a multiorgan carcinogen in animals. Target organs include the liver, thyroid, lung, skin, and soft tissues. There is no assumption of target tissue concordance from animals to humans, although site concordance would add support to a causal interpretation. This chapter reports on the cancer epidemiology evidence of TCDD and its congeners.

This review and analysis of the epidemiologic literature on dioxins and cancer begins by defining the scope of chemical exposures, cancers, and research reports to be considered. Then, following a brief summary of previous EPA assessments of epidemiologic literature, a description is given of the methods used in the present review. The original research reports are then discussed in four groups: (1) follow-up studies of chemical manufacturing and processing workers, (2) case-control studies in general populations, (3) studies of pulp and paper mill workers, and (4) other studies (including studies of pesticide applicators; Vietnam veterans with potential exposure to Agent Orange; residents of Seveso, Italy, exposed to TCDD during an accidental explosion of a phenoxy herbicide factory; and victims of contaminated rice oil poisonings). Because the discussions of the first two groups of studies are relatively lengthy, brief summaries are given at the end of each of those sections. Conclusions are drawn following an overall discussion of all the studies.

7.2. SCOPE

Epidemiologic studies of cancer among persons exposed to TCDD and other polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) are included in this review. Primary emphasis is placed on studies with exposures to TCDD itself, occurring primarily in the manufacture and use of 2,4,5-trichlorophenol, hexachlorophene, and the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Because exposures to 2,4,5-T and 2,4-dichloroacetic acid (2,4-D) often occur among the same groups who manufacture and use these herbicides, some studies of groups exposed only to 2,4-D are also included. Exposure to lower-chlorinated PCDDs (dichlorinated and trichlorinated isomers) may occur in the manufacture and use of 2,4-D. Also included are studies of groups exposed to higher-chlorinated PCDDs (i.e., the hexachlorinated, heptachlorinated, and octachlorinated isomers), occurring primarily in the manufacture and use of pentachlorophenol (PCP) and in the paper and pulp industries.

A major weakness in nearly all of these studies is the lack of good exposure information. Most studies rely solely on interviews and questionnaires of work history to ascertain exposure surrogates. Until recently, there was little, if any, verification of actual internal dose of these compounds. Some studies use chloracne as a surrogate for exposure to TCDD. This presence of chloracne usually indicates a high dose effect. The absence of chloracne does not indicate lack of exposure. Some of the recent cohort studies of chemical production workers (Fingerhut et al., 1991; Becher et al., 1996; Flesch-Janys, et al., 1995, 1996, 1999; Ott et al., 1996; Manz et al., 1991; Zober et al., 1990) do provide estimates of TCDD exposure in cohort samples via serum blood levels taken decades after cessation of exposure. However, these estimates have been chiefly used to provide support for preselected qualitative categories of estimated exposure. But these can also be used to determine possible dose-response trends and estimate the risk of cancer to populations with low-level exposure to TCDD (see Chapter 8). Measures of exposure by individual study have been discussed.

At the time of EPA's last review in 1988, evidence of human carcinogenicity of TCDD and the phenoxy herbicides focused on soft tissue sarcomas (STSs) and malignant lymphomas. Consequently, this report will update the strengths and weaknesses of the evidence pertaining to these cancers. But emerging as a more important topic are evaluations of the evidence of cancer at other sites. The case-control studies reviewed for EPA's last analysis generally considered herbicide applicators with potential exposures to both 2,4-D and 2,4,5-T. Recent case-control studies of U.S. farmer groups in which exposure to 2,4-D and 2,4,5-T can be separated (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) provide a validation mechanism to separate potential effects of these herbicides and, possibly, their different PCDD contaminants. Thus, these and other recent studies (Hardell and Eriksson, 1988; Eriksson et al., 1990; Woods et al., 1987) will be reviewed and compared with those discussed in EPA's earlier reports.

Five recent cohort mortality studies (Steenland et al., 1999; Fingerhut et al., 1991; Becher et al., 1996; Flesch-Janys et al., 1995, 1998, 1999; Manz et al., 1991; Ott et al., 1996; Zober et al., 1990; Kogevinas et al., 1997; Saracci et al., 1991; Hooiveld et al., 1996, 1998) totaling more than 23,000 workers potentially exposed to TCDD and/or phenoxy herbicides/chlorophenols provide a more important database for analyzing cancer effects and are discussed in Section 7.5. The first three of these, and especially the large U.S. study of Fingerhut et al. (1991) and its update by Steenland et al. (1999), as well as the Dutch cohort study by Hooiveld et al. (1996, 1998), are considered to be the most important new studies in the field of TCDD cancer epidemiology because of their attention to cohort selection, to TCDD exposures or exposure surrogates (chloracne), and to the fact that exposure to dioxin is associated with an increasing risk of cancer at multiple sites. The fifth study (Saracci et al., 1991; Kogevinas et al., 1997) encompasses all the occupational cohorts that are referenced here. Although it has the largest

cohort, it has less reliable information on the TCDD-exposed subcohort and only a little information that would allow a quantitative estimate of exposure. Two other studies of phenoxy acid manufacturers are included (Lynge, 1985, 1993, 1998; Coggon et al., 1986), but their usefulness is limited because of the low unsubstantiated exposure to TCDD. Also included is a study of occupationally exposed women (Kogevinas et al., 1993) who had probable exposure to TCDD.

Four recent cohort studies of workers in the pulp and paper mill industry are also included (Robinson et al., 1986; Jäppinen et al., 1987; Henneberger et al., 1989; Hertzman et al., 1997) because of potential for worker exposure to higher-chlorinated PCDDs but not hexa-, hepta-, or octaphenoxy herbicides, and one with exposure to hexa-, hepta-, and octochlorinated dioxin isomers. However, none of these studies provide any additional information about which PCDD exposures were likely, and these studies are not given much weight.

Studies of Vietnam veterans potentially exposed to TCDD in Agent Orange are reviewed briefly, with only two (Ketchum et al., 1996, 1999; Michalek et al., 1990, 1998) judged to have sufficient information on potential TCDD exposure to be useful for analysis of cancer. Also, the recent studies of cancer in Seveso, Italy, residents are discussed (Bertazzi et al., 1998, 1997, 1992, 1993, 1989a,b; Landi et al., 1998; Consonni et al., 1999; Mocarelli et al., 1991; Pesatori et al., 1999, 1992); these studies provide some exposure data, but the cancer response analysis is limited because of inadequate follow-up time (maximum of 20 years).

Finally, the studies of the rice oil poisonings of residents in Taiwan and Japan with polychlorinated biphenyl (PCB) and PCDF contaminants are reviewed (Kuratsune et al., 1988, 1975; Chen et al., 1980; Koda and Masuda, 1975; Rogan et al., 1988). Even though these poisoned oils did not contain TCDD, they did contain many TCDD-like congeners currently considered by EPA to have carcinogenic potential that can be compared to TCDD. Also, certain dioxin-like PCBs are suspected human carcinogens on the basis of their receptor-binding characteristics and animal studies. Non-dioxin-like PCBs are known animal carcinogens.

Only follow-up and case-control studies are considered in this review. Case reports, other clinical observations, and prevalence surveys are excluded. The review is restricted to studies that have been published or are about to be published and that are available in the open scientific literature. Prepublication reports and studies published only in abbreviated form (as well as abstracts or letters to editors) are included only where they supplement the published articles. These restrictions limit the review to studies that have received at least a minimum of peer review and that have been described fully enough to permit a thorough assessment of materials, methods, and results.

7.3. PREVIOUS EPA REVIEWS

In the Health Assessment Document for Polychlorinated Dibenzo-*p*-Dioxins, dated September 1985 (U.S. EPA, 1985), the majority of the epidemiology studies pertained to groups of herbicide applicators with potential exposure to phenoxy acids and/or chlorophenols. In that report, the analysis emphasized case-control studies of STSs and non-Hodgkin's lymphoma (NHL). That report concluded that the epidemiologic research available at that time provided "limited evidence for the carcinogenicity of phenoxy acids and/or chlorophenols in humans. However, with respect to the dioxin impurities contained therein, the evidence for the human carcinogenicity for TCDD based on the epidemiologic studies was only suggestive because of the difficulty of evaluating the risk of TCDD exposure in the presence of the confounding effects of phenoxy acids and/or chlorophenols." In its next report, the review draft dated June 1988 of A Cancer Risk-Specific Dose Estimate for TCDD (U.S. EPA, 1988), the focus was essentially the same, and EPA concluded that "the human evidence supporting an association between exposure to TCDD and cancer is considered inadequate."

7.4. REVIEW METHODS

This review will follow the spirit of the EPA Risk Assessment Guidelines of 1986 (U.S. EPA, 1987) by considering alternative explanations for results observed in epidemiologic studies. These explanations fall into the general categories of causality, chance, bias, and confounding. The basic approach is akin to a process of elimination, by which one attempts to determine the direction and to quantify the magnitude of the influence that chance, bias, and confounding may have had on the results of each study. Wherever possible, the results of all studies will be reported in units of relative risk estimates and 95% confidence limits.

Most biases in epidemiologic studies can be placed into one of two categories: biases of classification and biases of selection. Classification biases can result from inaccurate ascertainment of exposure, disease, or confounders. Selection biases can result from nonrepresentative sampling of populations, as in the selection of controls in case-control studies, or from incomplete participation by study subjects. Any bias gains tenability as an explanation for an observed result if empirical evidence can be adduced to buttress the mere suggestion that the bias might have occurred. Only those biases considered to be potentially important will be addressed explicitly in this review.

When imprecise exposure estimates are available, such as with much of the epidemiologic data on dioxin, estimates of risk can be potentially biased toward the null. Misclassification, if random, could potentially lead to a masking of a true effect.

Classification biases are of two kinds: differential and nondifferential. Differential misclassification will lead to either an exaggeration or an underestimation of an effect.

Nondifferential misclassification occurs when the exposure or disease classification is incorrect in a portion of the subjects (cases or controls). This type of bias is generally toward the null, and the risk estimate may reflect this. Such misclassification can happen when some subjects are classified as having exposure to dioxin when they really were not exposed. Similarly, some actually may have had exposure but were classified as not having had it. In studies where few or no effects were seen, researchers must seriously consider the problem of nondifferential misclassification. This can be the reason that nonpositive risk estimates or even disparate risk estimates are seen from different studies of the same effect. On the other hand, in studies with significant results, nondifferential misclassification is not likely to be a cause of a significant finding.

Recall bias may produce the opposite effect. Persons with a disease may tend to remember exposure to a substance better when they know that such exposure might be associated with the disease. This could potentially lead to inflated risk estimates. In fact, it has been suggested that such biases are present in many of the case-control studies on dioxin. The Swedish studies by Hardell and colleagues have been particularly singled out for criticism in this respect. That some recall bias may be present is confirmed in a later case-control study (Hardell and Eriksson, 1988) in which some reduction of risk estimates was produced by the use of cancer controls. But then this result could be the result of a general cancer effect as well.

Confounding bias is a tenable explanation for an association between an exposure and a disease if the hypothetical confounder can be named and if a good case can be made that it is a cause of the disease, that it was associated with the exposure in the study population, and that it was not adequately controlled in the study design or data analysis. This review will explicitly mention only those potential confounders that meet all of these criteria.

As stressed in previous EPA reviews (1985, 1988), concomitant exposures present a special problem of potential confounding in the literature on TCDD and related chemicals. As a noteworthy example, an association between 2,4,5-T exposure and a given cancer, if causal, could be due to 2,4,5-T itself, to TCDD, or to some other contaminant. The problem multiplies when it is recognized that, historically, many phenoxy acid herbicide preparations were mixtures of 2,4,5-T and 2,4-D and that many persons who manufactured, processed, and used these preparations were exposed to other chemicals as well. Nevertheless, it may be possible, by examining studies of persons exposed to different combinations of chemicals, to identify "threads" of commonality and differences in the results, especially when specific cancers are considered separately.

Publication bias, sometimes considered a form of selection bias, is the tendency for the results of a study to influence a judgment as to whether or not it will be published. The direction and magnitude of publication bias is difficult, if not impossible, to quantify. It is expected to be

a much greater problem in literature reviews and in studies relying on existing records than in original research in which substantial resources are devoted to collection of data of relatively high quality. The level of effort required for such studies creates a strong incentive to publish the results. There is a tendency to publish studies with positive results as opposed to studies with nonpositive findings.

Strength of association, as measured by the magnitude of the estimated relative risk, is an important feature of a study's results. The stronger the association, the stronger a bias or confounding factor would have to be to explain it. Because questions of bias and confounding are study-specific, no defensible criteria can be set up in advance to place relative risk values into categories of strength of association.

Trends in increased risk by degree of exposure and by time since first exposure (latency) are also important. Different hypothetical causal mechanisms might predict different exposure-response and latency patterns. Hypotheses of steadily increasing effect with increasing exposure (i.e., monotonic exposure-response functions) and hypotheses of effects early in the carcinogenic process (e.g., for factors that operate at the initiation stage) predict that increases in risk will be greatest among persons with relatively high degrees of exposure and after relatively long latency periods. Hypotheses of tumor promotion and/or initiation will be discussed in the appropriate sections.

Replication of results is important in all scientific research. When several studies have shown a positive association of effect with the same exposure but were conducted under different circumstances, the possibility that an unknown confounder or chance produced the observed elevated effect is minimized. When different investigators working with different populations using different methods confirm an original finding, the results are more believable.

The statistical aggregation of results from different studies (meta-analysis) has become a popular feature of epidemiologic literature reviews. In this review, results from separate studies are aggregated only when all key methodologic features and results are reasonably similar. The method of aggregation used here is to take the ratio of the sum of the cause-specific observed deaths to the sum of the cause-specific expected deaths for the individual studies. Because investigators recognize the value of varying their methods to test methodologic hypotheses, and because results often differ appreciably, aggregation of results is not often indicated and is done here with caution.

7.5. FOLLOW-UP STUDIES OF CHEMICAL MANUFACTURING AND PROCESSING WORKERS

7.5.1. United States

Fingerhut and colleagues (1990, 1991) reported a study of 5,172 males who had worked at 12 plants in the United States in the production of chemicals contaminated with TCDD. Five thousand of the cohort members (97%) were identified in company records as having been "assigned to a production or maintenance job in a process involving TCDD contamination" (Fingerhut et al., 1991). The remaining 172 cohort members were "identified in a previously published study on the basis of exposure to TCDD" (Fingerhut et al., 1991). This cohort subsumed, and thereby supplanted, company-specific cohorts from Dow Chemical USA (Ott et al., 1987; Cook, 1981) and the Monsanto Company (Zack and Gaffey, 1983; Zack and Suskind, 1980) that had been the subject of previous reports. This study was initiated in 1978 to determine whether health effects were apparent in humans who were exposed to 2,4,5-T. In 1978, toxicological, teratogenic, and carcinogenic effects data were released that indicated a cancer effect in animals. There was a concern about the potential effects of exposure to Agent Orange on Vietnam veterans and workers who produced products that were contaminated with dioxin (Fingerhut et al., 1992). Follow-up began in 1940 or on the date of the "first systematically documented assignment to a process involving TCDD contamination" (Fingerhut et al., 1991), whichever was later, and closed at the end of 1987. Comparisons were made with the United States population.

The authors stated that approximately 13% of the cohort of 5,172 workers had records of chloracne. The presence of a significant incidence of chloracne in a group of people is an indicator of relatively intense exposure to TCDD. Chloracne can be caused by higher-chlorinated PCDDs, PCDFs, and PCBs as well (O'Malley et al., 1990) and also by Ah receptor agonists such as brominated congeners and with naphthalenes. It is a highly specific indicator of exposure to these compounds because it virtually never occurs among unexposed persons. It is a nonsensitive indicator, however, because many highly exposed persons do not develop it (Manz et al., 1991; Caramaschi et al., 1981; Mocarelli et al., 1991). Exposure to other dioxin-like chemicals that can be found in the workplace produces a form of chloracne that could be indistinguishable from that produced by dioxin (Ott et al., 1993). These chemicals can be dioxin-like in their effects and act through the aryl hydroxylase (Ah) receptor.

Although all members of the cohort had specific assignments to TCDD exposure areas in common, exposures to multiple chemicals generally occur in the chemical industry. At one plant, for instance, considerable overlap existed among persons involved in the production of chlorophenols, 2,4,5-T, and 2,4-D (Ott et al., 1987; Bond et al., 1988, 1989a), and thus exposed to TCDD and higher- and lower-chlorinated PCDDs. Presumably, many persons throughout the

cohort had contact with other chemicals. Comprehensive surveys of chemical exposures were conducted in plant-specific cohorts and may be available through the authors.

Special attention was paid to results for the 3,036 workers who were followed for at least 20 years after first exposure. This group was again divided into those with less than 1 year (N=1,516) and those with more than 1 year (1,520) of exposure (referred to below as the long duration/latency subcohort). One year was chosen as the criterion for duration of exposure because an analysis of 253 workers from 2 plants showed that every worker with 1 or more years of exposure had a lipid-adjusted serum TCDD level greater than the mean value (7 ppt) in a comparison group of unexposed workers (Fingerhut et al., 1990). Although the average level for all 253 workers was 233 ppt, the average increased to 418 ppt in those 119 who were exposed for 1 or more years (Fingerhut et al., 1991). The average serum TCDD level in those exposed less than 1 year was 69 pg/g. The researchers described a plan, utilized by Steenland et al. (1999), that replaced this duration-based exposure scale by using "a dioxin exposure matrix constructed from historic process descriptions, analytic measurements of TCDD and industrial hygiene data . . . to develop the relative ranking of workers exposed to TCDD" (Fingerhut et al., 1990).

The cohort as a whole experienced an estimated 15% (95% CI = 1.0-1.3) elevation of mortality from all cancers combined, with a 46% elevation (95% CI = 1.2-1.8) among those in the long duration/latency subcohort (Table 7-1). An excess of deaths from cancers of connective and soft tissues (STSs) was apparent in the total cohort (RR = 3.4, CI = 0.9-8.6) and in the long duration/latency subcohort (RR = 9.2, CI = 1.9-27.0), but these results were based on only four deaths and three deaths, respectively, from two different plants. A 40% overall elevation in deaths (CI = 0.7-2.5) from NHL was confined to workers in the total cohort and was not seen in the long duration/latency subcohort. Results for Hodgkin's disease were highly imprecise, based on only three deaths (vs. 2.5 expected) in the total cohort. Lung cancer was elevated by 10% overall but by 40% (CI = 1.0-1.9) in the long duration/latency subcohort. A similar 40% excess of stomach cancer (CI = 0.4-3.5) in this subcohort was based on only four deaths; no excess was seen in the total cohort.

The investigators conducted a special study of connective and soft tissue cancers. A review of all available hospital records and tissue specimens failed to confirm the indications of STSs on two of the four death certificates that had been assigned to this cause-of-death category (Fingerhut et al., 1990). The review also provided evidence that two persons in plant 8 whose deaths had been assigned to other causes of death had actually had soft-tissue sarcomas. Because only the exposed cohort's death certificates were subjected to detailed review, the analytic comparisons with the United States population were required to be based strictly on death certificate information. The basic and well-known rule in such situations is that, absent evidence to the contrary, erroneous information on death certificates must be considered to have been

equally frequent in the two groups being compared. But Suruda et al. (1993), in a study of STS diagnoses in cohorts exposed to dioxins and chlorinated naphthalenes, found that death certificates are "relatively insensitive"for detecting STS and that the power of life-table analysis to detect excess risks of STS may be reduced compared with its utility in correctly estimating the risk of other cancers, such as colon cancer or rectal cancer. However, the correct identification of STS as the underlying cause of death on death certificates appears to be much better (82%), based on medical records, than first thought according to the results of this study. Medical records on the remaining 18% could not be found. If a death certificate gives as an underlying cause of death a STS and it is coded as 171x, it is very likely correctly coded, according to the authors. In an earlier study, this figure was estimated by Percy et al. (1981) to be 55%. This nondifferential misdiagnosis could potentially bias risk estimates downward (underestimate the true risks).

Four of the STSs that are discussed in Fingerhut's study (two are included in Fingerhut's life-table analysis while two others are discussed but did not qualify for inclusion in the life-table analysis) are actually from the Nitro, West Virginia, plant. The remaining two cases that were included in Fingerhut's life-table analysis are from a different plant in the study. One of these cases also suffered chloracne. The four cases from the Nitro, West Virginia, plant are also the subject of a later study by Collins et al. (1993). The two cases included in Fingerhut's life-table analysis had previously suffered chloracne from an incident in which 121 workers developed chloracne as a result of a trichlorophenol process accident on March 8, 1949 (Zack and Gaffey, 1983). Collins et al. (1993) included one more STS not previously discussed by Fingerhut from the same plant. The Collins et al. (1993) study is reviewed later.

If the properly diagnosed STSs were correctly assigned to their appropriate plants and the two incorrectly diagnosed STSs were removed, there would be one STS in plant 9 and three in plant 8. No STSs were found at the other plants. This unusually skewed distribution might possibly be related to the accident that happened in plant 8 in 1949. Or perhaps physicians in Nitro, West Virginia, are more likely to diagnose STS than are physicians in other areas of the country. Because of the rarity of STS, there was inadequate statistical power to expect to see STSs in the other individual plants. If an excess risk is associated with exposure to TCDD, then it might be several more years before this cohort will produce STSs at the other facilities that are part of the study.

Cases of STS include a diverse group of histological entities. All STSs arise only from mesenchymal tissue, and all share common features that make them alike in their basic intercellular and intracellular composition rather than different in their morphology and location. Characterizing them as fundamentally different because they are found in different sites of the body is perhaps inadequate for determination of the risk of cancer (Enzinger and Weiss, 1988).

The histological classification of STS is centered on a dozen distinctly different classes of mesenchymal cells that form six relatively well-defined but widely distributed organ systems. By considering the growth pattern and cell morphology with an evaluation of intracellular and extracellular products of the tumor cells, fairly precise histogenetic classification of STSs is possible (Hajdu, 1981). For human cancer risk assessment, all connective tissues developing from the same mesodermal tissue, expressing the same set of "proto-oncogenes"and surrounded by the same chemical milieu of the extracellular matrix, are expected to develop cancer following exposure to certain carcinogens. The grouping of these end-target organs together is therefore necessary to evaluate the risk from exposure to dioxin.

Confounding by cigarette smoking must be considered in interpreting the approximate 40% excess of lung cancer deaths in the long duration/latency subcohort (Table 7-2). For the United States as a whole, the authors (Fingerhut et al., 1990) computed age-adjusted proportions of 24% never smokers, 19% former smokers, and 57% current smokers in 1965 (roughly midway through the follow-up period). The corresponding proportions were 28% never smokers, 14% former smokers, and 59% current smokers among the 87 workers from the study of serum TCDD levels who were members of the long duration/latency subcohort as well. Assuming relative risks of lung cancer of 4.7 for former smokers and 10.9 for current smokers, the authors used a standard technique (Axelson and Steenland, 1988) to adjust the number of expected lung cancer deaths and found essentially no change in the results. It should be kept in mind that the sample of smoking histories was taken from only two plants but the excess in lung cancer risk was chiefly in two other plants. The generalization of smoking habits of employees in 2 of the 12 participating plants to that of the entire cohort may not be representative of the true smoking impact on the risk of lung cancer to the cohort. Most of the lung cancers (56 of 89 observed lung cancer deaths) came from 3 facilities. The remaining 7 plants contributed the other 33 lung cancers to the total because of the small sizes of the respective subcohorts and insufficient latency. It then would be possible to evaluate the effect of smoking on the risk of lung cancer at each individual plant. It should be remembered that national U.S. rates were used to derive expected deaths in each of the 12 plants. It is possible that local or regional rates may be a more appropriate comparison population for the cancer sites examined by the authors, although local rates may be unstable. In addition, if biomonitoring could be extended to the remaining 10 plants, a better idea could be derived concerning the dose levels associated with those plants experiencing higher lung cancer rates. The authors point out that deaths from other diseases associated with smoking, such as diseases of the heart and circulatory system and emphysema, were either not increased or significantly decreased in this cohort (Fingerhut et al., 1990). Although the possible contribution of factors such as smoking and occupational exposure cannot

be excluded, there is no evidence that smoking patterns in this cohort are entirely the reason for the elevated risk of lung cancer (Fingerhut et al., 1991).

One possible explanation for the increase is that the 87 surviving members of the long duration/latency subcohort did not show the well-known tendency for smoking to be more common among blue-collar workers than in the general population. A possible reason is that because smoking appreciably elevates the overall death rate, fewer and fewer smokers will remain in a fixed group of persons as time goes by. Thus, the use of the 87 *surviving* members of the long duration/latency subcohort may have underestimated the proportions of former and current smokers in the subcohort as a whole over the course of mortality follow-up. However, this same phenomenon is also present in the population from which expected deaths were generated, so the effect is probably nullified. The effect on the lung cancer risk as the proportion of smokers increased in the cohort is shown in Table 7-2. The lack of increased mortality from cardiovascular diseases as well as cancer of the buccal cavity and pharynx in this cohort, however, makes this explanation less likely. Furthermore, as the authors point out, mortality from nonmalignant respiratory disease (standard mortality ratio [SMR] = 96), which is often associated with smoking, was less than expected. This strengthens the argument that exposure to dioxin causes lung cancer.

On the other hand, the authors report a correlation coefficient of 0.72 between length of exposure and serum TCDD tissue level. This negative bias is potentially much greater than the positive bias that could possibly be produced by smoking. And because nondifferential bias is the only type of bias that could occur in the Fingerhut study, risk estimates are more than likely lower than the true risk. The only way that dioxin exposure could have a positive bias is if it prevents cancer and the exposure classification is 100% wrong.

The authors of this study also report that two of these cancer deaths were from mesothelioma, a finding that more than likely indicates exposure to asbestos. Although these two mesotheliomas occurred at plants 9 and 12, it is not known whether these persons were exposed in that job or in some previous job. Only one death from asbestosis was noted in the nonmalignant respiratory deaths, and this occurred in Plant 1. These three asbestos-related deaths were more than likely due to exposure in a previous occupation.

Fingerhut et al. (1991) has been updated by Steenland et al. (1999), of the same research group. The SMR for all cancers combined was 1.13 (95% CI = 1.02-1.25). The SMR for all cancers combined for the highest exposure group was 1.60 (95% CI = 1.15-1.82). Recent analyses support the finding that high exposure to TCDD results in an excess of cancer without any marked specificity. Steenland and colleagues' later analyses differ from Fingerhut's in that the authors applied a "job-exposure matrix"to a subcohort of 3,538 workers from the original 5,172 male workers and followed the entire cohort for 6 more years. This job exposure matrix is

not based upon ambient air levels of TCDD or even blood TCDD serum levels. It is based upon the concentration of TCDD (μg/g) present in the process materials to which the workers are exposed *times* the fraction of the day the worker was employed in that process *times* the "contact"level (meaning the likelihood the product will reach the skin or be inhaled) *times* the period of time the worker worked in proximity to TCDD. Steenland et al. did not consider workers and plants where records on the degree of exposure to TCDD were lacking, a detailed work history was lacking, or there was concurrent exposure to pentachlorophenol contaminated by higher chlorinated PCDDs/PCDFs. They also analyzed a subcohort of 608 workers with frank chloracne without regard for any of the exceptions mentioned above, and analyzed a subset of 393 of the 608 who fell into the subgroup of 3,538 workers above.

The results indicated that as cumulative exposure increased through seven exposure categories based upon their "job-exposure matrix," the calculated risk of overall cancer mortality tended to increase (all sites combined). In the chloracne cohort of 393 men mentioned, in the two highest septiles of cumulative exposure the risk was significant at 1.68 (CI = 1.19-2.30).

In the larger subcohort of 3,538, the results tended to be similar but less pronounced. Utilizing either the life-table analytical method or the Cox regression method, trends tended to be positive, although in an inspection of the seven categories, the increasing trends are not monotonic using either method, lagged or unlagged (Table 7-3).

Although the authors believe that this lack of linear trend in cancer with cumulative exposure as a continuous variable is due to the extreme skewedness of the data, this may have more to do with the way in which cumulative exposure is determined in the job-exposure matrix and the fact that the authors use seven exposure categories to generate risks. The fact that quantity of TCDD in process materials is used, rather than ambient air levels of TCDD or even blood serum levels of TCDD, to determine basic exposure potentially removes the estimation process for exposure even further from the truth. There is likely considerable variability in the cumulative exposure indices calculated for individuals in this cohort. Furthermore, the use of so many categories of exposure also makes individual risk calculations within each septile less stable and perhaps even unreliable, because they are based upon smaller numbers.

Despite these problems the authors were still able to detect significantly positive trends in total cancer, several site-specific cancers such as lung cancer, and even ischemic heart disease, especially when they considered the logarithm of cumulative exposure (the more appropriate test statistic for this kind of distribution of exposures). The finding concerning an increased risk of ischemic heart disease seems consistent with what is known about the interaction of serum dioxin with endogenous cholesterol and high-density lipoproteins. There appears to be an inverse relationship between serum TCDD level and high-density lipoprotein and a positive relationship with total cholesterol (Grubbs et al., 1995; Calvert et al., 1996).

Another observation is the finding that the risk of bladder cancer (16 cases) was increased by exposure to 4-aminobiphenyl at the one plant where 10 cases occurred. This is consistent with the fact that 4-aminobiphenyl is a strong bladder carcinogen. This could potentially bias the elevated overall cancer risk because these deaths are included. However, they will probably not affect site-specific cancers such as lung cancer, except that bladder cancer "competes" with other potential causes for the distinction of being designated the "underlying" cause of death. The authors also point out that exposure-related trends remained unchanged for smoking-related cancers when bladder cancers were omitted. This implies that the findings for all cancers remained unchanged when bladder cancers were omitted. The excess is about eight cases over expected.

The analysis done by Fingerhut in her first paper, showing that there is a high correlation between years of exposure to TCDD and in vivo serum levels of TCDD, based upon 253 workers, is strong evidence of a likely dose-response relationship. Endogenous markers of exposure are superior to exogenous man-made constructs. Although markers of exposure that are closer to the target organ for carcinogenicity are better indicators of the actual dose received by the organism at some given point in time, they still tell us little of what may have occurred by way of exposure in the past and exposures in the future. However, indexes of exposure such as "cumulative exposure" are likely to be more accurate and reliable when based upon actual dose measures.

In summary, Steenland et al. (1999) continues to support the hypothesis that dioxin is causally associated with an increased risk of cancer punctuated by increased selected site-specific risks such as lung cancer, STS, etc. There is a significant positive trend for cancer mortality with increasing exposure, with a 60% excess mortality from cancer in general in the highest exposure group. But in addition, the data suggest a potential for an added risk of ischemic heart disease.

The positive association of lung cancer in male workers observed in this study is also consistent with an excess of pulmonary tumors found in male mice and rats exposed to TCDD (see Chapter 6). These same animal data suggest the possibility of a protective hormonal effect from TCDD and the risk of pulmonary cancer in female rats. Because this study dealt with only male workers, this hypothesis could not be verified in female workers. On the other hand, no elevated risk of liver cancer is evident in male workers even in the long duration/latency subcohort. This is also consistent with rat data, where the tumors were only observed in female rats. If there is a promoting effect on liver cancer in human females due to hormonal effects, as suggested by the rat studies, it could not be verified.

Collins et al. (1993) suggested that there is an association of STS with exposure to 4-aminobiphenyl. The authors reported that workers who developed chloracne from an accident in which a chemical mix containing TCDD was scattered throughout a 2,4,5-trichlorophenol plant

had increased mortality from STS, bladder cancer, and respiratory cancer. All individuals who were identified in this study of 754 chemical employees as having STSs or lung cancers, and who were employed at the time of the 1949 accident, were potentially exposed to 4-aminobiphenyl as well as to TCDD. However, it is not known how many were actually working inside the plant when the accident occurred. 4-Aminobiphenyl is thought to be a bladder carcinogen from previous studies. However, this chemical has not been shown to be associated with STS or lung cancer in humans. Unfortunately, no tissue measurements are available to substantiate exposure to TCDD or exposure to 4-aminobiphenyl. It is also of interest that no significant increase in STSs was noted in the "chloracne-free" subgroup exposed to 4-aminobiphenyl. However, the authors report that an additional 106 persons also had indications of chloracne-type conditions noted in their medical files, presumably as a result of exposure to TCDD and not as a result of the accident. Although these individuals probably were heavily exposed to dioxin as well, these workers were included in the "no chloracne" subgroup for the purpose of analysis. It would be of interest to see what effect would occur to the risk estimates if these workers were included in the "chloracne" subgroup. Furthermore, plant employees who left work before March 8, 1949, or began work after November 22, 1949, were not included even if they had received exposure to dioxin or developed chloracne as a result of exposure. The major interest, according to the authors, was in the 122 workers who developed chloracne from the 1949 accident. The authors point out that the numbers are small and that confounding factors, such as misclassification of exposure, cannot be ruled out. 4-Aminobiphenyl has not been reported in plant 9, where one STS was diagnosed. This study presents an interesting explanation that has not been substantiated anywhere else.

It was also noted by Collins that toxicological evidence is available that supports the idea that STSs (i.e., angiosarcomas) have resulted from exposure to 4-aminobiphenyl (Schieferstein et al., 1985). Angiosarcomas and bladder cancer in females were found to be dose-related with oral consumption of 4-aminobiphenyl in drinking water. However, angiosarcomas of the liver arise mainly in the endothelial lining of blood vessels. This type of tissue is more likely susceptible to a hydrophilic carcinogen such as 4-aminobiphenyl during its passage through the blood vessel. Hydrophobic carcinogens such as TCDD might be expected to exert an influence on mesenchymal tissue from which most STSs arise, i.e., fibrosarcoma, histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, schwannoma, myxoid neurogenic sarcoma, and others. Therefore, the author's assumption that 4-aminobiphenyl can cause other types of STSs remains unproven and highly unlikely.

Ramlow et al. (1995) updated the study of a portion of an earlier cohort of workers studied by Ott et al. (1987). Some 770 workers involved in the manufacture of pentachlorophenol (PCP) were identified for a mortality study. PCP, a broad-spectrum pesticide,

is contaminated with hexachlorinated, septachlorinated, and octachlorinated dioxins but allegedly little or no TCDD as well as PCDFs. Follow-up continued until December 31, 1989. Expected deaths were estimated based upon U.S. white male death rates. Separately, a reference comparison population of employees from the same company but presumably without exposure to PCP was used to develop site-specific relative risk (RR) estimates. Fifty cancer deaths were observed, whereas 52.6 were expected based upon U.S. death rates. When stratified according to a 15-year lag time after initial exposure, and further stratified into subjectively determined cumulative H/OCDD high, medium, and low categories, there appeared to be little evidence of any consistently increased site-specific cancer risks that could be attributed to exposure to PCP other than those induced by the small numbers. The same could be said of the comparison with the nonexposed company cohort. Calculated relative risks by 15-year lag time in each of the three categories of exposure according to site revealed little that could be attributable to PCP exposure. The few significant cancer risks seen were based upon small numbers (kidney cancer, two deaths in the high-exposure category; gastric and duodenal ulcer, four deaths in the medium-exposure category; and accidents, nine deaths, high-exposure category). The authors, however, concluded that the few significantly increased site-specific deaths that were apparent could not be attributed conclusively to PCP exposure. This study could benefit by having TEQ-determined blood serums taken in order to substantiate if and how much exposure actually did occur to members of the cohort, and also a longer follow-up to accumulate additional deaths.

7.5.2. Germany

Manz and colleagues (1991) reported a study of 1,583 persons (1,184 men and 399 women) employed at a German chemical manufacturing facility that produced 2,4,5-T and its precursor, 2,4,5-trichlorophenol. In 1954, a chloracne outbreak had occurred in the working population of the plant, and after that, production of the TCDD contaminant was reduced. Cohort members worked at least 3 months from 1952 through 1984. The start of follow-up was not stated in the report, but presumably began on the date of accumulation of 3 months of employment. The follow-up period closed at the end of 1989. The cohort's mortality experience was compared with that of the West German population and with that of a cohort of workers at a gas supply company. Because limited data on the gas workers forced that comparison to be based on a subset of the TCDD-exposed cohort, and because the results did not differ materially between the analyses, only the results of the comparisons with West Germany are reported here.

The cohort was postdivided by duration of employment and by a three-category exposure scale based on TCDD measurements “in nonsystematic samples of precursor materials, products, waste, and soil from the grounds of the plant, mainly after the plant had closed in 1984" (Manz et al., 1991). This scale was validated to some extent by adipose tissue TCDD levels in 48

volunteers (mean = 296 ng/kg in 37 persons from the highest group, 83 ng/kg in 11 persons from the other two groups). On the basis of these results, the low and intermediate groups are combined for the present analysis.

For the males, this study, with 75 total cancer deaths expected and 24 expected in the high-exposure subcohort, was considerably smaller than the study by Fingerhut et al. (1991), which had 230 total cancer deaths expected and 78 in its long duration/latency subcohort (Table 7-4). Manz et al. presented detailed analyses only for all cancers combined. The high-exposure subcohort, and especially those with longer employment duration, experienced an excess of total cancer deaths (RR = 1.4, CI = 1.0-2.0 for the high-exposure group and RR = 2.6, CI = 1.2-4.9 for the high exposed/long duration subcohort) (Table 7-4). The authors concluded that "the increase in (total) cancer risk of 1.24-1.39 . . . cannot be explained completely by confounding factors, and . . . is associated with exposure to TCDD" (Manz et al., 1991). In a later abstract of an update of this same paper, Dwyer (1992) reported that after using a Cox regression analysis of nine major areas of employment within the plant, the area of work with the strongest relative risk for cancer mortality was 2,4,5-T production (RR = 2.7, CI = 1.7-4.2). These findings are similar to those of Fingerhut et al. (1991).

For the cohort as a whole, the estimated relative risk of lung cancer was 1.4 (CI = 1.0-2.0, 30 observed deaths). Smoking as an explanation for the observed increase is less likely because a comparison using the gas worker reference actually leads to an increased RR of 1.7 (CI = 1.1-2.4). Although smoking histories were not available for the entire Boehringer cohort, of the 361 men, 73% reported that they smoked. Similarly, 76% of 2,860 gas workers smoked. Substantial confounding based on smoking does not appear to be present because smoking seems to be similar in both plants. The estimate for stomach cancer was 1.2 (CI = 0.7-2.1, 12 observed deaths). Three deaths were observed from NHLs and none from connective and soft tissue cancers. (The authors described an additional three deaths from chronic lymphocytic leukemia as NHL deaths, but these deaths would not have been classified as non-Hodgkin's lymphomas in the other studies in this review.) Dr. Lennart Hardell pointed out (letter to David Bayliss, January 10, 1995) that under the most recent classification the category "non-Hodgkin's lymphoma" includes chronic lymphocytic leukemia as one type. Expected numbers of deaths from these cancers were not given. Based on the proportions of expected cancer deaths in the Fingerhut study, one might estimate that approximately 2.4 NHL deaths and 0.4 connective and soft tissue cancer deaths would have been expected in this cohort as a whole, and about 0.1 connective and soft tissue cancer deaths in the high-exposure subcohort. (The numbers of expected deaths from lung cancer, stomach cancer, or NHL in the high-exposure subcohort were not estimated because information is lacking on how many of the observed deaths from these cancers were in that subcohort.)

The authors reported exposure to other industrial chemicals, such as benzene and dimethylsulphite. In addition, manual laborers were "probably" exposed to asbestos to some extent. However, the authors maintain that this exposure explains neither the increased mortality from all cancers nor the patterns of associations with TCDD exposure groups.

Other possible sources of bias include a potential lack of comparability between cause of death ascertainment based on medical records (in some, perhaps many, cohort members) versus only use of death certificates for cause of death certification in the derivation of German national death rates. This is somewhat alleviated by the use of gas workers as a second comparison group. In these workers, the same methods were used for medical certification, making comparison of cause of death somewhat more accurate. However, this is offset by the fact that the gas workers may have somewhat better mortality experience because they had to work a minimum of 10 years to obtain entrance into their cohort, whereas the dioxin cohort had to work only a minimum of 3 months. This could have introduced survivorship bias in this group and consequently lower mortality and higher risk estimates.

Furthermore, the lack of an analysis of mortality data by time since first exposure for individual causes such as lung cancer makes it impossible to assess latent effects.

Of the 399 female cohort members, only 7% worked in high-exposure departments. In total, there were 54 deaths and an overall RR = 0.8 (CI = 0.6-1.0). The RR for all cancers was 0.9 (CI = 0.6-1.4), but the RR = 2.2 (CI = 1.0-4.1) for breast cancer was significantly increased based on 9 deaths. Kogevinas et al. (1997) and Saracci et al. (1991) also report a borderline significantly elevated risk of breast cancer based on nine cases who were exposed to TCDD or high chlorinated dioxins. This is an interesting result in view of a suggestion of reduced mammary cancer based on mechanistic studies and animal bioassays. However, at this point the data do not provide a sufficient basis for any conclusions.

In another update of the Manz et al. (1991) cohort, Flesch-Janys et al. (1995) extended the followup period to 1992. Lifetime exposure to the PCDDs and PCDFs (total toxic equivalencies) was estimated quantitatively for the entire cohort from a subcohort of the workers (n = 190) in the plant as well as estimated TCDD exposure alone. The Cox regression analysis provided estimated RR by dose generated according to successive quintiles of TCDD levels and total toxic equivalencies (TOTTEQ) or (PCDDs/DFs) matched by birth (5-year intervals). Gas workers constituted the first set of controls. The second set of controls were internal. They were formed from the first two quintiles and, lastly, the analysis was repeated excluding workers in the opiate department. TOTTEQs as discussed by Flesch-Janys et al. (1995) are not to be confused with the newer World Health Organization definition of TEQs. These Flesch-Janys TOTTEQs do not include any PCBTEQs or TCDD.

For TCDD alone, the highest relative risks for total cancer occurred in the highest quintile (divided into deciles) of TCDD exposure (RR = 3.30, 95% CI = 2.05-5.31). Estimated levels were between 344.7 and 3,890.2 ng/kg of blood fat, although mortality was elevated nonsignificantly in lower quintiles as well. These were dose-related. For TOTTEQ exposure, significant dose-related relative risks of total cancer were observed for the highest decile of TOTTEQ exposure as well (RR = 3.27, 95% CI = 2.04-5.26), although the concentrations were between 545.1 and 4,362 ng/kg of blood fat.

The authors concluded that the findings indicate a "strong dose-related relationship between mortality due to cancer" and exposure to polychlorinated dioxins and furans. One of the limitations to this kind of analysis is that it does not provide information regarding the contribution of the specific and most potent congener TCDD to the increased risk of cancer from exposure to TOTTEQ. The tables in the text of this paper suggest that when internal controls are used, the risk of cancer is greater for exposure to TCDD alone than with TOTTEQ, which includes TCDD. These data suggest that TCDD could be a confounding influence. However, there are many assumptions about estimates of the parameters utilized in this methodology.

Limitations in the calculation of risk estimates based upon exposure to TOTTEQ in this study are likely. Because the program computes estimates of the half lives of different congeners of the PCDDs and PCDFs from exposure data collected from 1986 to 1994, and these estimates are used in the calculaton of change in dose with time in job, the calculation of potentially inaccurate individual estimates of exposure based upon work histories that date back to as early as 1952 is possible.

Furthermore, no measurements are included from individuals who have died, some 414 (35%). Estimates of exposure from 190 live members of the cohort are generalized to the entire cohort through the regression techniques utilized. If any deaths are dose-related to TCDD, TCDF, or their congeners, their absence from the totals could underestimate doses for such individuals. This in turn could bias risk estimates toward the null, and this could be the explanation for the suggestion that the dose-response relationship for total cancer and increasing TOTTEQs is not stronger.

A corrected Table 4 (Erratum, Flesch-Janys et al., 1996) indicates that for cancer the RR is 2.69 (95% CI = 1.67-4.35). This did not change the bottom-line conclusion that there was a strong dose-dependent relation between mortality from cancer and exposure to polychlorinated dioxins and furans. This study was criticized in a letter to the editor (Swain, 1997) on the grounds that the exposure assessment was inadequate, the choice of reference population was inappropriate, and the statistical analysis was faulty. The author provided evidence in a rebuttal companion letter to the editor (Flesch-Janys, 1997) that the choices he made in the study were

not likely to produce any substantial biases in the results of the kind that were described by Swain.

In an effort to relate the risk of cancer to dose, Flesch-Janys et al. (1998) developed a lifetime cumulative exposure index on each of the 1,189 male German herbicide and insecticide workers discussed above and followed the cohort for another 3 years to the end of 1992. Cancer mortality based upon 124 cases was significantly increased (SMR = 1.41, 95% CI = 1.17-1.68). Mortality from lung cancer was also significantly increased (SMR = 1.51, 95% CI = 1.07-2.08) based upon 38 cases, as well as hematopoietic and lymphatic cancer (SMR = 2.16, 95% CI = 1.11-3.77) based upon 12 cases. Production department-specific dose rates that were used to develop exposure dose levels for all members of the cohort were derived from blood levels and working histories of 275 workers. Four categories of cumulative exposure were developed for TCDD as well as their corresponding TEQs. The cumulative PCDD/F (TEQs) levels were expressed as nanograms/kilograms blood fat times years of exposure and based upon some 382 blood samples as follows:

I.	1.0 ≤ TCDD < 125.2 ng/kg-years;	1.0 ≤ TEQ < 360.9
II.	125.2 ≤ TCDD < 627.1;	360.9 ≤ TEQ < 1,614.4
III.	627.1 ≤ TCDD < 2,503.0;	1,614.4 ≤ TEQ < 5,217.7
IV.	2,503.0 ≤ TCDD	5,217.7 ≤ TEQ

A significant trend of increasing risk with increasing cumulative PCDD/F was evident. The SMR for cancer was significantly increased (SMR = 1.73, 95% CI = 1.21-2.40) at the highest quartile (greater than 2,503 ng/kg-years) (Table 7-5). The authors concluded that these results indicated an elevated risk of total cancer mortality in a cohort with high exposure to PCDD/F, that a dose effect was evident for estimated TCDD levels on total cancer SMR analysis, and that these data could be used for quantitative cancer risk assessment for dioxin.

The authors provided an update to the mortality experience of this subgroup of females from the Manz et al. (1991) study by following them through 1995 (Flesch-Janys et al., 1999). For individuals known to be alive in 1995, mailed questionnaires were sent to elicit information on any cancer diagnoses within the period to 1995. If cancer had been diagnosed during this period, efforts were then made to secure medical records to substantiate the cancer diagnosis. Cancers at particular sites were added to the cancer deaths at that same site to develop incidence data in the cohort. Standardized incidence ratios (SIRs) were developed for all sites with two or more cases. The authors found that the risk of breast cancer was elevated (SIR = 1.55, 95% CI 0.98-2.32) based upon 23 cases. The risk of cancer in general was elevated only slightly (SIR = 1.10, 95% CI = 0.83-1.42). The finding of an increased risk of breast cancer is somewhat contradictory to the suggestion that TCDD/estrogen interactions decrease tumor incidence in organs such as in the mammary gland of Sprague-Dawley female rats (Chapter 6, p. 6-36;

Carcinogenicity of TCDD in Animals). The authors also found a dose-response relationship with I-TEQ (ng/kg blood lipid) as follows:

I-TEQ	RR	95% CI
0 - 1,900.9	0.99	0.4 - 2.05
1,901.0 - 2,823.9	1.5	0.55-3.28
> 2,824.0	2.56	1.23 - 4.71

The authors point out that this cohort is very small, and they maintain that no definite conclusions on individual contributions to the elevated risk can be drawn. They recommend an extension of the follow-up, including additional determinations of blood levels .

These criticisms are not meant to discourage further work in this area. This is one approach that could be taken to analyze whether TCDDs, TCDFs, and their congeners other than TCDD are associated with increasing risks of cancer and other adverse health effects. All of these potential problems could be reduced if exposure data could be collected over a longer span of time and specimens could be included from deceased members who died from diseases that might be attributable to exposure to TCDDs, TCDFs, and their congeners.

Becher et al. (1996) updated the earlier study by Manz et al. (1991). They included three additional cohorts of workers exposed to TCDD in three different factories in Germany, although at lower levels. The cohort of 399 women was not updated and was not studied further. However, the remaining workers within that production facility and two of the three cohorts were followed until the end of 1989. The fourth cohort, which he calls Cohort II, was followed until December 1992. The authors compared mortality within these cohorts to that based upon German national mortality rates. Altogether, some 2,479 workers from the 4 plants were studied. A total of 138 deaths from all malignant diseases produced a borderline significant SMR of 119 (95% CI = 100 - 141). The risk increased with latency and was highest in cohort I, the original study by Manz et al. (1991). It was within this plant that the highest TCDD blood levels were recorded; i.e., 3 to 2,252 ng/kg blood fat. An increased mortality from respiratory cancer (SMR = 154, 95% CI = 115-202), cancer of the buccal cavity and pharynx (SMR = 295, 95% CI = 135-560), and NHL (SMR = 326, 95% CI = 119-710) was found in the total cohort. The authors conclude that their findings are consistent with results from other cohorts, which showed an increased overall cancer mortality and mortality of respiratory cancer after long-term exposure to these phenoxy herbicides and dioxin. Combining several cohorts in order to increase the size of the study population could lead to underestimating risks if the dioxin exposures as evidenced by blood fat measurements are varied over a wide range from one plant to the next. On the other hand, this latter update is an improvement over the earlier study, which relied on gas workers who had to have worked a minimum of 10 years before they could be included in the comparison dioxin-exposed cohort. This eliminated potential survivorship bias, although it increased the potential for the healthy worker effect to play a role.

In another investigation in Germany, Zober and colleagues (1990) studied persons employed at another German chemical manufacturing facility where 2,4,5-trichlorophenol was produced. An uncontrolled decomposition reaction in 1953 and subsequent cleanup activities resulted in substantial TCDD exposures. The cohort contained 247 persons who had worked at the plant from 1953 through 1987, 51% of whom had developed chloracne or erythema (a skin condition that may be suggestive of chloracne), with mortality follow-up covering the same calendar period. Seventy-eight persons had died (RR = 0.95); 23 had died of cancer (RR = 1.2) (CI = 0.8-1.7). Expected deaths were based on national mortality rates in the Federal Republic of Germany. When workers with chloracne (N=114 chloracne plus 13 erythema) were looked at separately, the risk of cancer as expressed by the SMR rose to 1.4 (OBS= 16, CI = 0.9-2.1). Again, within this highly exposed subgroup, if the analysis is restricted to only those workers who were observed 20 or more years after first employment, the SMR was significant at 2.0 (OBS=14, CI = 1.2-3.2). For lung cancer, the SMR is of borderline significance at 2.5 (OBS=5, CI = 1.0-5.3). The authors report that the results "do not support a strong association between cancer mortality and TCDD, but they do suggest that some hazard may have been produced."

Three subcohorts were defined on the basis of the potential for varying degrees of exposure. Subcohort C1 contained 69 persons known to be exposed to TCDD during the accident period. Cohorts C2 (84 persons) and C3 (94 persons) contained workers thought to be exposed to lesser amounts of TCDD. Recent TCDD levels in blood samples from small numbers of persons in each group suggested that exposures were higher in C1 (median 24.5 ppt, 11 samples) than they were in C2 (median 9.5 ppt, 7 samples) or C3 (median 8.4 ppt, 10 samples). Thus, C2 and C3 are grouped together in this review. A second stratification by the authors divides the total cohort into 127 persons with chloracne (N = 114) and erythema (N = 13) versus 120 persons with neither. The average serum TCDD levels in the two subcohorts are 15 ppt and 5.8 ppt, based on 16 samples (with chloracne) and 12 samples (without chloracne), respectively. The two stratifications provide similar results. Only the results of the first stratification, i.e., C1, C2, and C3, are presented here.

This study, with only 20 expected cancer deaths in the total cohort and 4 expected cancer deaths in the members of subcohort C1 with 20 or more years of latency, is much smaller than the studies by Fingerhut et al. (1991) and Manz et al. (1991). The authors, however, did provide detailed analyses of data on specific cancers (Table 7-6).

Elevated mortality rates from lung cancer, stomach cancer, and all cancers combined were confined largely to the members of subcohort C1 with long latency. The confidence intervals for the relative risk estimates are extremely wide, however. No deaths from cancers of connective and soft tissues or from NHL were observed, and expected numbers of deaths from these cancers were not reported. However, one mesothelioma was reported in a plant supervisor

with known asbestos exposure. Based on the proportions of all expected cancer deaths due to these cancers in the study by Fingerhut et al. (1991), one might estimate that approximately 0.6 NHL deaths and 0.1 connective and soft tissue cancer deaths would have been expected in this cohort as a whole, and about 0.2 NHL deaths and less than 0.1 connective and soft tissue cancer deaths among the members of subcohort C1 with long latency. This study lacks power to detect a significant site-specific cancer risk at most sites because of its small size.

In an update of this study, Ott and Zober (1996) added an additional 4 years of follow-up and reduced the size of the cohort slightly to just the 243 male members. They subsequently divided the cohort into four exposure categories based upon estimated TCDD dose expressed in μg/kg body weight. The development of this surrogate involved an appproach that included detailed accounts of each employee's work activities, analyses of TCDD in blood lipid of 138 employees back calculated to time of initial exposure utilizing a half-life estimate of 5.8 years for internal TCDD dose, and internally derived estimates of elimination rates of TCDD. Four categories of cumulative exposure were developed as follows: under 0.1 μg/kg body wieght estimated TCDD dose, 0.1 to 0.99, 1.0 to 1.99, and 2.0+ μg/kg body wieght. They calculated standard mortality ratios (SMRs) for total cancer in each category as well as site-specific cancer mortality after a 20-year latency. By the end of 1992, 47 men were diagnosed with cancer while 31 had died. The risk of cancer tended to increase with dose, although not significantly, because of the reduced power to detect a significant risk based upon decreasing size of the subcategories in the higher dose categories. At TCDD cumulative doses greater than 1 μg/kg, the SMR is 1.6 (95% CI = 0.9-2.6) (Table 7-7).

However, after 20 years' latency, the risk of cancer became significant in the exposure category $\geq$ 1 μg/kg body weight (SMR = 1.97, 95% CI = 1.05-3.36). Of the 13 cancer deaths in this category, 6 of these were due to lung cancer. The risk of lung cancer was also significant in this category (SMR = 3.06, 95% CI = 1.12-6.66). The same pattern of increasing risk with increasing dose was true based upon standard incidence ratios, although the increase was less pronounced. In the higher exposure category, greater than 1 μg/kg body weight, the SIR without regard to latency was 1.3 (95% CI = 0.8-2.0). For lung cancer, based on 8 cases the SIR was significantly elevated at 2.2 (95% CI = 1.0-4.3). The authors concluded that their findings were consistent with a carcinogenic effect induced by TCDD at the high dose category ($\geq$ 1 μg/kg body weight). The authors did note that because the cohort was small, the risk estimates could be affected by selection bias and/or confounding bias.

7.5.3. Ten-Country Study by International Agency for Research on Cancer

A historical cohort study of cancer mortality in 18,390 production workers or sprayers exposed to chlorophenoxy herbicides and/or chlorophenols was reported by Saracci et al. (1991).

Exposure was reconstructed through questionnaires, factory or spraying records, and job histories. Workers were classified as exposed (N = 13,482), probably exposed (N = 416), exposure unknown (N = 541), and nonexposed (N = 3,951). The exposed group contained everyone known to have sprayed chlorophenoxy herbicides and everyone who had worked in any of certain specified departments at factories producing chlorophenoxy herbicides. The criteria for duration or level of exposure required for selection was reported for only 3 of the 10 countries and only 4 of the 20 cohorts; these ranged from at least 1 month to 1 year. For all the other cohorts, the criterion for inclusion was to have ever been employed in production or spraying of these herbicides. The cohort contained 1,537 female workers, but results were not presented separately, except for female breast and genital organ cancers by phenoxy herbicide exposure. Average follow-up for the cohort was 17 years; 5% of eligible workers were lost to follow-up. Three of the cohorts comprising over 10,000 workers have also been reported in separate publications but for different follow-up periods (Lynge, 1985, 1987, 1993; Coggon et al., 1986; Kogevinas et al., 1993); these are discussed briefly in this report following this discussion. Several other occupational cohorts discussed in this report are also included.

Also included in the analysis was a division of the cohort (probable vs. unlikely) by whether or not exposure to TCDD occurred. No definition is given for "probable" exposure to TCDD; exposure to phenoxy herbicides does not necessarily imply exposure to TCDD. The "probably exposed" category includes production workers at two plants producing PCP, 2-(2,4-dichlorophenoxy)propanoic acid (2,4-DP; dichlorprop), 4-(2,4-dichlorophenoxy)butanoic acid (2,4-DB), (4-chloro-2-methylphenoxy)acetic acid (MCPA), or 2-(4-chloro-2-methylphenoxy)-propanoic acid (MCPP; mecoprop). There is not likely to be any TCDD in these processes. Those "unlikely exposed" appear to be so classified because they worked in different factories. There were 181 cases of chloracne among workers in the cohort.

The results are presented below by each of the two divisions of the total cohort: phenoxy herbicide (PH) and/or chlorophenols, and probable TCDD exposure. For the cohort division by PH and chlorophenols, no excess was observed for all-cause mortality, for all malignant neoplasms, for most common epithelial cancers, or for lymphomas. The four STS deaths were all in the "exposed to phenoxy herbicides and chlorophenols" subcohort (RR = 2.0, CI = 0.5-5.2) and all appeared 10 to 19 years after first exposure (RR = 6.1, CI = 1.6-15.5), with the excess risk limited to exposed sprayers (RR = 8.8, CI = 1.8-25.8) based on three observed deaths. None were observed in the 20 years or more category. Increases were also noted in the exposed group for mortality from thyroid cancer (RR = 3.7, CI = 1.0-9.4) based on four deaths, cancer of the testis (RR = 2.2, CI = 0.9-4.6) based on seven deaths, other endocrine glands (RR = 4.6, CI = 0.9-13.5) based on three deaths, and nose and nasal cavities (RR = 2.9, CI = 0.6-8.5) based on three deaths. An increase in lung cancer mortality was limited to the "probably exposed" (to

phenoxy herbicide and chlorophenols) group (RR = 2.2, CI = 1.1-4.0) based on 11 observed deaths.

The authors provided an additional analysis of STS, including five additional cases who were either alive at the end of follow-up or who had died from another cause. They concluded that the results suggest that STS in these workers "is compatible with a causal role for chlorophenoxy herbicides, though not specifically for those probably contaminated with TCDD."

The authors present only a limited analysis based on 215 and 294 expected total cancer deaths in the "probable" vs. "unlikely" exposed groups, respectively. There was a slight increase in mortality from all cancers for the probably versus unlikely exposed groups (RR = 1.1, CI = 1.0-1.2 versus RR = 0.9, CI = 0.8-1.1), but no increase in either STS or NHL based on 4 and 11 total cases, respectively. There was also an increased mortality for testicular cancer in the group probably exposed to TCDD versus those probably not exposed (RR = 3.0 vs. 1.6) based on seven total deaths, and for thyroid cancer (RR = 4.3 vs. 3.1) based on four total deaths. These latter two differences are not significant and, while interesting because of TCDD's known effects on these organs, add little to the information base.

While the Saracci et al. cohort was significantly larger than the other three worker cohorts (Steenland et al., 1999; Fingerhut et al., 1991; Manz et al., 1991; Zober et al., 1990), the lack of both a clear definition of exposure and uniformity of exposure classification between and within plants makes the results difficult to interpret and lessens the confidence in these results. When several studies have shown a positive association of effect with the same exposure but were conducted under different circumstances, the possibility that an unknown confounder or chance produced the observed elevated effect is minimized. When different investigators working with different populations using different methods confirm an original finding, the results are more believable. TCDD tissue levels were available only from a sample of 9 of the 181 workers with chloracne (median = 340 ng/kg, range 98 to 659 ng/kg). For 17 external controls, the median was 16 ng/kg while the range was 0 to 23.3 ng/kg. This suggests that some of the controls were exposed to TCDD. Unfortunately, no further analysis was presented on these workers.

There are several problems with this study. A portion of the Saracci et al. cohort consists of Danish workers from the Lynge (1985) study. None of them are reported by Saracci et al. (1991) as having had any exposure to 2,4,5-T. Lynge indicates that 2,4,5-T was produced at the Kemisk Vaerk Køge (KVK) facility in Denmark from 1951 until the end of 1980. However, in a later update (Lynge, 1993), the author maintains that the excess is due to exposure to phenoxy herbicides other than 2,4,5-T because only 5.3 tons of 2,4,5-T were produced in 1951-1952. This statement is somewhat contradicted in the author's methods paper (Lynge, 1987), where the author discloses that 350 tons of 2,4,5-T esters were produced during the period 1951-1981, on the basis of purchased 2,4,5-T acid. Perhaps more exposure to 2,4,5-T occurred than was

asserted by the author. This suggests the possibility that exposure misclassification may be present in the Saracci et al. study. There may be potentially as many as 3,844 workers who had exposure to 2,4,5-T and consequently TCDD. Many if not all of them were considered as unexposed in the Saracci et al. study.

Lynge in her studies reported on five histologically confirmed cases of STS. These are listed as cases 2, 3, 4, 5, and 9 in Table IV of the Saracci et al. study. Two were considered alive in the Saracci et al. study, even though in the later 1993 Lynge study these same two are listed as deceased. The remaining three are reported by Saracci et al. as deceased. Two of these three are coded to cancer sites other than STS; only one is correctly coded to STS. This suggests that underreporting of STS as the underlying cause of death is a problem in this study, which is consistent with the findings of Suruda (1993) that STS is underreported generally on death certificates. Added evidence of underreporting of STS is provided by the death certificate's cause of death for the two who were deceased after 1984. Both were coded to a cancer site other than STS. Altogether, four out of five of the confirmed STSs in the Lynge study were coded to causes other than STS.

In a followup study of this same cohort (Kogevinas et al., 1995), two nested case-control studies were conducted on 11 identified cases of STS and 32 NHL cases from this cohort. Four STSs and 20 NHLs were included in the earlier IARC study as deceased with the given diagnosis. These were matched with 55 and 158 controls, respectively, by country of residence, sex, and age through the use of incidence density sampling.

A panel of 3 industrial hygienists carried out the assessment of exposure to 21 chemicals or mixtures without knowledge of the subject's case control status. Live cases were included as well as deceased cases that were coded to causes other than code 171, "sarcomas of connective and other soft tissue," of the 9th Revision of the International Classification of Diseases and Causes of Death. Few actual tissue measurements of serum TCDD or other contaminants were available on any of the cases or controls.

The authors found a significantly elevated risk of STS from exposure to "any dioxin or furan" (OR = 5.6; 95% CI = 1.1-28); a nonsignificant increased risk with respect to TCDD (OR = 5.2; 95% CI = 0.85-32), and a significantly increased risk from exposure to "any phenoxy herbicide" (OR = 10.2; 95% CI = 1.2-91). There is also the suggestion of an increasing risk of STS with increasing intensity of exposure to TCDD. However, these are based upon small numbers and are subject to much variability. Additionally, there may be a problem with random misclassification in the estimates of intensity of exposure because the designation of intensity was a subjective decision by the three industrial hygienists.

However, these findings tend to support the likelihood that exposure to any dioxin or furan as well as TCDD alone is responsible for the elevated risk of STS seen in these workers

from many different countries. There is a suggestion of a weak increased risk of NHL from exposure to "any dioxin or furan" (OR = 1.84; CI = 0.8-4.3) and to TCDD (OR = 1.93; CI = 0.7-5.1). These studies suggest an association with total PCDD/DF TEQ exposure.

In a recent update of this IARC study, Kogevinas et al. (1997) expanded the study group to 26,976 workers by adding additional cohorts of workers from 12 plants in the United States (Fingerhut et al., 1991) and 4 plants in Germany (Becher et al., 1996; Manz et al., 1991; Flesh-Janys et al., 1995). A core protocol was developed by the participating countries to find appropriate study populations of workers who produced or sprayed phenoxy herbicides or chlorophenols. The study coordination was handled by IARC. The enlarged cohort includes almost all of the phenoxy herbicide production workers who have ever been studied. Vital status follow-up has been updated for most of the cohort.

The authors separated from the cohort those workers who were exposed to phenoxy herbicides believed not to be contaminated with TCDD on the basis of information abstracted from individual job records and company exposure questionnaires. This includes some 4,160 workers, mainly from Denmark and the Netherlands. Thus 1,012 women and 20,851 men remain who presumably were exposed to varying amounts of TCDD in their jobs. Of the 36 cohorts examined, measurements of serum TCDD have been done on 573 workers from 10 companies in 7 countries. Measured mean blood serum TCDD levels (pg/g) range from a mean low of 3.2 pg/g in one German plant to a high of 401.7 pg/g in another German plant. Some of these blood serum levels could be considered so low as to be indistinguishable from population levels outside of the plants where the measurements were taken. However, it should not be assumed that these current levels reflect exposures received by the members of the cohorts at the time of exposure in the past. They could either reflect very little exposure received over the years during and after employment in the industry (background levels) or they could represent reduced levels following reductions expected after the 7-year half life of dioxin in the body has been factored in. Conditions have probably improved at these plants over the years.

The authors report that among those exposed to TCDD containing phenoxy herbicides, mortality from malignant neoplasms (710 deaths; SMR = 1.12, 95% CI = 1.04-1.21) was slightly but significantly elevated. Incidence of STS, lung cancer, and NHL was also elevated, but not significantly so. The authors conclude that exposure to herbicides contaminated with TCDD and higher chlorinated dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers.

However, the same problems that plagued the Saracci et al. (1991) study also appear to plague this update. If the mean blood serum TCDD data and the confidence intervals provided around these means are any indication, it would appear that exposures varied considerably from one plant to the next. Many if not most workers had exposures similar to those of the

comparison populations from which the expected deaths were derived. Following such workers through time to determine their risk for the development of diseases related to exposure to TCDD will produce few if any significantly elevated risks that could be attributable to exposure to TCDD and will only serve to depress the SMRs.

Furthermore, although it was noted above that Kogevinas and his colleagues separated some 4,160 workers (mostly Danish) believed not to be exposed to phenoxy herbicides containing TCDD, some of these workers may actually have had exposure to 2,4,5-T and therefore its contaminant TCDD. In an earlier methods paper (Lynge, 1987) discussing job departments and production processes in the two plants that are the subject of her study of Danish workers (Lynge, 1985; 1993), she describes how "limited amounts of 2,4,5-T have been processed" in the Kemisk Vaerk Køge plant, "mainly in the formation of esters based on a purchased acid." The handling of 2,4,5-T lasted from 1951 to 1981. However, in Table 1 of Kogevinas et al. (1997), some 2,118 of the 2,341 workers at the two Danish plants are listed as having no exposure to "TCDD or higher chlorinated dioxins." Coincidentally, several STSs were identified from that same plant (Lynge, 1985, 1993).

In summary, this study is very little improved from the earlier study by Saracci et al. (1991). The few blood serum TCDD samples that have been measured differ so much that they indicate great variability in what the actual exposures might have been. And because many if not most of these workers have very likely always had blood serum TCDD levels close to background, the inclusion of such workers in the study cohort could introduce a potential bias in the results and could serve to drive estimated risk ratios toward the null. Furthermore, the definitions utilized in the feeder studies to decide who should be included or excluded cannot be easily "retrofitted" to meet the rigor required by the core protocol of the present study. Theoretically, all cohort members should enter the study at the *same* time. The study should have only *one* ending date and there should be only *one* qualifying period of employment (or exposure), not several, before inclusion as a member of the cohort, say 3 months or 6 months. There are questions that can be raised concerning the quality of the follow-up in each study, and whether the vital statistics and comparison populations are similar from one country to the next. The potential problems that need to be addressed are numerous and overwhelming.

The nested soft tissue case-control sarcoma study and the non-Hodgkin's lymphoma case-control study by Kogevinas et. al. (1995) discussed earlier in this chapter are methodologically superior to the conglomerate larger cohort study by Kogevinas et al. (1997). They have none of the design problems of the cohort study, although they are still limited by the lack of endogenous measurements of exposure similar to the parent cohort study. This chief drawback, i.e., the use of occupational data regarding proximity of the subjects to materials contaminated with dioxin as a surrogate for exposure, raises the possibility that misclassification of exposure led to a

reduction in risk estimates. Although this appears not to be the case with the STS study, where the risk ratios were significantly elevated, it could be a problem with the lymphoma study and other planned studies of site-specific cancer where no elevated risk was found. However, it is noteworthy that a significantly elevated risk of STS was found in association with exposure to materials contaminated with dioxin. Tallying the STS cases across all study cohorts in Kogevinas et. al. (1997) and matching them with members from the same international cohort to produce the excess significant risk estimates despite the drawbacks mentioned lends support to the theory that dioxin activates the Ah receptor to produce the STSs as well as other site-specific cancers.

7.5.4. Other Studies

Four studies containing portions of the same cohort reported above were reported elsewhere (Lynge, 1985, 1987, 1993, 1998; Coggon et al., 1986; Kogevinas et al., 1993; Bueno de Mesquita et al., 1993; Hooiveld et al., 1996, 1998). Lynge (1985) reported a study of cancer incidence among persons employed in the manufacture of phenoxy herbicides in Denmark. The cohort consisted of 4,459 persons from two factories. One factory contributed 615 cohort members who had worked in the years 1951-1981. The only phenoxy acids manufactured and packaged at this plant were MCPA and mecoprop, unlikely to contain TCDD. The other factory, Kemisk Vaerk Køge, contributed 3,844 cohort members who had worked in the years 1933-1981. At this plant, MCPA, 2,4-D, and lesser amounts of mecoprop, dichlorprop, and 2,4,5-T were manufactured and packaged. The investigators were unable to classify cohort members by the specific types of phenoxy herbicides to which they were exposed. However, in this plant, where exposure to TCDD-contaminated 2,4,5-T probably did occur, a significant excess risk of STS (4 observed vs. 1.00 expected, CI = 1.09-10.24) was noted by the author in those workers who had achieved a minimum 10 years of latency. Unfortunately, individual tissue measurements of TCDD were not included in this study.

In an update of the earlier study, Lynge (1993) continues to report an increase in the risk of STS with four cases reported to be in persons exposed to phenoxy herbicides (standardized incidence ratio [SIR] = 2.3, CI = 0.6-5.8). Just as before, this excess occurred in workers employed for more than 1 year in the Kemisk Vaerk Køge factory (SIR = 6.4, CI = 1.3-18.7). The author concluded that her study continues to provide evidence that exposure to phenoxy herbicides increases the risk of STS.

However, Lynge maintains that only small amounts of 2,4-D and “negligible” amounts of 2,4,5-T were produced at the KVK factory. That this amount of 2,4,5-T was negligible is somewhat at odds with data from an earlier paper in which she discussed the design of her ongoing cohort study (Lynge, 1987). In the 1987 paper, she reported that although 5.3 tons of

2,4,5-trichlorophenol were produced in 1951 and 1952, 350 tons of 2,4,5-T esters were produced from 1951 to 1981 based on purchased 2,4,5-T acid. This varied from zero to as much as 63 tons in any one year. Very likely, the term "negligible" is used in a relative sense—relative to the other herbicides in the KVK factory, which were produced in much larger amounts. Actual exposure to 2,4,5-T may have been greater than the impression given in Lynge's 1993 study. Most of the potential exposure was to MCPA, MCPP, 2,4-DP, and various dyes and pigments. MCPA, MCPP, 2,4-DP, and the nondioxin-containing phenoxy herbicides have not heretofore been seriously thought of as possible causes of cancer in humans.

Lynge also found that the risk of NHL was not elevated in persons potentially exposed to phenoxy herbicides. She did find what she calls a "puzzling" 3.5-fold excess risk in employees of KVK employed in other manufacturing departments. No detailed information on production in these areas was included in the study.

Little additional information is provided concerning any increased risks of other forms of cancer, except for a statement that multiple myeloma and cervical cancer in women and malignant melanoma in men were significantly increased. No numbers are given for these statements. A significant excess risk of lung cancer seen in the earlier study is now borderline significant in this study (obs = 13, SIR = 1.6, CI = 0.9-2.8). The author had planned to have serum tissues in some of her subjects analyzed for their PCDD and PCDF content although none have been forthcoming.

In a later update, Lynge (1998) identified 2,119 workers from the two factories described above who had exposure to phenoxy herbicides, 940 in the manufacture and packaging of phenoxy herbicides and 1,179 in manual service functions. These workers were followed until December 31, 1993, and all tumors diagnosed during this time were tallied and compared with cancer incidence rates for the Danish population for sex, 5-year age, and calendar-time period. Standard incidence ratios were calculated for numerous tumor sites including STS and NHL. The overall cancer incidence was lower than expected (SIR = 0.87) based upon 204 observed cases. The SIR for STS was 1.62 (95% CI = 0.4-4.1) based upon four observed cases, all among men employed at the KVK, where the SIR was 2.38 (95% CI = 0.7-6.1). On the other hand, there were only six cases of NHL, and the SIR was 1.10 (CI 0.4-2.6). The author concluded that on the basis of small numbers there is a suggestion that an increased risk of STS is associated with exposure to MCPA and related phenoxy herbicides. However, the author maintains that there is no indication of an increased risk of NHL or of other cancer diseases as well. The author does caution the reader that these findings are based upon small numbers. Few cancer cases (including deaths) have been identified thus far. It may require several more years of follow-up before any conclusive findings can be derived from this data.

Coggon and colleagues (1986) conducted a study of 5,754 workers at a British plant that manufactured and formulated MCPA from 1947 until 1982 and operated its own aerial and tractor-mounted spraying service from 1947 until 1972. The authors stated that other phenoxy acids were handled "at times" and that "in comparison with MCPA, 2,4,5-T was handled only on a small scale." Overall mortality was less than that of the national population, as was mortality from cancer. Among workers whose jobs meant potential exposure to MCPA, there was a deficit of deaths from cancer, all sites (297 observed versus 314.0 expected), but with one STS occurring when 0.6 were expected. If a rural adjustment factor were applied, the expected deaths would be 276.3. This would produce an SMR of 106. No significant site-specific deaths were reported. As MCPA contains no 2,4,5-T, these persons would not have exposure to dioxin. However, because no exposure information was collected it would be difficult to confirm this.

Coggon et al. (1991) conducted a study of four British cohorts of manufacturers of phenoxy herbicides, including 2,4,5-T, comprising 2,239 men employed sometime during the period 1963 to 1985. All four of these cohorts were included in the Saracci et al. study previously discussed. Follow-up was to the end of 1987 through the National Health Service Central Register and the National Insurance Index. Comparisons were with the national population. Factory A produced 2,4,5-T beginning in 1968, while the remaining three factories formulated it beginning in 1959, 1960, and 1970, respectively. No tissue measurements were conducted on any members of the cohort. A slight excess of lung cancer was noted (19 observed, 14.2 expected). Two NHLs also were observed (0.87 expected). No STSs were observed (0.18 expected). Total cancer also was not increased (37 observed, 36.85 expected).

This cohort has not been followed for a long enough time to expect latent effects to manifest themselves. The authors assumed that the slight increase in lung cancer was probably due to cigarette smoking or a chance occurrence based on the observation that most of the lung cancer deaths occurred less than 10 years after first exposure to phenoxy compounds. Phenoxy herbicides produced or formulated at these factories included 2,4-D, MCPA, 2,4-DP, 2-methyl-4 chlorophenoxy butyric acid (MCPB), MCPP, phenoxybutyric acid (PBA), parachlorophenoxyacetic acid (PCPA), and phenoxyacetic acid (PAA), as well as other herbicides. The author says they were exposed to a multiplicity of chemicals. Except for the slight increase in lung cancer, which is in the same direction as the findings from the earlier cohort studies, this study contributes little to the elucidation of the risk of cancer from exposure to TCDD.

Kogevinas and colleagues (1993) studied a group of 701 occupationally exposed women enrolled in IARC's International Registry of Persons Exposed to Phenoxy Herbicides and Their Contaminants. These workers are also included in the Saracci et al. (1991) study as well as the Kogevinas et al. (1997) study. The likelihood of exposure to TCDD was based on individual job

histories, company records, and company exposure questionnaires. Actual measurements of TCDD serum levels in women were not available, according to the authors, so that confirmation of exposure could not be accomplished. Both national cancer incidence rates and national death rates were used to generate expected cases and deaths utilizing the methods of the Saracci IARC study.

The overall cancer risk did not exceed expected (SIR = 96, CI = 0.6-1.4) based on 29 cases. However, the group with the greatest potential for exposure to TCDD-contaminated chlorophenoxy herbicides produced a significant excess risk of cancer of all sites (SIR = 222, CI = 1.0-4.2) based on nine cases. The risk was observed within the first 10 years of exposure, with no elevated risk appearing after the 10th year of observation. For those women who had probable exposure to TCDD, the risk of dying from cancer was slightly elevated as well (SMR = 165, CI = 0.4-4.8) based on three deaths.

This study suffers from many of the same problems as the Saracci et al. (1991) and Kogevinas et al. (1997) studies. In addition, it is a study of a small population and as such cannot be considered sensitive to the detection of small risks. These same workers were also subject to exposure to other toxic chemicals in the workplace, which may also have an effect on the risk of cancer.

However, the elevated cancer risk in women exposed to TCDD-contaminated phenoxy herbicides is consistent with a hypothesis of overall increased cancer risk seen in other studies from exposure to TCDD or TCDD-like contaminants.

Recently, another study was published (Bueno de Mesquita et al., 1993) of a cohort of 2,310 workers in two plants involved in the manufacture and preparation of phenoxy herbicides (not necessarily 2,4,5-T) in the Netherlands. These workers were also included in the IARC International Registry of Persons Exposed to Phenoxy Herbicides and Their Contaminants and hence were part of the Saracci et al. (1991) study. Some 963 were considered by the author to be exposed to phenoxy herbicides, while 1,111 were considered not exposed. The follow-up periods were somewhat skewed between the two subcohorts as well. The workers of one plant were followed from 1955 to 1985, and those at the other were followed from 1965 to 1986.

Only a slight increase occurred in total cancer mortality based on 31 deaths (SMR = 107, 95% CI = 73-152) utilizing The Netherlands' national rates. A slightly higher risk of total cancer was seen based on 10 deaths (SMR = 137, CI = 66-252) in 139 workers probably exposed to dioxins during or immediately after a 1963 industrial accident in which dioxin was released into the atmosphere.

When compared with nonexposed workers, mortality due to all cancers was insignificantly elevated (RR = 1.7, 95% CI = 0.9-3.4) while that due to respiratory cancer was

also insignificantly elevated (RR = 1.7, 95% CI = 0.5-6.3). This group was too small to provide enough power to detect significant site-specific cancers.

Although the size of the cohort seems large, actually only about 549 workers in Factory A had a potential for exposure to TCDD-contaminated 2,4,5-T and the higher chlorinated dioxins. No one at Factory B was exposed to 2,4,5-T because it was not produced there. At Factory A, the SMR for lung cancer was elevated insignificantly to 165 based on 6 deaths in the 20-year latent category. No serum dioxin measurements are available to substantiate exposure to dioxin. However, the authors did conclude that the SMR of 73 for Factory A, the SMR of 118 for Factory B, and the SMR of 137 for the cohort exposed to the accident are not inconsistent with the possibility of a carcinogenic effect of TCDD in humans.

Hooiveld and co-workers (1996) updated the earlier study by adding additional years of follow up to December 31, 1991. Cancer mortality remained statistically significantly high (SMR = 146, 95% CI = 109-192) in factory A. By latency after 20 years, a statistically significant SMR = 160 (95% CI = 110-225) is evident. On the other hand, no unusually high mortality occurred in factory B, possibly because of the small size of the cohort and the fact that few deaths from cancer were expected. The authors concluded that relative risks were highest in the highest exposure category, indicating a dose-response relationship with TCDD exposure level.

Hooiveld et al. (1998) in still another update studied the 562 workers exposed to 2,4,5-T that were discussed earlier. The authors followed the cohort to December 31, 1991, and identified 139 deaths to the 549 males of the cohort. In addition, serum TCDD levels were also gathered on 47 surviving workers of this cohort. Of these, 14 were exposed in the accident of 1963. Seventeen were exposed to phenoxy herbicides or chlorophenols but were not involved in the accident. The remaining 16 of the 47 were never exposed to phenoxy herbicides or chlorophenols. The arithmetic mean serum TCDD levels of the three groups defined as accident, exposed but no accident, and nonexposed were, respectively, 96.3, 16.6, and 7.6 ppt. These data were collected in 1993. On the basis of these data the authors extrapolated back in time to get some idea of what the maximum potential serum TCDD levels could have been at the time of the accident. These estimated values were 1,841.8, 244.1, and 7.6 ppt, respectively. The SMRs in 140 male workers who were exposed during the accident and who presumably had higher levels of serum TCDD also exhibited a significantly higher risk of malignant neoplasms (SMR = 1.7, 95% CI = 1.1-2.7) while in the larger exposed group of 549 male workers, with lower levels of serum TCDD, the risk of malignant neoplasms was significant as well (SMR = 1.5, 95% CI = 1.1-1.9).

However, when mortality in the 549 exposed workers was contrasted against mortality in the 482 nonexposed workers from the larger cohort, the exposed group exhibited a significantly

increased risk of death from cancer (RR = 4.1, 95% CI = 1.8-9.0) and specifically, respiratory cancer (SMR = 7.5, 95% CI = 1.0-56.1). The authors concluded that the results of this cohort study support the evidence of an exposure-related high risk of cancer in workers exposed to phenoxy herbicides, chlorophenols, and their contaminants.

Wiklund and Holm (1986) studied a massive cohort of 354,620 Swedish men who were recorded as having an agriculture or forestry job according to the census of 1960, versus 1,725,845 Swedish men in all other industries. The primary exposure in those jobs was postulated to be primarily MCPA, and 2,4-D and 2,4,5-T to a lesser extent. The authors found that the relative risk of STS was 0.9. This study has several deficiencies that reduce its usefulness in determining the risk of STS due to exposure to TCDD: (1) a lack of individualized exposure data (men were classified into six major subgroups by occupation from census data); (2) only 15% of Swedish agricultural and forestry workers were estimated to be exposed to phenoxyacetic acids (a smaller percentage was exposed to dioxin-contaminated phenoxy herbicides) and 2% to chlorophenols; (3) Swedish agricultural workers have a decreased cancer risk and tend to use health services less frequently; (4) classifying workers according to a 1-week employment status in October of 1960 as reported in a census invites the possibility of misclassification; and (5) the crude rate of STS in agricultural and forestry workers based on data in the study was 5.45 per 100,000 person-years, versus 5.00 per 100,000 person-years in the remaining workers. Both rates are high compared with rates from other nations (1 to 3 per 100,000 person-years).

A few years later, Wiklund et al. (1988, 1989) produced two new cohort studies that superficially appear to contradict the earlier findings of Hardell and Eriksson. Wiklund et al. followed some 20,245 licensed pesticide applicators in Sweden from date of license in 1965 or after until December 31, 1984. Some 72% were estimated to have been exposed to phenoxy herbicides 1 day or longer (based on questionnaire data sent to a random sample of 273 persons in the cohort). The relative risk for STS reported in the first study was found to be 0.9, with a mean follow-up time of 13.9 years. Even after a 10-year latency, the risk for STS was only 1.0 based on four deaths. With respect to the second study of all other cancer sites, major significant deficits were found in several sites followed for an average of 12.2 years until December 31, 1982. No report is given concerning loss to follow-up or vital status.

The authors describe a major disadvantage of these studies to be a “lack of individual exposure data” and that information is available “for only a sample of the cohort.” Even the length of exposure of individual applicators to phenoxy herbicides is not available. What is presented is information that herbicide use in the 1950s was only 19%, and in the 1960s it increased to just 49%. By the 1970s, however, it was up to 67%. On the other hand, pesticide use is reported to be 92% during the same period. This seems to indicate that perhaps less than

half had any exposure to the phenoxy herbicides at the time of licensing and perhaps for many years afterwards. Furthermore, no information is presented about the presence or absence of chloracne, another marker of exposure to TCDD.

In addition to missing important information regarding the vital status of this cohort by the end of the follow-up, no information is available concerning the distribution of person-years "at risk" generated by the "lost to follow-up" group. Among the cancer sites reported to have significantly reduced risks are total cancer, liver, pancreas, lung, and kidney.

Furthermore, the extent of exposure to the agent of concern, TCDD, may not be extensive among licensed applicators in Sweden. The entire discussion is centered on exposure to "phenoxy herbicides." The authors state that the most widely used phenoxy herbicides in Sweden are MCPA, mecoprop, and dichlorprop. None of these contain TCDD as a contaminant. 2,4-D and 2,4,5-T have also been used to a "lesser extent" according to the authors. Sweden prohibited the use of 2,4,5-T in 1977. If, as the authors state, only 19% used herbicides in the 1950s, increasing to 49% in the 1960s, it suggests that far fewer applicators were exposed to small quantities of TCDD for a long enough period of time to produce any effects. Furthermore, only 68.2% of the cohort could have attained the age of 59 by the close of the study in 1984. This hints at the likelihood that the full impact of exposure on mortality has not yet been achieved. In fact, the authors report that the "latency time may anyhow be too short to detect increasing risks of cancer . . . ."

7.5.5. Summary

The cohorts assembled by Fingerhut et al. (1991), Steenland et al. (1999), Manz et al. (1991), Becker et al. (1996), Flesch-Janys et al. (1995, 1998, 1999), Zober et al. (1990), and Ott et al. (1996) are important because they contain sizable proportions of persons with substantial TCDD exposures. These exposures were documented, at least in subsets of the cohorts, by blood and/or adipose tissue measurements, workplace measurements, and the occurrence of chloracne. The Saracci et al. (1991) cohort and later Kogevinas et al. (1997), while significantly larger, were assembled with nonuniform exposure criteria for TCDD exposure, leading to less confidence in the results.

The exposures and methods in the three studies in males (Fingerhut et al., 1991; Manz et al., 1991; Sober et al., 1990) were similar enough to warrant aggregating the results. Within each study, relative risks were estimated by summing the observed and expected numbers of deaths across categories of age, race, and calendar time, and then dividing the totals to produce relative risk estimates in the form of standardized mortality ratios. Thus, aggregate relative risks can be obtained simply by summing the observed and expected numbers of deaths across the studies. Alternatively, the aggregate relative risk could have been derived by weighting the individual

relative risks from each study by the inverse of the variance. A separate analysis of the three studies using estimates of lifetime dose intake is presented in Section 8.5. As shown in Table 7-8, the studies by Manz et al. (1991), Becker et al. (1996), Flesch-Janys et al. (1995, 1998, 1999), Zober et al. (1990), and Ott et al. (1996) add to the information provided by the study by Fingerhut et al. (1991) and Steenland et al. (1999), i.e., they increase the precision of the relative risk estimates (as indicated by a narrowing of the confidence intervals). They suggest increased risk—especially among persons with relatively high exposure and relatively long latency—for connective and soft tissue cancers, for lung cancer, and for all cancers combined.

The elevations for these cancers also appear to be more pronounced in the subcohorts of relatively high exposure and relatively long latency than in the total cohorts. Because they come from comparisons between blue-collar workers and national populations, it is reasonable to suspect that these estimates—especially for lung cancer—are influenced to some degree by confounding from cigarette smoking. However, the limited analyses presented suggest that the association is not a chance occurrence (Table 7-2). The counterinfluences of the healthy worker effect, exposure misclassification, and/or diagnostic error would tend to force risk estimates downward.

The results in males are consistent with results from animal studies. In Chapter 6, it was shown that in a lifetime TCDD bioassay male rats developed lung cancer, and in an initiation-promotion study ovariectomized rats exposed to TCDD developed lung tumors, while intact rats similarly exposed did not. Furthermore, the mice in the NCI study developed fibromas and fibrosarcomas. Also, TCDD affects the immune system and has been shown to be a tumor promotor in animal liver, lung, and skin assays. Either or both of these actions could lead to increased total cancer. With respect to health effects in females, the study by Saracci et al. (1991) and its update by Kogevinas et al. (1997) suggest a possible increase in breast cancer, but the results are considered preliminary in view of the small numbers and less certain exposure. On the other hand, although Kogevinas et al. (1993) reported an increase in cancer incidence from all causes among women who were exposed to chlorophenoxy herbicides contaminated with TCDD, no excess was observed for breast cancer. Still, in another study by Bertazzi et al. (1993, 1997, 1998) to be discussed later in the section on Seveso, Italy, a nonsignificant deficit of breast cancer and endometrial cancer was seen in women living in geographical areas contaminated by dioxin. TCDD exposure might be expected to result in decreased breast cancer in females, on the basis of similar observations in rats and on TCDD's action on downregulation of the estrogen receptor in the mammary gland. However, this is species-, tissue-, and age-specific.

In conclusion, these studies in occupationally exposed workers are highly supportive of a causal relationship between exposure to phenoxy herbicides and the risk of cancer.

7.6. CASE-CONTROL STUDIES IN GENERAL POPULATIONS

In this section on case-control studies, the discussion will focus chiefly on the cancer sites, i.e., STS and NHL, that have been suggested by the earlier Swedish studies as being associated with exposure to the phenoxy herbicides. This is a reflection of the intense interest shown in these two cancer sites over the past decade. Few, if any, case-control studies have been completed on other cancer sites. And of course, if other cancer sites are not studied, the risk of cancer cannot be evaluated.

7.6.1. Sweden

Hardell, Eriksson, and colleagues conducted four studies of STSs (Hardell and Sandström, 1979; Eriksson et al., 1981, 1990; Hardell and Eriksson, 1988) and one study of malignant lymphomas (Hardell et al., 1981) among men living in different parts of Sweden. In all studies, cases and their matched controls were considered exposed if they reported phenoxy acid or chlorophenol exposures lasting at least 1 day and occurring at least 5 years before the case's date of diagnosis. These studies were initiated by clinical observations in 1976 made by Dr. Hardell and his colleagues at the Center of Oncology, University Hospital, Umea, Sweden, and documented in his 1977 case report (Hardell, 1977).

The nature of the phenoxy acid exposures differed across the Swedish study locales. In northern Sweden, most exposures occurred in the use of 2,4,5-T and 2,4-D in combination in forestry applications, often by knapsack spraying (Hardell and Sandström, 1979; Hardell and Eriksson, 1988; Hardell et al., 1981; Hardell, 1981a,b). Phenoxy acid exposures not involving 2,4,5-T became progressively more common, on a proportional basis, in the central and southern regions in which agricultural herbicide uses predominated (Eriksson et al., 1981, 1990). Although exposures not involving 2,4,5-T made up only 22% of all phenoxy acid exposures in the first northern sarcoma study (Hardell and Sandström, 1979; Hardell, 1981a, b), they accounted for 27% in the study in central Sweden (Eriksson et al., 1990) and 58% in the study in southern Sweden (Eriksson et al., 1981). Exposures defined only as phenoxy acid exposures are therefore less useful as indicators of exposure to TCDD and related compounds in southern Sweden than in the central and northern parts of the country. Furthermore, none of these studies provide information on how much exposure each subject may have had.

The reports contain little information on the specific chlorophenol preparations to which the cases and controls were exposed. Occasional statements in some of the manuscripts suggest that most chlorophenol exposures occurred in the sawmill and pulp industries, that they primarily involved pentachlorophenol, and that they seldom involved trichlorophenols. Thus, most of the reported chlorophenol exposures entailed exposures to the higher-chlorinated PCDDs and PCDFs but not to TCDD.

Because exposure prevalences were generally low and because phenoxy acids and chlorophenols tend to be used in different occupations, very few persons reported joint exposures. Thus, it is efficient to control potential confounding in the analysis of data from these studies by comparing each exposure category (phenoxy acids vs. chlorophenols) with the category composed of all persons who reported no exposure to phenoxy acids or chlorophenols. Based on this method of analysis, relative risk estimates from all five studies are presented in Table 7-9, with the sarcoma studies arranged in order of publication. The measure of effect here is the "odds ratio" that is an estimate of the RR when the cancer is relatively rare and henceforth will be called the RR.

The results for 2,4,5-T are the only results pertinent to TCDD exposures only. Because of the small number of cases and controls reporting 2,4,5-T use in southern Sweden, the confidence interval for the relative risk estimate from the study in that part of the country (Eriksson et al., 1981) is extremely wide. A separate relative risk estimate for 2,4,5-T could not be computed from the data in the second northern sarcoma study (Hardell and Eriksson, 1988). The published report, however, did state that all of the cases and most of the controls exposed to phenoxy acids were exposed to preparations including 2,4,5-T (Hardell and Eriksson, 1988). The report also gave a relative risk of 3.5 for TCDD exposure, but no confidence interval or counts of cases and controls were provided.

The studies were conducted in two phases. The lymphoma study (Hardell et al., 1981), the first northern sarcoma study (Hardell and Sandström, 1979), and the southern sarcoma study (Eriksson et al., 1981) were published between 1979 and 1981. The remaining two sarcoma studies (Hardell and Eriksson, 1988; Eriksson et al., 1990) appeared about a decade later. The relative risk estimates from these more recent studies are consistently lower than those from the earlier studies (Table 7-9). Thus, systematic differences between the two sets of studies may be an explanation for the heterogeneity of results.

The first set of studies received a considerable amount of criticism concerning the methods by which the exposure information had been obtained (Hardell, 1981b; Cole, 1980). The basic concern was the possibility of bias from differential exposure misclassification between cases and controls (sometimes called "observational bias" or "interviewer and recall bias"), with false-negative reports of exposure suspected as being more common among the controls and false-positive reports more common among the cases. Much of the discussion focused on telephone interviews that were conducted by research staff who were aware of the purpose of the study and of the case or control status of the respondents. These interviews were conducted with selected participants to confirm reported exposures and to resolve uncertainties on postal questionnaires, which were the primary sources of exposure information. For living cases, controls were selected from the Swedish National Population Registry. For deceased

cases, controls were selected from the Swedish National Registry for Causes of Death. Hardell controlled for age by stratifying his cases and controls into four age groups and calculated Mantel-Haenszel point estimates of the odds ratios. As the criticisms of these procedures have echoed through the years (Bond et al., 1989b; Colton, 1986), no quantitative analysis has been made of the degree of bias that would have been required to produce the very strong associations reported in the first three studies (Table 7-9). Of greater importance, analyses by Hardell based solely on the questionnaire information (Hardell, 1981b) have been largely overlooked. These analyses produced relative risk estimates very similar to those obtained when the information from the supplemental interviews was used.

Hardell also enrolled a series of colon cancer patients (Hardell, 1981) as a sort of "positive control" group. In contrast to STSs and malignant lymphomas, colon cancer turned out not to be associated strongly with phenoxy acid or chlorophenol exposures. Hardell and Eriksson made a similar finding in one of the newer studies (Hardell and Eriksson, 1988) when they included a control group consisting of a variety of cancers along with a set of general population controls. The cancer controls were drawn at random from the Swedish Regional Cancer Registry.

Despite Hardell's conclusion that "the previously reported associations . . . cannot to any essential degree be explained by observational bias in the studies" (Hardell, 1981b), he and his colleagues imposed procedures designed to reduce the potential for such bias in their subsequent studies (Eriksson et al., 1990; Hardell et al., 1981). When lower relative risk estimates were produced (Table 7-9), the researchers suggested that one explanation might have been the improved methods of exposure assessment. Again, controls were from national population registries. A second explanation suggested by the authors is that the use of cancer referents could have reduced recall bias.

The investigators suggested that another explanation for the reduced relative risk estimate for phenoxy acids and STSs in the study in central Sweden (Table 7-9) "could be the decade in which exposure occurred" (Eriksson et al., 1990), with the implication that exposures were higher in earlier decades. They supported this suggestion with an analysis in which only those phenoxy acid exposures occurring in the 1950s were considered. This analysis yielded a higher relative risk estimate of 2.3 (95% CI = 1.0-5.4). Unfortunately, no basis of comparison exists because analyses by calendar time of exposure were not conducted in any of the other studies. However, this is reasonable given what we know about processes.

As an alternative explanation for the lack of an elevated relative risk estimate in connection with chlorophenols in the second northern sarcoma study (Table 7-9), the authors offered "random variation" due to a low number of exposed subjects (Hardell and Eriksson, 1988). The prevalence of chlorophenol exposures among the controls in that study (10.9%) was several times *higher* than in the earlier northern sarcoma study (2.9%) (Hardell and Sandström,

1979) and virtually identical to the prevalence in the lymphoma study (10.4%) (Hardell et al., 1981). The phenoxy acid exposure prevalences were highly uniform in all three northern studies: 7.2% in the lymphoma study (Hardell et al., 1981), 6.8% in the first sarcoma study (Hardell and Sandström, 1979), and 7.1% in the second sarcoma study (Hardell and Eriksson, 1988). The chlorophenol exposure prevalence among the controls in the first northern sarcoma study (Hardell and Sandström, 1979) seems to have been low. However, the overall consistency of some excess risk is perhaps more important than actual levels of the excess.

For three of the studies by Hardell and colleagues, relative risk estimates can be computed restricting the data to persons who had worked in agriculture and the other occupational categories in which the exposures of interest tended predominantly to occur (Table 7-10). For the lymphoma study (Hardell et al., 1981) and the sarcoma study in southern Sweden (Eriksson et al., 1981), the results for exposure to phenoxy acids, chlorophenols, or both in the restricted analyses are virtually identical to those obtained with the data for all subjects (Table 7-9). For the sarcoma study in central Sweden (Eriksson et al., 1990), however, the relative risk for phenoxy acids was higher (2.3) within the special occupational categories than among all subjects.

Interestingly, Eriksson and his colleagues stated that the association with the risk of STS seemed to strengthen with exposure to the higher-chlorinated dioxin isomers. His conclusion was that not only may TCDD be a risk factor for STS, but also that other higher-chlorinated dioxins may be risk factors.

The risk calculated for exposure to 2,4,5-T in the 1950s was somewhat higher at 2.94 (95% CI = 1.1-8.0). However, exposure to 2,4,5-T during the span of the study was nonsignificant at 1.8 (95% CI = 0.9-3.9), excluding the chlorophenols. Exposure to dioxin-containing phenoxyacetic acids or chlorophenols, excluding nondioxin-containing herbicides, produced a significant risk estimate of 2.4 (95% CI = 1.3-4.5). Exposure to high-grade pentachlorophenols produced a risk ratio of 3.9 (95% CI = 1.2-12.9).

These analyses are important because many of the mechanisms by which biases might occur would be related to occupation. For instance, biases in case identification, control selection, or nonparticipation that might be related to occupational status (e.g., by its link to socioeconomic status) would not be expected to be as great in analyses conducted within the occupational categories as in analyses of the overall data. The potential for confounding by occupational exposures encountered in the same lines of work would also be reduced in the occupationally restricted analyses. Several researchers and reviewers (Johnson, 1990; Pearce et al., 1985; Blair et al., 1985) have noted reports of farmers being at increased risk of malignant lymphomas and other cancers and have mentioned a wide range of potentially responsible exposures, “including pesticides, solvents, oils and fuels, dusts, paints, welding fumes, zoonotic

viruses, microbes, and fungi" (Blair et al., 1985). (Studies of farmers and other agricultural workers are not included in this review because mere membership in these occupational categories is insufficient as an indicator of exposure to such substances as 2,4,5-T or chlorophenols.)

In the original reports, occasional attempts to assess exposure-response trends produced mixed results. In general, the reported exposure periods were short in all of the studies. In the first northern sarcoma study, for instance, 93% of all reported phenoxy acid exposures lasted 1 year or less, 74% lasted 6 months or less, and 33% lasted 30 days or less (Hardell and Sandström, 1979; Hardell, 1981b). Reported exposures in southern Sweden were even briefer, with 53% lasting 30 days or less (Eriksson et al., 1981).

Hardell et al. recently aggregated the four STS studies in a re-analysis examining exposures to herbicides contaminated with TCDD and other dioxins (Hardell et al., 1991). Increasing trends in risk with duration of exposure (<1 year and ≥1 year) and "latency" (5-19 years and ≥20 years since first exposure) were numerically impressive, being based on the totals of 434 cases and 948 controls from all the studies (Table 7-11). The problem of concomitant exposures was not solved in these analyses, however, and an analysis of the aggregated data obscured the pronounced heterogeneity of results among the individual studies (Table 7-10).

Regardless of the exposure definition, considerable heterogeneity exists among the relative risk estimates from the four STS studies (Table 7-10). (Tests of homogeneity yield two-tailed *p*-values of 0.002 for phenoxy acids, chlorophenols, or both; 0.02 for phenoxy acids; 0.03 for 2,4,5-T; and 0.01 for chlorophenols.) In this circumstance, aggregation of results across studies is not indicated and, instead, a search should be made for explanations for the heterogeneity.

Two additional studies of malignant lymphomas and one study of STSs were conducted by independent research teams in southern Sweden. Olsson and Brandt's (1988) study consisted of 167 men diagnosed with NHL in the years 1978-1981 and 140 controls from the Swedish National Population Registry. Men who reported handling phenoxy acids or chlorophenols for at least 1 day were considered exposed. However, the main focus of the study was to evaluate the contribution of organic solvent exposure to the risk of NHL. Persson et al. (1989) studied 54 cases of Hodgkin's disease, 106 cases of NHL, and 275 controls of both genders from the population registry of Sweden. The cases were diagnosed in the years 1964-1986, but only those who were still alive in 1986 were included. The authors did not ask specific questions about phenoxy acid use. Wingren et al. (1990) studied 96 men with STSs diagnosed in the years 1975-1982, 450 general population controls, and 200 cancer controls from the regional cancer registry. Because the results did not differ substantially between the two control groups, only those obtained from analyses with the general population controls are reported here. The authors had

to resort to job-associated uses, of which one was called "unspecified chemical work, potential exposure to phenoxy herbicides and chlorophenols," because only limited information could be obtained about specific chemical exposures from postal questionnaires and selected supplemental telephone interviews. Results from these three studies are summarized in Table 7-12. Persson et al. (1989) found strong associations, Wingren et al. (1990) found an association of intermediate strength, and Olsson and Brandt (1988) found very little association. These studies are limited by the lack of specificity in their exposure information.

7.6.2. United States

Zahm, Cantor, and colleagues from the National Cancer Institute have reported results from three case-control studies of exposure to 2,4,5-T or 2,4-T as well as other pesticides and herbicides in four Great Plains States (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992). The first study was conducted in Kansas (Hoar et al., 1986). It included STSs, Hodgkin's disease, and NHLs, but detailed analyses were confined to the NHLs. The two subsequent studies, one conducted in eastern Nebraska (Zahm et al., 1990) and the other in Iowa and Minnesota (Cantor et al., 1992), evaluated NHLs. Cancer risks at other sites from exposure to 2,4-D calculated from these groups are the subject of later studies. These studies did not consider chlorophenol exposures, and only those persons who ever lived or worked on a farm were asked questions about pesticide exposures. Farmers and nonfarmers were asked about home and garden use of pesticides. Thus, all nonfarmers were considered unexposed. As in southern Sweden (Table 7-10), the vast majority of phenoxy acid exposures did not involve 2,4,5-T, and those that did virtually always involved 2,4-D as well. The relevance of these studies to the focus on TCDD and related compounds in this review is therefore somewhat limited. Only 3 out of 299 cases and 18 out of 1,005 controls were exposed to 2,4,5-T, the herbicide known to be contaminated with dioxin.

Results for 2,4,5-T from the three studies are summarized in Table 7-13. Among all subjects and among farmers, only the study in eastern Nebraska (Zahm et al., 1990) suggests an increase in risk. All three studies were conducted with virtually identical methods, and no information on herbicide application methods in any of the reports indicate any exposure conditions peculiar to eastern Nebraska.

The third set of relative risk estimates in Table 7-13 was computed using the investigators' procedure of including only the exposed farmers and the unexposed nonfarmers, with the unexposed farmers excluded. Comparing exposed farmers with unexposed nonfarmers makes it possible that risk estimates could be influenced by confounding effects that are germane to farmers, i.e., exposure to other pesticides or herbicides in large quantities. Furthermore, if the results of follow-up efforts are markedly different in farmers than in nonfarmers, this difference

also might add some uncertainty to the accuracy of risk estimates. In these analyses, the relative risk estimates from the studies in Kansas, Iowa, and Minnesota are somewhat higher and the estimate from the eastern Nebraska study is somewhat lower than in the two more conventional analyses.

Formal homogeneity tests across the three studies yield two-tailed *p*-values of 0.4 in the analysis of all subjects, 0.3 in the analysis restricted to farmers, and 0.6 in the third analysis. Ordinarily, especially considering the virtually identical methods used in the three studies, these results would be considered sufficient justification to compute summary estimates. Summary (maximum likelihood) estimates of relative risk are virtually identical in all three groups of subjects, with point estimates of 1.2, lower 95% confidence limits of 0.8, and upper 95% confidence limits of 1.7 to 1.8.

Woods and colleagues (1987) conducted a study of STSs and NHLs in western Washington State. In this study, the principal method of phenoxy acid and chlorophenol exposure assessment was to place job titles, activities, and chemical preparations reported during interviews into categories of potential exposure. The categories were created "in consultation with local industrial and university representatives who had long-term experience with forestry, wood products, and agricultural industries in the Pacific Northwest" (Woods et al., 1987). No statement is given about the relative prevalence of 2,4-D and 2,4,5-T among the phenoxy acids used in this region. The authors did not present any information regarding tissue levels of TCDD in either cases or controls.

The results (Table 7-14) show no association between STSs or NHLs and estimated potential for exposure to phenoxy acids or chlorophenols. The authors report, however, that the relative risk of NHLs associated with more than 15 years of potential exposure to phenoxy acids increased with time since the accumulation of that exposure. The relative estimates were 1.3 (95% CI = 0.9-2.2) for exposures more than 5 years before diagnosis, 1.7 (95% CI = 1.0-2.8) for exposures more than 15 years before, and 2.5 (95% CI = 0.5-13.0) for exposures more than 25 years before. The authors stated that similar trends were not seen in any of the analyses of STSs and phenoxy acids or of either cancer in connection with chlorophenol exposures. It is not possible with the available data from this study to conduct analyses restricted to persons who worked in forestry, agriculture, and the wood products industry, and in which the exposed persons are those who reported specific exposures to phenoxy acids or chlorophenols.

The western Washington State study reported two unique results. One consisted of elevated relative risks in connection with a history of chloracne based on personal interviews: 3.3 (95% CI = 0.8-14.0) for STSs and 2.1 (95% CI = 0.6-7.0) for NHLs. However, the diagnoses were not medically confirmed, and because only 1% of all cases and controls reported chloracne histories, the confidence intervals were extremely wide. The other intriguing result consisted of

elevated relative risks of STSs among persons with Scandinavian surnames (12% of the cases and controls). The estimates from this analysis were 2.8 (95% CI = 0.5-15.6) for "high" estimated potential for phenoxy acid exposure and 7.2 (95% CI = 2.1-24.7) for "high" estimated potential for exposure to chlorophenols. The authors noted that similarly elevated relative risks were not found for NHLs.

In a later study of the same study population, Woods and Polissar (1989) found a significant excess risk (OR = 1.33, 95% CI = 1.03-1.7) of NHL among farmers compared with nonfarmers. When further examined to determine if 2,4-D or 2,4,5-T was responsible, risks from both tended to be nonsignificantly decreased. However, frequency of use of these herbicides was not considered by the authors.

Brown et al. (1990) conducted a population-based, case-control interview study of 578 white males with leukemia in Iowa and Minnesota matched to 1,245 controls living in those same States. The purpose of the study was to investigate potential agricultural hazards that may be related to a diagnosis of leukemia. The cases were derived from the Iowa Tumor Registry and a network of hospitals and pathology laboratories in Nebraska between March 1981 and October 1983. Areas with little farm activity were excluded from the study. There was a slight but marginally significant elevation of leukemia risk (OR = 1.2, CI = 1.0-1.5) in farmers versus nonfarmers. But for those who mixed, handled, or applied 2,4,5-T, the risk was slightly but nonsignificantly elevated (OR = 1.3, CI = 0.7-2.2).

Eriksson and Karlsson (1992), in a population-based case-control study of 275 myeloma cases matched with 275 controls in 4 counties of northern Sweden, found a significant excess of myeloma (OR = 2.22, CI = 1.15-4.66) in persons who worked with phenoxy herbicides. Significant associations were also found with "farming," DDT, and certain domestic animals. Specific exposures to dioxins or dibenzofurans were not determined.

In another case-control study of Iowa agricultural influences on multiple myeloma, Brown et al. (1993), using similar methodology as in her earlier study, matched 173 white males with multiple myeloma to 650 controls from Iowa. Although a slight nonsignificant elevated risk (OR = 1.2, CI = 0.8-1.7) was seen in farmers, the risk of multiple myeloma from exposure to 2,4,5-T was found to be nonsignificant (OR = 0.9, CI = 0.4-2.1). The same was true for numerous other herbicides, pesticides, and insecticides.

The authors concluded that there was little evidence to suggest any association of multiple myeloma with farming or pesticides. Neither of these studies on leukemia or multiple myeloma has shown that exposure to dioxin occurred. This is only presumed; no actual measurements were taken. Both of these studies could be considered hypothesis-generating studies because they involved multiple exposures to many different chemicals used in farming.

The major problem with U.S. case-control studies is that specific exposure to TCDD and

related compounds is not identified or quantified, although information on the use of 2,4,5-T and 2,4-D is available in some studies. In some, only potential exposure to phenoxy herbicides is the exposure surrogate. This limits the usefulness of these studies.

7.6.3. New Zealand

Smith, Pearce, and colleagues conducted two studies of STSs (Smith et al., 1982a, 1983, 1984; Smith and Pearce, 1986) and one study of NHLs (Pearce et al., 1986, 1987) among men in New Zealand. In these studies, persons were first asked whether or not they "had worked in particular occupations in which there was potential for exposure to phenoxyherbicides or chlorophenols" (Smith et al., 1984). If the response was affirmative, "a series of subsidiary questions were asked to clarify the work done and the actual potential for exposure, firstly in general terms, and then in specific terms, seeking the identity of the chemicals used" (Pearce et al., 1986). The authors indicated that 2,4,5-T was widely used as a phenoxy acid herbicide in New Zealand over the years pertinent to these studies (i.e., prior to the early 1980s) (Smith et al., 1984). Thus, in these studies, the phenoxy acid exposure designation was considered a suitable indicator of exposure to 2,4,5-T and, thus, to TCDD. Typical uses of 2,4,5-T were in the spraying of gorse, blackberry, pasture, cereal, and peas. No actual measurements of TCDD were made in these studies.

In the analyses of phenoxy acids, the authors distinguished between "potential" and "probable or definite" exposure. The latter category was created by deleting persons with only "possible" exposures from those with "potential" exposures. It is not clear whether the "probable or definite" designation included inferences from job titles, activities, and the like, or whether it was based solely on affirmative responses to specific questions about phenoxy acid exposures. For chlorophenols, only the "potential" designation was employed.

In these studies, the controls were patients diagnosed with other cancers. Unlike a control group selected from the entire study population, a cancer control group offers less certainty about the degree to which its exposure distribution represents that of the study population, but greater certainty that differential exposure misclassification through elimination of interviewer bias and recall bias is negligible. However, inclusion of cancer sites in the controls that may be associated with the exposure could potentially bias the risk estimate toward the null. In these particular studies, the cancer controls had an additional advantage in minimizing any bias that might have resulted from the inability of the researchers to include patients diagnosed at private hospitals. Private hospitals in New Zealand have only recently been contributing to the National Cancer Registry. In an interim report of the NHL study, a second control group was drawn from the New Zealand electoral roll. The authors concluded that this control group "gave very similar

findings to those obtained with the main control group of other cancer patients" (Pearce et al., 1986).

Another unique feature of the New Zealand STS studies is that, like the mortality follow-up studies of chemical manufacturing and processing workers previously reviewed, they included only those cases classified to the International Classification of Diseases (World Health Organization, 1977) category 171, malignant neoplasms of the soft and connective tissues. This category, which does not include STSs occurring in parenchymatous organs such as the stomach or uterus, accounted for about 60% of the STS cases in the studies in Sweden (Fingerhut et al., 1984). There is no indication from the Swedish studies, however, that the associations with phenoxy acids or chlorophenols differed between STSs that would be classified in category 171 and those that would be classified in the categories for the involved organs (Hardell and Sandström, 1979; Eriksson et al., 1981; Hardell and Eriksson, 1988; Eriksson et al., 1990; Hardell, 1981a,b).

In the New Zealand study, investigators divided their STS research into two studies with very similar, but not identical, methods. The first study (Smith et al., 1982a, 1983, 1984) consisted of patients and controls with cancer registrations in the years 1976-1980. The second study (Smith and Pearce, 1986) extended case finding through 1982 and was the subject of an extremely abbreviated report. The controls in the second study consisted of 315 of the 338 cancer controls from the NHL study (Pearce et al., 1985) whose cancer registrations were during the period 1977-1981. (The results for the additional 23 controls, who were interviewed near the end of the NHL study, evidently were unavailable at the time the analyses for the second STS study were conducted.)

The first sarcoma study (Smith et al., 1982a, 1983, 1984) reported very similar results for phenoxy acids and chlorophenols when all subjects were included in the analyses, with relative risk estimates of 1.3 for any "potential" exposure and 1.6 for exposures ("definite or probable" for phenoxy acids, "potential" for chlorophenols) lasting more than 1 day and occurring more than 5 years prior to diagnosis (Table 7-14). For phenoxy acid exposures classified by the latter definition, sufficient data were presented to permit an analysis restricted to farmers. Thirty of the 82 cases, 13 of the 17 exposed cases, 44 of the controls, and 9 of the 13 exposed controls were farmers. Thus, the estimated relative risk is 3.0 (95% CI = 1.1-8.3) among farmers. Controlling for farming by ("indirect") standardization yields an estimated relative risk of 1.9 (95% CI = 0.8-4.5). Thus, as in some studies previously reviewed, accounting for the farmer/nonfarmer distinction has a material impact on the results from this study.

Very few details were presented for the second sarcoma study (Smith and Pearce, 1986). In comparison with a relative risk of 1.6 in the first study, the second study reported a relative risk of 0.8 for the principal measure of phenoxy acid exposure (Table 7-14, homogeneity-test *p*-

value = 0.2 contrasting the two studies). The exposure prevalences in the two control groups were virtually identical (14.1% in the first study and 14.6% in the second), but the prevalences in the two case groups differed (exposure odds ratio = 2.0, 95% CI = 0.7-5.4). Because of this difference, and because a relative risk estimate restricted to farmers cannot be computed with the data available from the second study, aggregation of the results would not be warranted.

The NHL study (Pearce et al., 1986, 1987) reported little or no association with phenoxy acids and a somewhat stronger association with chlorophenols (Table 7-15). The latter association did not increase when the more restrictive measure of exposure was used. The various activities involving exposure to chlorophenols include the treatment of fence posts as well as treating pelts in meat works tanneries. Data that would permit an analysis restricted to farmers were not reported.

The authors continue to maintain that herbicide spraying is a full-time occupation in New Zealand and that none of the STS or malignant lymphoma cases had been commercial sprayers. Smith et al. (1984) estimated the prevalence of current and former commercial sprayers at approximately 1,500, which would be 0.17% of the male population of New Zealand in the early 1970s (Waterhouse et al., 1982). On the null hypothesis, therefore, only about 0.1 commercial sprayers would be expected among the cases in each of the two STS studies, and about 0.3 commercial sprayers would be expected among the NHL cases. Thus, STS risk could have been increased manyfold and NHL risk could have been increased about threefold before even one commercial sprayer would be expected in any of the case groups. As a consequence, the absence of commercial sprayers in any of the case groups is not strong evidence against an effect.

In a letter to the editor, Pearce (1989) produced tabular data from his earlier case-control study by duration of use and by frequency of use. Although he maintained that his data exhibited little evidence of an association with NHL, a nonsignificant increase in the risk was seen in the category 10-19 days of use per year (OR = 2.2, 95% CI = 0.4-12.6) before dropping back to 1.1 in the category greater than 19 years.

In a study of nine selected applicators in New Zealand who had sprayed herbicides (and hence 2,4,5-T) for a minimum of 180 months, Smith et al. (1992) found a high correlation between tissue levels of TCDD and months sprayed. This is analogous to Fingerhut's finding that tissue levels of TCDD correlate well with duration of employment in the herbicide manufacturing industry. TCDD serum levels ranged from 131.0 ppt in a sprayer with 31 years of spraying to a low of 3.0 ppt in a sprayer who sprayed for only 7 years. The average was 53 ppt for the nine sprayers who sprayed an average of 16 years. Actually, the mean average TCDD serum level in Fingerhut's lowest exposure group who worked less than 1 year was higher (69 ppt) than the mean average of sprayers in the Smith et al. study. Smith's conclusions were based on his analysis that brief exposures to TCDD probably do not contribute to the increased cancer

risks seen in studies in other countries. Although it is an interesting inference, this conclusion may be somewhat overstated without some information regarding what the tissue levels of TCDD were in the individual cases and controls of those other studies, information that only recently is becoming available and not for all studies.

Unfortunately, the finding suggested by several occupational accidents, such as in Seveso, Italy, and Nitro, West Virginia, that one-time large doses of exposure to TCDD could, in fact, lead to residual high tissue levels of serum TCDD years later, could not be tested in the studies of Swedes. Hardell and colleagues have provided little information regarding tissue levels of TCDD, past or present, in individuals who were participants in their studies. One study by Nygren et al. (1986) is cited frequently as evidence that Swedish subjects who were involved in spraying phenoxy herbicides have low levels of TCDD in adipose tissue samples. Thirty-one patients from the Regional Hospital in Umea were each relieved of a sample of adipose tissue for analysis of dioxin content. After "careful interviewing," it was determined that 13 of these patients had "sprayed" herbicide at some time during their past. Adipose tissue measurements indicated a mean of 2 ppt of TCDD. The remaining 18 nonsprayers revealed a mean of 3 ppt.

However, in correspondence with C. Rappe (1987) regarding this study, it was determined that in the only three cases that were STSs, adipose tissue measurements of TCDD are reported to be 2, 2, and 9 ppt. The one STS with the highest TCDD level (9 ppt) of any of the 31 subjects is stated by the authors to have had only 10 days of "knapsack spraying" some 25 to 29 years earlier. What is striking about these 13 "cases" is that the total levels of *all* chlorinated dioxins are considerably greater, i.e., from 168 ppt to as much as 936 ppt per patient, and that TCDD levels are a mere fraction of the total. There is no TEQ conversion here. The vast majority consist of the higher-chlorinated PCDDs. It is not clear that spraying herbicides is or ever was a major occupational endeavor of this group of 13 or that any of these patients was exposed to TCDD in large quantities. Based on recent correspondence with Hardell (1993), none of the patients reported by Nygren were members of any of his case-control studies. Nor does Nygren claim in his study that any of the cases he considered are from Hardell or Eriksson's studies. The total PCDD levels in the three STSs ranged from 674 ppt to 792 ppt (Rappe, 1987). These were nearly all highly chlorinated. Although the cases with tissue samples came from Hardell's clinic, they did not come from any of his case-control studies. In fact, since these case-control studies were done in the late 1970s and early 1980s, most, if not all, subjects were deceased by the time that the technology became available to measure serum TCDD levels.

This analysis provides little information on tissue levels in Swedish applicators with STS. Furthermore, there may be some differences in applicator practices between New Zealand and other countries such as Sweden. Professional applicators in New Zealand are registered with the New Zealand Agricultural Chemicals Board (Smith et al., 1982b, 1992). And although it might

appear that they could be expected to receive a great deal of exposure to TCDD, more than half of the applicators show serum TCDD levels below 50 ppt (Smith et al., 1992). Considering that they were spraying 2,4,5-T for 7 to 31 years until just recently, it seems remarkable that the distribution of serum TCDD levels is as low as it is. The authors report that professional pesticide applicators in New Zealand are "perhaps the group most heavily exposed to agricultural use of 2,4,5-T in the world." In other studies, shorter exposures to large quantities of TCDD-containing herbicides have occurred to a few personnel such as in the Ranch Hands cohort; Seveso, Italy; and the Nitro, West Virginia, accident. In Fingerhut's study, employees with less than 1 year of exposure to phenoxyacetic acids had mean serum levels averaging 69 ppt TCDD.

7.6.4. Italy

Vineis and colleagues conducted a case-control study of STSs in three provinces in northern Italy (Vineis et al., 1986). Phenoxy acid exposure classifications were based on job information provided on interviews or questionnaires. The assessments were made by "two experts with experience in chemical aspects of agriculture." Cases and controls were classified into three categories: "certainly unexposed," "exposure could not be ruled out" (abbreviated below as "possibly exposed"), and "certainly exposed." The authors implied that phenoxy acid herbicides of all types (2,4-D, 2,4,5-T, and MCPA) were used in the area during the periods of interest, but were able to document only the use of 2,4-D and MCPA. Thus, this study may have limited relevance to TCDD exposures.

The study indicated an inverse association between possible or certain phenoxy acid exposure and STS risk among men and a positive association among women (Table 7-16). This latter association was restricted to women who were alive at the time the exposure information was collected. (In the other studies in this review, in which the results were stratified by vital status at the time of the interview, no appreciable differences were found.) As shown in Table 7-16, when the analysis is restricted to persons who had ever worked in agriculture ("farmers"), the relative risk among all women is reduced from 1.9 to 1.1. Sufficient data are not available for an analysis that is both restricted to farming women and stratified by vital status.

The authors offered overmatching by location of residence as an explanation for the lack of association among deceased subjects. It would be extraordinary for overmatching or nondifferential misclassification (the latter being the usual explanation when reduced relative risks are obtained with exposure information from proxy respondents) to be so strong as to bias a relative risk of 2.4 to 0.8.

Rice is the principal agricultural crop in the study area, and rice weeding was historically a predominantly female occupation. (Of 29 rice weeders in the study, all but two were women.)

Rice weeding during the period 1950-1955 was manual and contact with the phenoxy herbicides was mainly through the skin.

Among all women in this study, rice weeding during the early 1950s is associated with a relative risk of 2.3 (95% CI = 0.7-7.7). When the analysis is restricted to women who were farmers, however, the relative risk drops to 1.4 (95% CI = 0.3-6.5).

7.6.5. Finland

Lampi et al. (1992) completed a case-control study of colon cancer, bladder cancer, soft tissues, lymphoma, and leukemia in the municipality of Karkola, Finland, where residents consumed fish from a local lake that was contaminated with chlorophenols. The main employer in Jarvela, the industrial center of Karkola, is a sawmill that has been operating since before the 1940s. Large amounts of chlorophenol have been found in the ground water between the sawmill and the intake plant for the drinking water. A person was considered exposed if he answered positively to any one of a series of questions about personal exposure asked on a questionnaire. These include sawmill work, farming, source and duration of drinking, and quantity of fish consumed. Four controls per case were randomly selected from the national population registry of the Tiirismaa health-care district which includes Karkola. However, exclusion of controls who failed to reply as well as nonparticipant cases resulted in a final 3 to 1 ratio of matching. One hundred and twenty-three cases were matched by age, sex, and residing in the Tiirismaa health-care district at the time the cancer was diagnosed, with up to 494 controls depending on whether a reply was received for each of the questions asked.

No increased risk of colon or bladder cancer was associated with any of the exposure categories listed. However, an elevated risk of NHL from exposure to consumption of fish and/or drinking water was found (RR = 6.9, 95% CI = 1.1-70.0). The authors concluded that this could be attributable to chlorophenol exposure through the consumption of fish or the drinking water. The authors also noted a nonsignificant slightly increased risk of STS (RR = 4.0, CI = 0.3-55) in persons exposed to “drinking water” and/or “residence” and/or “fungicide” (tetrachlorophenol, the main ingredient of the fungicide, has been used by the sawmill since the 1940s to inhibit the growth of bluestain fungus in timber) and/or “fish” based upon only three cases versus two controls.

Levels of chlorophenol found in the drinking water of Jarvela ranged from 70 to 140 μg/L. This is reported by the authors to be near the maximum allowable levels. Fish from nearby Lake Valkjarvi, which are caught for local consumption, contain high levels of chlorophenols as well, i.e., 175 μg/kg in perch and 925 μg/kg in zander per net weight.

Although PCDDs and PCDFs have been found in technical and commercial products, this population was not likely to be exposed to these substances in great quantities if at all, according

to the authors. It was reported by the authors that none were found in contaminated drinking water. No actual personal measurements of any of the chlorophenols or the phenoxy herbicides were taken during the conduct of this study. Additionally, the number of cases per cancer site is small, thus providing little power to detect significantly elevated risks where they are not now seen. Efforts should be undertaken to determine if fish are contaminated by PCDDs or PCDFs.

7.6.6. Summary

From the standpoint of exposures to TCDD, the most important results from general-population case-control studies come from those studies conducted in northern Sweden (Hardell and Sandström, 1979; Hardell and Eriksson, 1988; Hardell et al., 1981), central Sweden (Eriksson et al., 1990), and New Zealand (Smith et al., 1982a, 1983, 1984; Smith and Pearce, 1986; Pearce et al., 1986, 1987). These studies were conducted in areas in which high proportions of phenoxy acid exposures involved 2,4,5-T. The exposure-assessment methods in these studies included the posing of specific questions about particular chemicals and herbicide preparations. Moreover, for all but the NHL study in New Zealand (Pearce et al., 1986, 1987), available data permit analyses restricted to farmers and the other occupational categories within which the relevant exposures predominantly occur.

For STSs, the Swedish studies are perhaps best represented by a relative risk of 2.3 (95% CI = 1.0-5.4) for phenoxy acids among workers in agriculture, horticulture, and forestry in the study in central Sweden (Table 7-10) (Eriksson et al., 1990). This is justified by the following factors: the proportion of exposures to 2,4,5-T was high in this study, the methods of assessment were better, and there were analyses within relevant occupational categories. The authors in their current studies have redesigned their methods to accommodate readers' criticisms of their earlier studies and have made an effort to present risk estimates that are adjusted to reflect these criticisms.

The relative risk estimate of 3.0 (95% CI = 1.1-8.3) for phenoxy acid exposure among farmers in the first STS study in New Zealand (Smith et al., 1982a, 1983, 1984) seems to indicate that farming may be a confounder in this study. Indirect standardization for farming produces a relative risk of 1.9 (95% CI = 0.8-4.5).

For malignant lymphomas, the case-control studies provide less evidence of a positive association. The relative risk estimates from the study by Hardell and colleagues (Hardell et al., 1981) were very high, even among persons employed in the special occupational groups, but this study was conducted before the researchers had improved their data collection methods. The studies in New Zealand (Pearce et al., 1986, 1987), Kansas (Hoar et al., 1986), eastern Nebraska (Zahm et al., 1990), and Iowa and Minnesota (Cantor et al., 1992) are more consistent with a much smaller increase in risk, or no increase at all, from exposures to TCDD.

The remaining case-control studies (Eriksson et al., 1981; Olsson and Brandt, 1988; Persson et al., 1989; Wingren et al., 1990; Woods et al., 1987) offer mixed results, some suggesting increases in the risk of STS or malignant lymphoma and others suggesting little or no increase. The informativeness of each of these studies, however, is limited by one or more of the following important drawbacks: study areas in which most phenoxy acid exposures did not involve 2,4,5-T, a lack of information on specific chemicals and preparations to which cases and controls were exposed, and an inability with available data to conduct analyses restricted to farmers and the other occupational groups in which the exposures of interest primarily occur. Apparently, farming as an occupation appears to affect risk estimates based on the findings from several studies where occupation is considered and should be considered as a potential confounder.

Vineis et al. (1992) presents the hypothesis that the excess risk of NHL seen among farmers exposed to phenoxy herbicides may be caused by viruses. Such viruses induce proliferation and immortalization of B-cells, followed by T-cell impairment leading to cell-mediated immunity. Increased risks of NHL have been observed in immunologically deficient individuals. Hypothetically, the same effect could be the result of exposure to TCDD, as suggested in some mouse studies (see Chapter 4, Immunotoxicity).

Lampi et al. (1992) conclude that the role of contamination of drinking water and fish due to chlorophenol from sawmills must be considered as a possible cause of the significantly elevated risk of NHL seen in Finland.

7.7. STUDIES OF PULP AND PAPER MILL WORKERS

Table 7-17 summarizes results for cancers of interest from three follow-up studies of pulp and paper mill workers. A fourth study, not summarized in the table, produced inconsistent results based upon choice of analytical method used. Both potentially produce biases that are contradictory and will redue accuracy in the estimates. These studies are important because of the potential for exposure to PCDDs and PCDFs in this line of work. The study by Robinson et al. (1986) was of 3,572 persons who had worked for at least 1 year between 1945 and 1955 at any of five mills in the States of California, Oregon, or Washington. The study by Jäppinen et al. (1987) was of 3,454 workers in the Finnish pulp and paper industry who had worked continuously for at least 1 year between 1945 and 1961. The study by Henneberger et al. (1989) was of 883 persons who had worked for at least 1 year at a mill in New Hampshire. Jäppinen et al. (1987) studied cancer incidence. The other two studies were mortality studies.

Individually and in the aggregate, these studies give little indication of appreciable increases in the risk of NHLs, lung cancer, or stomach cancer among pulp and paper mill workers. Overall, the rate of all cancers combined was somewhat lower than expected. None of

the studies examined connective and soft tissue cancers specifically. Analyses of specific cancers by work location, duration of employment, and latency were only occasionally conducted in these studies. No consistent results were found that would alter substantially the impression given by the results for the total cohorts. These studies do not specifically mention exposure to the PCDDs/PCDFs and are not designed to evaluate the risk of cancer from PCDDs/PCDFs.

Other studies of cancer among paper and pulp mill workers have been restricted to information on deaths, using either proportional mortality ratios (Milham, 1976; Milham and Demers, 1984; Schwartz, 1988; Solet et al., 1989) or mortality odds ratios (Wingren et al., 1991) as measures of relative risk. These studies are not highly informative because they usually rely on minimal information in death records and because they are subject to an upward bias due to the "healthy worker effect" (i.e., a tendency for employed groups to have favorable total mortality experience and causes of death other than cancers, when compared with the general population). The degree of bias in such studies varies, but it can be appreciable. For instance, in the cohort studied by Robinson et al. (1986), 915 deaths from all causes were observed and 1,150.3 were expected. If the relative risk estimates for stomach cancer and NHLs had been computed as proportional mortality ratios or mortality odds ratios, they would have been 1.5 and 1.7, respectively, instead of the values of 1.2 and 1.3 that were obtained from the authors' more valid comparisons of mortality rates (Table 7-17).

A more recent mortality and cancer incidence cohort study of 26,000 British Columbia (B.C.) sawmill workers by Hertzman et al. (1997) offered mixed results regarding the cancer-causing potential of exposure to chlorophenates that are contaminated with hexa-, hepta-, and octa-chlorinated dioxin isomers but not TCDD. An analysis was accomplished in two parts. First, B.C. vital statistics were used to generate expected deaths while B.C. incidence rates (from the B.C. Cancer Agency) were used to generate expected cases. However, person-years were generated in two ways. The first was to truncate the accumulation of person-years at the time the subject was lost to follow-up; in the second analysis person-years were accumulated until the end of the study period, which was 1990 even if the subject could not be traced to the end of 1992. This treatment of the data served to produce conflicting results. In the former method multiple significantly elevated site-specific cancer risks as well as significant total cancer appeared, whereas in the latter analysis site-specific standard mortality ratios (SMRs) and total cancer were all nonsignificant and close to what would be expected if there were no risk from exposure. Presumably, this discrepancy in the findings is due to an inability of the authors to identify vital status on 3,791 sawmill workers (14.3% of the total). Furthermore, those members of the cohort who were diagnosed with cancer outside of British Columbia could not be included in the analysis because these cases would not be known to the B.C. Cancer Agency. The authors

assumed this loss would be around 4.4%, on the basis of deaths that were recorded outside of British Columbia. A combination of these two factors could explain the disparity. Perhaps if the remaining 14.3% could be followed until vital status was determined, and the underlying cause of death could be identified on the 4.4%, more accurate estimates of the true site-specific cancer risks would be known and, consequently, the studies's two sets of results would converge.

Another problem with this study is that the observed deaths do not appear to add up from one table to the next where they should and no explanation is provided. The authors conclude that their results are "consistent with the borderline positive associations seen in other recently reported studies of chlorophenate-exposed workforces." This conclusion may be somewhat overstated given the potential problems with this study, which appears to have ended prematurely prior to the completion of vital status followup.

7.8. OTHER STUDIES

Studies of pesticide applicators are not informative because they contain little information on specific compounds and preparations to which individual persons were exposed, and so there is no evidence of exposure to TCDD. Studies with no information of this type include studies of licensed pesticide applicators by Wang and MacMahon (1979), Barthel (1981), Blair et al. (1983), Wiklund et al. (1987), Corrao et al. (1989), and a study of gardeners by Hansen et al. (1992). These studies contribute little or nothing to the discussion of TCDD or compounds like TCDD.

Axelson and Sundell assembled a cohort of 348 Swedish railroad workers who had applied amitrol, 2,4-D, and 2,4,5-T (Axelson and Sundell, 1974). In the most recent report (Axelson et al., 1980), 17 deaths from tumors were observed (11.85 expected, relative risk 1.43, $p = .09$). The relative risk estimate for lung cancer was 1.4 (three observed deaths, $p = .37$) and the estimate for stomach cancer was 2.2 (three observed deaths, $p = .15$). Again, as in most studies, no actual measurements of TCDD are available from this paper. Only potential exposure to the herbicides 2,4-D and 2,4,5-T are mentioned without any effort to quantify the exposure.

Riihimäki et al. (1982, 1983) followed a cohort of 1,971 Finnish men who had applied 2,4-D and 2,4,5-T. With allowance for a 10-year latency period, 20 cancer deaths were observed (24.3 expected, RR = 0.8, 95% CI = 0.5-1.2). The relative risk for lung cancer was 1.1 (12 deaths observed, 95% CI = 0.6-1.8). The author points out that because of limitations in the study materials, only powerful carcinogenic effects are likely to be seen.

7.8.1. Vietnam Veterans

Distributions of TCDD levels in serum and adipose tissue are typically indistinguishable between Vietnam veterans and comparison populations unless the Vietnam veterans group has

been carefully defined on the basis of military records to have engaged in activities known to have involved herbicide exposure (Centers for Disease Control Veterans Health Studies, 1988; Devine et al., 1990; Gross et al., 1984; Kahn et al., 1988; Kang et al., 1991; Pirkle et al., 1989; Schecter et al., 1989). Thus, the mere designation "Vietnam veteran" is insufficient as an indicator of exposure to 2,4,5-T or TCDD exposure. This conclusion is also supported by Stellman and Stellman's (1986) review of military records for the purpose of developing an Agent Orange exposure index. Stellman and Stellman drew the further conclusion that "it is impossible to give any credence to any health effects study in which assignment of herbicide exposure levels to individual veterans is based solely on self-reports" (Stellman and Stellman, 1986). It is also insufficient to base an exposure index among Vietnam veterans on such crude information as military branch (Army, Marine, etc.), corps, or region of duty within Vietnam. Thus, a large number of studies of cancer experience among Vietnam veterans are uninformative from the standpoint of hypothetical effects of TCDD. These include studies by Breslin et al. (1988), the Centers for Disease Control (1987), Dalager et al. (1991, 1995a,b), Fett et al. (1987), Greenwald et al. (1984), Kang et al. (1986), Kogan and Clapp (1988), Lawrence et al. (1985), O'Brien et al. (1991), and Watanabe et al. (1995).

One Vietnam veteran study by Kang et al. (1987) that further examined mortality in a subgroup of veterans who had ventured into areas at the time when Agent Orange was being sprayed reported a nonsignificant odds ratio of 8.64 (CI = 0.77-111.84) for STS. The number of cases was not provided. Presumably, these would be ground troops with a high likelihood of exposure.

The only study of cancer among Vietnam veterans at present with information on activities involving TCDD exposure is a small mortality study by Michalek et al. (1990) of 1,261 Air Force veterans of Operation Ranch Hand. These persons were responsible for the aerial herbicide spraying missions in Vietnam. The researchers compared the Ranch Hand group with a group of 19,101 other Air Force veterans who were mainly involved in cargo missions in Southeast Asia and who did not have herbicide exposure. A total of 12 cancer deaths were observed in the Ranch Hand cohort (17.0 expected, RR = 0.7, 95% CI = 0.3-1.1) by December 31, 1987, the cutoff date for followup. Interestingly, one of these was a STS. Out of 229 deaths reported in the comparison population, one STS death was also found. Calculated death rates of all specific cancers of interest in this review were equal to or less than the rates in the comparison group, with the exception of bone, connective tissue, skin, breast, and genitourinary organs. These numbers are too small for any meaningful comparisons.

Serum TCDD measurements were taken on 888 Ranch Hands (total). A few of the Ranch Hands, who were enlisted ground crew, exhibited serum levels above 200 ppt of TCDD, but the median serum level was 12.4 ppt (range 0 to 618 ppt) for the entire group. The median serum

level in the controls averaged 4.2 ppt (Wolfe et al., 1990). The subgroups of Ranch Hands that appear to have had the greatest exposure are nonflying enlisted personnel. The median serum TCDD levels in 407 of them was 23.6 ppt. The next highest levels were in flying enlisted personnel with a median of 17.2 ppt. The remaining Ranch Hands exhibited levels that were not much elevated (under 10 ppt) from background (flying officers, both pilots and navigators, as well as nonflying officers). Based upon these findings, it is likely that the majority of Ranch Hands received little exposure to TCDD. Not a great deal of cancer mortality can be expected in this relatively youthful group, which had not reached the 20-year latency milestone.

In a followup report through 1992 published in 1994 on the Ranch Hands (Wolfe et al. 1994), the authors report 111 deaths in the Ranch Hands versus 111.47 expected in a cohort of 1,261. Twenty-six deaths from cancer were reported versus 30.68 expected. Again no increased risk of any site-specific cancer was found over expected. The comparison population from which expected deaths were generated is very likely the same 19,080 Air Force veterans discussed above who flew or serviced C-130 cargo aircraft in Southeast Asia during the same period that the Ranch Hands were active in Vietnam, although it is not specifically stated in that report. It would be of greater interest and more useful to continue follow-up of the enlisted Ranch Hands only. They appear to be the subgroup with the greatest exposure, although their TCDD levels cannot be considered high. Further follow-up of officers probably will not reveal useful information that could be attributed to exposure to TCDD.

A more appropriate group in which to observe effects are members of the South Vietnamese Army who did the mainstay of the spraying around the perimeters of the military bases in Vietnam.

In another update of the Ranch Hands study, Ketchum et al. (1996) reported on mortality through December 31, 1993. The number of reported cancer deaths increased to 30 versus 33.22 expected (SMR = 0.90, 95% CI = 0.63-1.27). Presumably, the comparison population is the same as the one discussed above, i.e., 19,101 other Air Force veterans, but not stated in the report by Ketchum. No unusual excess cancer risks occurred to any of the three main subgroups of Ranch Hands discussed above. But then, it is still a relatively youthful cohort and few person-years have aggregated beyond the 20th year since exposure, too few to do an adequate latency analysis. It is reported by the authors that some 991 Ranch Hands have quantifiable dioxin levels (presumably blood levels, although not stated). The authors maintain that survival time was not significantly associated with dioxin levels. There was apparently no effort to assess levels of dioxin in each of the three main subgroups, but only between those who were deceased and alive. The levels overall were somewhat higher in the deceased ($\overline{X}$ = 35.0 ppt) versus the living ($\overline{X}$ = 26.7 ppt). The number of deceased Ranch Hands with dioxin levels was 23, precluding assessment of dioxin level averages in deceased veterans by occupational category. Overall,

there is little in this report to support the hypothesis that exposure to dioxin is or is not causally related to an increased risk of cancer. But of course, this study is subject to the same limitations. The levels of dioxin found are not much greater than background and the mortality is still rather low. Furthermore, the analysis should be confined to that group with the highest levels of serum dioxin, i.e., the enlisted nonflying Ranch Hands.

In a slightly different analysis of the same cohort of Ranch Hands that was followed for the same period of time until December 31, 1993, Michalek and colleagues (1998) assessed mortality in the different occupational subgroups—pilots and navigators, administrative officers, enlisted flight engineers, and finally, enlisted ground personnel—observed for less than 20 years since service and after 20 years since service in Vietnam for certain site-specific cancers. The authors found no significant increase in the risk of death from cancer, all sites combined (SMR = 1.1), for persons who survived more than 20 years since military service, while they reported a nonsignificant increase in the number of deaths due to cancers of the bronchus and lung (SMR = 1.3) in Ranch Hands in that group. The authors reported that this latter finding was consistent with an increase in respiratory cancer mortality seen in Fingerhut et al. (1991) in workers observed for 20 years. Michalek recommends that followup should continue to determine whether these slight increases persist. A nonsignificant increase in deaths due to digestive diseases (SMR = 1.7, CI = 0.9-3.2) was reported but not evaluated. A single STS occurred to a Ranch Hand officer (OBS = 1, Exp = 0.3). Again, this study is subject to the same limitations as in earlier renditions. It is based on small numbers and very few deaths from cancer. Dioxin levels were summarized but not analyzed.

Ketchum et al. (1999) simulated what the risks of cancer would be in Ranch Hands on the basis of expected dioxin exposures extrapolated from current dioxin measurements back to the time of exposure as if such hypothetical exposures were real at the time. The authors assumed a first order model for dioxin elimination from the body and a half-life of 8.7 years in constructing synthetic exposure levels at the time when military service ended in Vietnam. The comparison population again was the same group of Air Force veterans that served in Southeast Asia at the same time as the Ranch Hands but did not serve in Vietnam. The Ranch Hands were subdivided into three groups designated as having “background,” ”low,” or “high” exposure. The “background” Ranch Hands consisted of only those personnel whose current measurements of dioxin level never exceeded 10 ppt. The “low” and “high” categories consisted of personnel whose current levels were over 10 ppt. After extrapolation to the supposed “initial” levels at the time they left the service, if the “initial” level exceeded 94 ppt then the Ranch Hands were considered to have “high” exposure. If the “initial” level was under 94 ppt then the Ranch Hands were considered to have had only “low” exposure.

The risk of cancer at sites other than skin in Ranch Hands with less than 20 years of observation from end of service was significantly elevated only in the "low" exposure group (OR=3.4, CI = 1.5-8.0). Although the "high" exposure category also was elevated, it was not significant (OR=2.7, CI = 0.9-8.0). The risks calculated in the more-than-20-years-since-service group were even less remarkable. Based upon 39 individuals diagnosed with cancer who fell into this category, the risks were all under 1.0 and nonsignificant. The findings seem to resemble an *inverse* relationship of cancer with that of latency and dose. The authors believed that their results were inconsistent with that of the Fingerhut et al. (1991) study, and felt that the increased risks seen within 20 years from service may not have been due to dioxin exposure.

The most important question concerns the possibility that misclassification of exposure may have contributed to the supposed inverse relationship of exposure with risk. The assumption that Ranch Hands with a current dioxin measurement under 10 ppt should be placed in a "background" category may be inaccurate. It seems possible that with a lapse of as much as 25 years since service in Vietnam, the actual exposure in these individuals could have been anywhere from 40 ppt to more than 80 ppt. Furthermore, without checking to determine if exposure to dioxins had *not* occurred following service in Vietnam, the authors cannot be certain that the high current levels measured were not due to post-Vietnam exposure to dioxin, in which case the "initial" exposure determinations may be exaggerated.

Furthermore, considering the tabular data, were person-years allocated back to the higher extrapolated exposure and latency categories when the expected cases were calculated for each category? This could explain the apparent inverse relationship of risk to exposure.

Lastly, the authors stated that their results differed from those of Fingerhut and her colleagues discussed earlier. Actually, the "current" measurements that were derived in the Fingerhut study were considerably greater than the "current" measurements seen in this study. As it is likely that most of the Ranch Hands were exposed to only low levels of dioxin, it would be inappropriate to compare the results of this study with those of Fingerhut and her colleagues.

7.8.2. Residents of Seveso, Italy

Residents of Seveso, Italy, were exposed to TCDD in a chemical accident in 1976. Nearly 200 cases of chloracne reported (Caramaschi et al., 1981). Children (Bertazzi et al., 1992) and adults (Bertazzi et al., 1989a,b) who were exposed at the time of the accident are being studied separately. The group residing in the zone (zone A) of highest potential exposure (determined by levels of dioxin found in the soil) consists of 556 adults and 306 children. The group residing in the zone of intermediate estimated exposure (zone B) is larger, with 3,920 adults and 2,727 children. The group with lowest estimated exposure (zone R) is larger still, with 26,227 adults and 16,604 children. The accuracy of the three estimated exposure zones has

been questioned (Caramaschi et al., 1981; Merlo et al., 1986; Ratti et al., 1987; Merlo and Puntoni, 1986), especially because the ranking does not correspond to the occurrence of chloracne in the area. Some parts of region R are almost adjacent to the site of the accident and the factory where the accident happened, while region B begins about 1 kilometer away. Even the nearest part of the "referent" region to the site of the accident is located about the same distance as the nearest part of region B. Only region A and region R appear to come closest to the site. It is entirely likely that many persons residing in region R were exposed to TCDD.

There is no question that at least some of the residents of the most heavily contaminated area (zone A) received considerable exposure to TCDD (Mocarelli et al., 1991). The 1990 analysis, based on tissue specimens taken in 1976, found that the highest detected levels were recorded just after the accident. Six children at the time who subsequently developed severe chloracne had serum TCDD levels ranging from 12,100 ppt to 56,000 ppt. Four other persons with slightly less severe chloracne exhibited levels ranging from 828 ppt to 17,300 ppt. These were similar to those of nine other residents of zone A who did not develop chloracne whose serum TCDD levels ranged from 1,770 to 10,400 ppt (Mocarelli et al., 1991). None of the latter group of nine were reported to be ill at the time of sampling.

Support for the original division of the area of exposure into the three zones (A, B, R) was strengthened by data from studies of tissue levels of plasma TCDD by Landi et al. (1996, 1998). Twenty years after the accident, randomly selected residents of the three areas affected were chosen to have their tissue plasma TCDD levels measured. Plasma TCDD levels were measured in 62 subjects from zones A and B. Their mean tissue levels ranged from 1.2 ppt to 89.9 ppt with a geometric mean value of 53.2 ppt (n = 7) in zone A. In zone B (n = 51) the mean was 11.0. In the non-ABR region (n = 52), it was 4.9 ppt. In the most polluted areas of the three zones, in adults over 13 years of age the estimated median TCDD levels were 443 ppt (zone A, 177 residents), 87 ppt (zone B, 54 residents), and 15 ppt (zone R, 17 residents), respectively (Bertazzi et al., 1998).

The authors report that women have significantly higher TCDD levels than men in the entire study area which they maintain are not due to location, consumption of meat, age, body mass index, or even smoking. Levels decrease by distance from the accident site, according to the authors. However, none of these levels appear to be excessively large. The authors caution that "elevated TCDD levels in women may contribute to adverse reproductive, developmental, and cancer outcomes."

The population in zones A, B, and R around Seveso were initially followed for 10 years (Bertazzi et al., 1992, 1989a,b) to 1986. Ten cancer deaths, too few to support a meaningful analysis of specific cancers, have been observed among children (Bertazzi et al., 1992). (Bertazzi et al., 1989b). No excesses of mortality from lung cancer, stomach cancer, or all

cancers combined were apparent. A moderate and statistically imprecise elevation in the death rate from a subset of the cancers that make up the NHLs is evident in the second 5-year period of follow-up. An excess of greater relative magnitude, but even more imprecisely estimated, in mortality from cancers of connective and soft tissues appears to have occurred in the same time period.

In a preliminary study of cancer incidence in the same Seveso population (Pesatori et al., 1992), the relative risk estimate of connective, subcutaneous STS of males living in zone R is reported to be significantly elevated at 2.81 based on six cases (CI = 1.1-7.4). In zones A and B, none were observed, but 0.4 were expected to occur in males and 0.2 in females. For females, the risk in zone R of STS was 1.43 based on two cases. Other cancer sites that are also elevated are certain hematologic neoplasms in males (lymphoreticulosarcoma) and hepatobiliary tract cancers in both males and females.

One year later, in a cancer incidence study (Pesatori et al., 1993) of a population of young persons (ages 0 to 19 years) with some small changes in the definition parameters, the number of identified cancer cases equaled 17, although the followup period remained unchanged. The authors observed a slight tendency toward increased leukemia (5 observed versus 2.6 expected) and cancer of the thyroid ((2 observed versus 0.4 expected) based upon a small number of cases. These results are equivocal.

Bertazzi et al. (1993) refined his earlier study to include a more complete vital status ascertainment without adding additional years of follow-up to the cancer incidence data in the contaminated areas surrounding the factory where the accident took place. Cancer occurrence ascertainment was confined chiefly to the Lombardy region of Italy (with a population of 9 million persons) because only there can be found an efficient hospital and discharge registration system, according to the authors. Lombardy hospitals routinely provide hospitalization data to the regional health department.

Of note in this update is the information that only 14 cases of cancer were reported to have occurred in zone A. This is not unexpected, based on population estimates. This number was based on the assignment of addresses by the municipal vital statistics offices. But it is far too small to produce any meaningful results. However, in the more populated zone B, with about 4,800 residents, and zone R, with some 32,000 residents, several findings were noted (Table 7-18). In zone B, hepatobiliary cancer in females (RR = 3.3, 95% CI = 1.3-8.1), lymphoreticulosarcoma in men (RR = 5.7, 95% CI = 1.7-19.0), and multiple myeloma in women (RR = 5.3, 95% CI = 1.2-22.6) were significantly elevated.

In zone R, STSs in men (RR = 2.8, 95% CI = 1.0-7.3) were the only site-specific cancers that were significantly elevated. Cancer of the genitourinary system in women was significantly depressed (RR = 0.8, 95% CI = 0.6-1.0) chiefly because of a low risk of cancer of the uterus.

This is consistent with the animal data that suggest estrogen-induced protective effects in female rats.

The authors explain that the absence of cancer among the chloracne victims is not unexpected at this time because of the relatively young age of the group and the small number of individuals affected. They state that at this time only 0.5 *total* cancer deaths could be expected in this subgroup.

The fact that elevated risks of cancers have appeared within a relatively short period of time following the accident may have been the result of exposures received from a 2,4,5-T production plant that existed in that area many years prior to the accident. Earlier potential exposure to dioxin from the preexisting plant could have been the initiating event for the cancers. Furthermore, hematopoietic tumors have a shorter latency than most carcinomas.

In their update of their earlier studies of the Seveso population, Bertazzi et al. (1997, 1998) continue to report excess risks of cancer mortality resulting from the accident. The populations around Seveso were followed for 15 years until December 31, 1991, with the following results: There was no increase in overall cancer mortality in any zone utilizing the population outside of zones A, B, and R as a comparison. Zone A had the fewest number of exposed persons. Only 6 male (13.5 expected) and 10 female (8.5 expected) cancer deaths have been reported after 15 years of observation in zone A, too few to provide any meaningful information regarding potential increased cancer risks. On the other hand, in zone B significant excess cancer mortality risks occurred at four sites in males (rectum, pleura, lymphohemopoietic, and leukemia) but only one in females (myeloma) (Table 7-19).

In zone R significant excess mortality risks were observed at two sites: esophagus in males and bone cancer in females. These significantly elevated site-specific mortality risks are based on a sufficient number of deaths as to rule out the possibility of a small-numbers effect. Only males in zone R reported any deaths from STSs (4 observed versus 1.9 expected) and this was not significant. The authors conclude that the specific excesses seen here could not be explained by bias or confounding and that their association with dioxin exposure is plausible. There appears to be little consistency in the reported findings. Again, not much can be concluded based upon mortality data after only 15 years' follow-up from the time of the accident. The authors pointed out that the study had several limitations linked to exposure categorization, time elapsed since exposure, and small size.

A more recent follow-up (Bertazzi et al., 2001a) of the same group of residents in Zones A and B was completed after 20.5 years on December 31, 1996. No reports of findings in Zone R and in the reference region are presented although the authors report that results from the "least contaminated zone R failed to suggest increased cancer risks." The residents of zones A and B continued to exhibit effects similar to those reported in the earlier updates.

All cancer mortality was modestly increased. When latency is considered from the time of the accident, the risk increases modestly in males (RR = 1.1, 95%CI = 1.0, 1.3) in regions A & B combined, but not in females. This analysis assumes that all effects may have been induced by exposure from the explosion despite the fact that the factory occupied the site for many years. Specific cancer sites that also exhibit elevated risks, both sexes combined, are cancer of the rectum (RR = 1.8; 95%CI = 1.0-3.3); lymphatic and hemopoietic cancer (RR = 1.7; 95%CI = 1.2-2.5) and Hodgkin's disease (RR = 3.1; 95% CI = 1.1-8.6). After 15 years, the risks for non-Hodgkin's lymphoma and myeloid leukemia were significantly elevated (RR = 2.8; 95% CI = 1.1-7.0) and (RR = 3.8; 95% CI = 1.2-12.5), respectively.

Female mortality was significantly elevated for lymphohemopoietic system (RR = 1.8; 95%CI = 1.1-3.2) and multiple myeloma (RR = 3.2; 95%CI = 1.2-8.8). No latent trends are evident in females (Table 7-20).

However, in males all cancer mortality was significantly elevated (RR = 1.1; 95%CI = 1.0-1.3). After 15 years latency, all cancer mortality the risk increased significantly elevated (RR = 1.3; 95%CI = 1.0-1.7). Rectal cancer (RR = 2.4; 95%CI = 1.2- 4.6) and lung cancer (RR = 1.3; 95%CI = 1.0- 1.7) were also significantly elevated after 15 years latency. Risks were elevated in the shorter latent categories of these same two site-specific cancers. No apparent trend of increasing or decreasing risks were evident when latency was considered at other selected sites as well from the time of the accident. But then, the potential influence of exposures received by the residents of the community from the preexisting factory cannot be assessed for its effect on the relative risks and latency.

No soft tissue sarcomas were observed in zones A and B. However, less than one case would have been expected to occur by the end of the followup. For instance, in Zone A, where exposure was highest, the expectation of a STS was only 0.1, there was little power to detect a significant risk in that region.

In a special study group of 182 persons exhibiting chloracne, mostly children, and who might be expected to have had much greater exposure to dioxin than most, only two had died by the end of the follow-up extension. Interestingly, 114 of these individuals with chloracne resided in zone R and the reference region. Efforts should be made to confirm the TCDD dioxin levels by blood lipid analyses on all 182 members of this group. They should form a separate group for study.

Estimated exposure levels in the blood of random samples of residents of zones A and B at different time intervals are provided in Table 7-22. During the 16- to 18-year lapse from the initial blood lipid measurements in 1976-1977 until 1993-1994, there appears to have been a near 7-fold drop in blood levels of TCDD. This is consistent with what would be expected given the approximate 7 year half life expectation of TCDD in the body.

The results of this latest update continue to support the finding of an increased risk of certain site-specific cancers in the population exposed by the industrial accident in1976 although all cancer risk is only modestly increased. This can be explained by the fact that the most heavily exposed members of the population (Zone A) make up only 12% of the population of the two zones examined by the authors and that the blood levels over time as evidenced in Table 7-22 have fallen as expected during the 20.5 year span of time since the accident. Furthermore, the observed blood lipid levels of TCDD initially were, on average, much less than those observed by Fingerhut et al. (1991) in industrial workers in the U.S. (Section 7.5.1.) who were involved in the making of chemicals contaminated with TCDD. The accident in Seveso produced an intense exposure to the population of that region that may have supplemented potential earlier exposures received by workers at the preexisting factory and residents living nearby but, in general, body burden levels were within an order of magnitude of background levels at the time when total TEQ is considered.

After the accident, little additional exposure would have been expected to occur directly except as part of the contamination of the surrounding crops and animals in the region, possibly through the food chain. Any additional exposure received in this way probably would be minuscule compared with the greater exposure received by the industrial chemical workers over a long period of time. This is reflected in the blood lipid levels seen in such workers. Furthermore, there is no follow-up of this group beyond the 20.5th year. Hence, latent effects, if any, may not have had a chance to be expressed yet. Not so with the industrial workers in Fingerhut et al. (1991) who were followed for over 30 years. The Seveso population should continue to remain under surveillance for a longer follow-up period. More attention should be given toward identifying exposed persons in Zone R and in the reference region through blood lipid analyses so that they can be included for study. Despite these issues concerning estimates of dose, the authors have stated that their results support the evaluation of TCDD as a human carcinogen, especially with the increased estimates of relative risk for several causes of cancer in the >15 year latency period.

In a commentary on this study by Smith and Lopipero (2001), two “key” problems were identified. The “likely” exposure levels back-calculated to the time when the exposures had occurred indicate that the weighted average for the two highest exposure zones in Seveso is only 136 ng/kg TCDD versus a mean of 3,600 ng/kg TCDD in the combined U.S. industrial cohorts. Smith and Lopipero concluded that one would not expect to find detectable increases in all-cancer mortality in the Seveso cohort for any latency. Thus, in their opinion, the results do not add to or subtract from the findings from the industrial cohorts. Secondly, they point out, smoking in the Seveso population may have influenced risk estimates of several causes of death

that are associated with smoking, thus presenting the potential of a confounding effect. Slightly elevated risks of lung cancer, myocardial infarction, and chronic respiratory disease are evident.

Bertazzi et al. (2001b) in a rebuttal agreed that exposures appear to be less than those of the industrial cohorts, but they are still two orders higher than background environmental exposures to TCDD, hence the increase in cancer mortality cannot be considered to be totally unexpected. These authors also argue that smoking is not necessarily the cause of the increase in the cancer mortality. Dioxin exposure also has been related to increased cardiovascular mortality in recent studies and that if smoking were a cause of the increased cancer, then one would see an increase in the risk of cancer of the larynx, esophagus, pancreas, and bladder and these risks were not elevated in Seveso males after 15 years of observation.

Pesatori et al. (1999) briefly reported on the 20-year followup of the incidence of cancer in the same cohort but in combined zone A and B. The risk of lymphatic and hematopoietic neoplasms was borderline significantly increased in adult females (RR = 1.7; 95% CI = 1.0-2.9) and in adult males (RR = 1.6; 95% CI = 1.0-2.7). The authors also report that biliary tract (four cases) and central nervous system neoplasms (six) were also elevated in females. Rectal (12) and pleural (3) tumors were elevated among males. Significance levels are not provided. STSs were elevated only in R-zone males (RR = 2.2; 95% CI = 0.9-5.1) based on seven cases. The RR for sarcomas any site was 1.3 based upon 15 cases. No other information is available from this sketchy description.

7.8.3. Rice Oil Poisonings in Taiwan and Japan Involving Compounds Structurally Related to Dioxin

This section discusses two similar incidents involving ingestion of rice cooked with oils accidently poisoned with PCBs and PCDFs. PCBs and PCDFs are structurally similar to the polychlorinated dioxins, and some of these are considered to be dioxin-like in their activity. The dioxin-like effects of these compounds are mediated through a cytosolic receptor (Chapter 2). The dioxin-like polychlorinated biphenyl congeners, chlorinated dibenzofurans, and dioxins that have a high affinity to bind the Ah receptor induce similar effects in both animals and humans but appear to differ quantitatively in toxicity (Ahlborg, Chapter 3 and 4). They appear to harm growth and reproduction, they damage the immune system, and they also appear to cause cancer. These same effects have been observed in a number of different species, including humans.

Two accidents involving ingestion of food contaminated with PCBs and dibenzofurans, in Yusho (Japan) and Yu-Cheng (Taiwan), have been reported. The Yusho incident involved 1,900 people who in 1968 accidentally consumed up to 2 grams each of PCBs that had leaked into the rice oil at the facility where the rice oil was canned. The PCBs were primarily Kanechlor 400 that had been used as a heat exchange medium thousands of times. Commercial-preparation

Kanechlor 400 had a concentration that was 49% chlorinated. The use of this medium for exchange of heat resulted in an increase in the dibenzofuran contamination of approximately 250 times. The final mixture that was actually present in the rice oil had a ratio of one molecule of PCDFs to every 200 molecules of PCBs.

These victims suffered many ill effects from their massive exposure that lasted only a few months. Tissue studies by the Japanese of the victims indicated that some of the PCBs and PCDFs were retained for many years after the initial exposure. Certain congeners of the PCDFs are eliminated at a slower rate than PCBs. Concentrations measured several years following the Yusho accident indicated that the mass ratio of PCDFs to PCBs remaining in the adipose tissue of the victims was about 1 to 4 (Kuratsune et al., 1975). Japanese researchers have attributed most of the noncancer toxic effects to the presence of the PCDFs, although these effects are consistent with PCB exposure. These toxic effects include comedo formation, acneform eruptions, hyperpigmentation, and hyperkeratosis. In addition, ocular lesions such as swollen meibomian glands filled with yellow infarct-like material and pigmentation of the conjunctiva were seen, similar to effects of TCDD. For further discussion of these and other effects, see Part B of Chapter 7, which addresses noncancer health effects in humans.

Kuratsune et al. (1988) reported a significantly increased risk of liver cancer in male victims (9 observed vs. 1.6 expected; SMR = 559, $p<.01$) and a nonsignificantly increased risk in female victims (2 observed vs. 0.66 expected; SMR = 304), as well as a significantly increased risk of lung cancer in male victims (8 observed vs. 2.45 expected; SMR = 326, $p<.01$). Some 1,761 patients (887 males and 874 females) were followed from date of registration to the end of 1983, 15 years after the accident in October of 1968. Thirty-three male cancer deaths had occurred by this time versus 15.51 expected. In female victims, 8 cancer deaths had occurred while 10.55 were expected. Comparisons were with the age-, sex-, and cause-specific death rates of Japan and, separately, of Nagasaki and Fukuoka prefectures in 1970, 1975, and 1980. The author reports that the risk of liver cancer remained elevated even after the influence of latency, alcohol consumption, and liver disease had been evaluated. Kuratsune said that because there was an uneven distribution of deaths in the provinces where most of the victims lived, it was too early to draw any conclusions. Apparently, most of the liver cancers occurred in Fukuoka prefecture. A statistically significant excess mortality was still present in males of Fukuoka even when liver cancer deaths occurring less than 9 years after the accident were eliminated. The author stated, “Such a markedly uneven geographical distribution of deaths can hardly be explained by exposure to the toxic rice oil alone.” However, he cautioned that his findings suggest that the poisoning might have caused liver cancer at least in male patients. He concludes, “Our findings should not be disregarded, however, because the hepatocarcinogenicity

of PCBs in animals has been well documented." Deaths from chronic liver diseases and cirrhosis were also elevated but not significantly.

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

7.9. SUMMARY AND CONCLUSIONS

The strongest evidence that exposure to TCDD leads to an increased risk of generalized cancers at multiple organ sites, including lung cancer, comes from the four occupational cohort studies (Fingerhut et al., 1991; Steenland et al., 1999; Manz et al., 1991; Flesch-Janys et al., 1995, 1998, 1999; Becher et al., 1996; Zober et al., 1990; Ott et al., 1996; Bueno de Mesquita et al., 1993; Hooiveld et al., 1996, 1998) discussed earlier as well as studies of the victims of the 1976 Seveso accident in Italy (Caramaschi et al., 1981; Bertazzi et al., 1989a,b, 1992, 1993, 1997, 1998, 2001a; Landi et al., 1996, 1998; Pesatori et al., 1993, 1999). See Table 7-20 and 7-21. These studies provide evidence of in vivo exposure to TCDD, with actual measurements of TCDD serum levels in exposed individuals or their surrogates positively correlated with significantly increased risks of cancer mortality of between 40% and 100% (SMRs range generally from 1.4 to 2.0). Although it is clear that congeners of the PCDDs/PCDFs are also present in the blood serum of exposed subjects, TCDD predominates. Flesch-Janys et al. (1995, 1998, 1999), in fact, have provided measurement data showing that when the PCDD/PCDF congeners were converted to their toxic equivalences (TOTTEQs) they were found to be dose-related to increasing risks of cancer, cardiovascular disease, and ischemic heart disease. In the

Yusho accident (Kuratsune, 1988), victims exposed to PCBs and dibenzofurans that were similar in structure to TCDD also reported a significant risk of lung cancer, as did the subjects of the occupational cohort studies mentioned in this summary. At the highest levels of exposure, the cancer risks are statistically significant. These data, together with the presence of dose-response relationships in the occupational studies, lend support to the concept of a likely causal relationship between cancer at multiple sites and exposure to TCDD, its congeners, and dioxin-like congeners of the PCBs, based on epidemiological studies.

Although some confounding or synergism by tobacco smoke cannot be excluded entirely, the limited analyses conducted and the lack of an excess risk of other smoking-related noncancer diseases suggests that smoking as a confounder cannot entirely explain the significantly elevated cancer risks seen in these studies. Although it is likely that exposure to asbestos fibers occurred prior to employment in the herbicide manufacturing industry in a few subjects, it is improbable that the two or three cases of asbestos-related diseases seen in these cohorts indicate widespread confounding from asbestos. Furthermore, if other chemicals and hazardous agents are present in the workplace of the chemical industry, that could be responsible for the excess cancer risks seen in these studies whose sources have not been identified, except for 4-aminobyphenyl. The 4-aminobyphenyl exposures were identified in one plant only, in one cohort studied, and were suggested as a cause of the bladder cancers observed in these studies. But this observation does not explain the increased risks of total cancer seen in the remaining cohorts, where it has either not been looked for or not been found. The idea that other hazardous agents present in the phenoxy herbicide industry are causing the increases in the risk of all cancer in these cohorts is unlikely because this is a rare event in occupational studies, and there is no reported association between exposure to other hazardous cancer agents and the increase in the risk of all cancers that have been reported in this industry despite extensive study. Furthermore, in the Seveso accident, residents living in the local area received almost exclusive exposure to TCDD, and have exhibited some significantly elevated site-specific risks of cancer that appears to be dose-related to TCDD.

Some studies discussed in this chapter report little or no increased risk of cancer from exposure to TCDD or its congeners. These studies generally suffer from one or more deficiencies that render them not relevant to provide information that could assist in determining the carcinogenicity of dioxins. These deficiencies fall into the following categories that impact the statistical power to detect an effect, if it was present: no measurements of in vivo exposure to TCDD, leading to misclassification of exposure between subjects and controls; the measured exposures are lower than those seen in the studies cited above and similar to those of the comparison population; and finally, there has been no consideration of latency. In short, these non- or weakly positive studies lack one or more strengths of the cohort studies discussed above.

From case-control and follow-up studies, STS has previously been reported to provide some evidence of an association with PCDD and its congeners. The original reports by Hardell (1977); Hardell and Sandstrom (1979), Eriksson et al. (1981, 1990), and Hardell and Eriksson (1988) of an association between STS and exposures involving TCDD-contaminated phenoxy herbicides have been extensively questioned (see Section 7.6.1). The degree of risk, as estimated in later studies by Hardell's research group, does not appear to be as great as originally suggested. The results of the recent Lynge (1998) study suggest that exposure to MCPA and related phenoxy herbicides may by itself increase the risk of STS. The results from the cohort study by Fingerhut et al. (1991) of 5,000 chemical production and processing workers exposed to TCDD are supportive of an association between TCDD exposure and STS, although the association is not statistically significant. These findings are similar to those from the 10- and 15-year follow-up studies of victims exposed to TCDD in Seveso (Bertazzi et al., 1989a,b, 1993, 1997, 1998) in Region R, although the numbers are small and no in vivo exposure information is available. The large IARC Registry cohort mortality study by Kogevinas et al. (1997) and Saracci et al. (1991) also suggests an association between STS and TCDD and the higher chlorinated dioxins. In a recently published nested case-control study by Kogevinas et al. (1995) based upon diagnosed cases of STS from the Saracci Study, support is also given to the finding of an association of exposure to other dioxin congeners, although the association with TCDD is stronger. The first New Zealand sarcoma study (Smith et al., 1983, 1984) also appeared to produce positive results when the analysis, presented above, was restricted to farmers to minimize bias. But because of conflicting data or even contradictory evidence regarding the likelihood of exposure to TCDD, a direct linkage could not be made that exposure specifically increases the risk of STS. Therefore, the epidemiologic findings regarding an association between exposure to TCDD or other dioxin-like compounds and STS do not add significantly to the weight of the evidence regarding human cancer hazard of these compounds.

Earlier suggestions of an increased risk of malignant lymphomas from exposure to TCDD have not been substantiated, but recent evidence suggests an association between NHL and exposure to the herbicide 2,4-D (Zahm and Blair, 1992), which may contain dioxins other than 2,3,7,8-TCDD. The evidence from two large industrial cohort studies (Fingerhut et al., 1991; Steenland et al., 1999; Saracci et al., 1991; Kogevinas et al., 1997), except for the Seveso accident, suggest little, if any, evidence of increased risk of NHL. In the Bertazzi et al. (2001a) study, a statistically significant excess of NHL occurs in the latent category (15+ years). The limited evidence of TCDD exposure that can be extracted from the extensive case-control studies on NHL by the National Cancer Institute (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) also does not indicate a consistent and pronounced increase in risk. At the present time,

existing studies do not present a consistent picture of increased risks of malignant lymphoma among persons probably exposed to TCDD.

Few studies of females are to be found in the case-control and cohort studies of the effects of exposure to dioxin. The only reported female cohort with good TCDD exposure surrogate information was that of Manz et al. (1991), which reported a borderline statistically significant increase in breast cancer. Although Saracci et al. (1991) did report reduced female breast and genital organ cancer mortality, this was based on few observed deaths and on exposure to chlorophenoxy herbicide, rather than TCDD. In the later update and expansion of this cohort Kogevinas et al. (1997) provided evidence of a reversal of this deficit and produced a borderline significant excess risk of breast cancer in females. Bertazzi et al. (1993, 1997, 1998, 2001a) reported nonsignificant deficits in the risk of breast and endometrial cancers in women living in geographical areas around Seveso contaminated by dioxins. Although Kogevinas et al. (1993) noted an increase in cancer incidence among female workers most likely exposed to TCDD, no increase in breast cancer incidence was observed in a small cohort studied. In sum, TCDD cancer experience for women may differ from that of men, but currently there are few epidemiologic data to support this conclusion.

Animal studies suggest that males and females respond differently to TCDD and its congeners. Dioxins have been shown to reduce estrogen levels in reproductive tissues and are also known to reduce estrogen-receptor binding in rat and mouse liver. The female mouse liver is more sensitive than the male mouse liver. These antiestrogenic effects might be responsible for decreased tumor incidences seen in the mammary gland, uterus, and pituitary of TCDD-treated female rats, although the decreases occurred in the high-dose group and may be due to decreased body weight. Antiestrogenic effects may also be partially responsible for increased liver cancer seen in female but not male rats (see Part II, Chapter 6, Sections 6.4.1 and 6.5.4). These female rat liver tumors may be ovary-dependent, while at the same time the ovaries appear to protect against TCDD-mediated tumor promotion in the rat lung (see Section 6.4.2). Thus, these complex mechanisms might very well affect human carcinogenicity of dioxin-like compounds in males and females differently.

TCDD-related receptor-mediated responses on cell differentiation and proliferation, hormonal effects, and immune suppression probably produce multiorgan sensitivity and contribute to the overall increased mortality from all malignancies combined seen in the four production worker subcohorts and Seveso victims with higher estimated PCDD exposures. The increased relative mortality risks (SMRs =1.4 to 2.0) seen in the most exposed subcohorts are consistent and statistically significant. This is important because significant increases in common tumors are difficult to demonstrate in epidemiological studies, even when dealing with relative risks generated from incidence data. With mortality data, which do not include those who

survived their cancer, it is even more unlikely that an effect will be detected when present, given the insensitive nature of the epidemiological method. Therefore, a significantly elevated risk of mortality from generalized cancer should be considered a significant contributor to the evaluation of cancer hazard, particularly when the mode of action of the subject compounds is consistent with promotion of existing lesions and/or immune suppression and multisite carcinogenesis.

In conclusion, although there are uncertainties associated with the epidemiologic evidence that could have influenced the risk estimates rendering these data "limited," the overall weight of evidence from the epidemiologic studies suggests that the generally increased risk of overall cancer is more likely than not due to exposure to TCDD and its congeners. The consistency of this finding in the four major cohort studies and the Seveso victims is corroborated by animal studies that show TCDD to be a multisite, multisex, and multispecies carcinogen with a mechanistic basis.

Table 7-1. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in United States, by exposure duration and latency

Cancer	Measure[a]	Latency <20 years	Latency ≥20 years		Total cohort
			Exposure <1 year	Exposure ≥1 year	
Connective and soft tissues	Observed deaths	1	0	3	4
	Relative risk	1.4	0.02	9.22	3.4
	95% confidence interval	0.1 - 7.0	0.0 - 15.0	1.90 - 27.0	0.9 - 8.6
Hodgkin's disease	Observed deaths	2	0	1	3
	Relative risk	1.1	0.0	2.8	1.2
	95% confidence interval	0.2 - 3.5	0.0 - 15.0	0.1 - 15.3	0.3 - 3.3
Non-Hodgkin's lymphomas	Observed deaths	6	2	2	10
	Relative risk	1.6	1.5	0.9	1.4
	95% confidence interval	0.7 - 3.4	0.2 - 4.9	0.1 - 3.30	0.7 - 2.5
Lung cancer	Observed deaths	32	17	40	89
	Relative risk	0.9	1.0	1.4	1.1
	95% confidence interval	0.7 - 1.3	0.6 - 1.5	1.0 - 1.9	0.9 - 1.4
Stomach cancer	Observed deaths	3	3	4	10
	Relative risk	0.6	1.8	1.4	1.0
	95% confidence interval	1.5 - 1.6	0.4 - 5.2	0.4 - 3.5	0.5 - 1.9
All combined	Observed deaths	103	48	114	265
	Relative risk	1.05	1.02	1.46	1.15
	95% confidence interval	0.8 - 1.2	0.76 - 1.4	1.2 - 1.8	1.0 - 1.3

[a]Relative risks and confidence intervals are based on rounded values and may differ slightly from those in the original reports (Fingerhut et al., 1990, 1991).

Source: Fingerhut et al., 1991.

Table 7-2. Relative risks of lung cancer in subcohort of chemical manufacturing workers exposed to TCDD in United States for at least 1 year and with at least 20 years latency, adjusted for alternative hypotheses about its smoking distribution

Proportion of subcohort (percent)[a]			Expected lung cancer deaths (40 observed)	Relative risk	95% confidence interval
Never smokers	Former smokers	Current smokers			
24	19	57	28.8	1.4	1.0 - 1.9
28	14	59	29.2	1.4	1.0 - 1.8
25	10	65	30.5	1.3	0.9 - 1.8
20	15	65	31.2	1.3	0.9 - 1.7
15	15	70	33.2	1.2	0.9 - 1.6
10	20	70	33.9	1.2	0.9 - 1.6
15	10	75	34.4	1.2	0.8 - 1.6
10	15	75	35.1	1.1	0.8 - 1.5

[a]The first set of proportions assumes no difference between the subcohort and the U.S. population. The second set is basedon 87 surviving members of the subcohort (Fingerhut et al., 1990). The remaining sets are hypothetical values used to test thesensitivity of the results. Relative risks of lung cancer are assumed to be 4.7 for former smokers and 10.9 for current smokers (Fingerhut et al., 1990).

Source: Fingerhut et al., 1991.

Table 7-3. Life-table results for exposure-level subcohorts: standardized mortality ratios (SMRs) for total cancer by cumulative exposure categories to TCDD content in process materials with and without 15-year lag time for total cancer; U.S. population as referent

SMR (No. of observed deaths)				
Category	**Exposure level[a]**	**No lag**	**Exposure level[a]**	**15 year lag**
Septile 1	0 to <19	1.14 (34)	0 to <39	0.98 (67)
Septile 2	19 to <139	1.15 (39)	39 to <224	0.90 (27)
Septile 3	139 to <581	0.85 (29)	224 to <791	1.14 (31)
Septile 4	581 to <1,650	1.10 (36)	791 to <2,120	1.18 (30)
Septile 5	1,650 to <5,740	1.15 (40)	2,120 to <6,140	1.33 (34)
Septile 6	5,740 to <20,200	1.34 (38)	6,140 to <15,800	1.69[b] (33)
Septile 7	≥ 20,200	1.60[b] (40)	≥ 15,800	1.54[b] (34)
Two-sided *p* for trend CE LCE		0.02 .10		0.02 .002

[a] Estimated exposure = product of concentration of TCDD (μg/g) in process materials × contact level × fraction of day exposed × time.
[b] $p < .05$, two-sided.

CE = Cumulative exposure.
LCE = Logarithm of cumulative exposure.

Source: Steenland et al., 1999.

Table 7-4. Relative risks of all cancers combined in study of chemical manufacturing workers exposed to TCDD in Germany, by duration and category of exposure

		Exposure category (median adipose TCDD level)		
Exposure duration	**Measure**	**Low and medium (60 ng/kg)**	**High (137 ng/kg)**	**Total**
<20 years	Observed deaths	49	26	75
	Relative risk	1.1	1.2	1.1
	95% confidence interval	0.8 - 1.4	0.8 - 1.8	0.9 - 1.4
≥20 years	Observed deaths	10	8	18
	Relative risk	1.5	2.6	1.9
	95% confidence interval	0.8 - 2.7	1.2 - 4.9	1.1 - 2.9
Total	Observed deaths	59	34	93
	Relative risk	1.2	1.4	1.2
	95% confidence interval	0.9 - 1.5	1.0 - 2.0	1.0 - 1.5

Source: Manz et al., 1991.

Table 7-5. Relative risks of all cancers combined in study of chemical manufacturing workers exposed to TCDD (ng/kg) in blood in Germany by industry of exposure

TCDD content (ng/kg)	Observed deaths	Relative risk	95% confidence interval
0 to <125.2	28	1.24	0.82 to 1.79
125.2 to < 627.1	29	1.34	0.9 to 1.92
627.1 to < 2,503.0	31	1.34	0.91 to 1.90
≥ 2,503.0	36	1.73	1.21 to 2.40
Total	124	1.41	1.17 to 1.68

Source: Flesch-Janys et al., 1998.

Table 7-6. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in Germany, by median blood TCDD level and latency

Subcohort (median blood TCDD level)	Cancer	Measure	Time since first exposure <20 years	Time since first exposure ≥20 years	Total
C1 (24.5 ppt)	Lung	Observed deaths	1	3	4
		Relative risk	1.2	2.5	2.0
		95% confidence interval	0.1 - 6.2	0.6 - 6.9	0.6 - 4.8
	Stomach	Observed deaths	1	2	3
		Relative risk	2.0	4.0	3.0
		95% confidence interval	0.1 - 9.7	0.7 - 13.2	0.8 - 8.1
	All combined	Observed deaths	2	7	9
		Relative risk	0.7	1.7	1.3
		95% confidence interval	0.1 - 2.4	0.7 - 3.3	0.6 - 2.4
C2 (9.5 ppt) and C3 (8.4 ppt)	Lung	Observed deaths	0	2	2
		Relative risk	0.0	1.0	0.5
		95% confidence interval	0.0 - 1.8	0.2 - 3.4	0.1 - 1.8
	Stomach	Observed deaths	0	0	0
		Relative risk	0.0	0.0	0.0
		95% confidence interval	0.0 - 3.2	0.0 - 3.9	0.0 - 1.7
	All combined	Observed deaths	5	9	14
		Relative risk	0.8	1.3	1.1
		95% confidence interval	0.3 - 1.9	0.6 - 2.4	0.6 - 1.8
Total cohort	Lung	Observed deaths	1	5	6
		Relative risk	0.4	1.6	1.1
		95% confidence interval	0.0 - 2.0	0.6 - 3.5	0.4 - 2.2
	Stomach	Observed deaths	1	2	3
		Relative risk	0.7	1.6	1.1
		95% confidence interval	0.0 - 3.4	0.3 - 5.2	0.3 - 3.0
	All combined	Observed deaths	7	16	23
		Relative risk	0.8	1.5	1.2
		95% confidence interval	0.4 - 1.6	0.9 - 2.3	0.8 - 1.7

Source: Zober et al., 1990.

Table 7-7. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in Germany, by TCDD dose (μg/kg body weight), 1992

Cause of death	Total			TCDD < 0.1 μg/kg body weight			TCDD 0.1- 0.99 μg/kg body weight			TCDD ≥ 1 μg/kg body weight		
Category	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**
Malignant neoplasms	31	1.2	(0.8 to 1.7)	8	0.8	(0.4 to 1.6)	8	1.2	(0.5 to 2.3)	15	1.6	(0.9 to 2.6)
Respiratory system	11	1.4	(0.7 to 2.5)	3	1.0	(0.2 to 2.9)	1	0.5	(0.0 to 2.7)	7	2.4	(1.0 to 5.0)
Residual sites	5	1.6	(1.6 to 3.6)	2	1.6	(0.2 to 5.7)	1	1.2	(0.0 to 6.4)	2	1.9	(0.2 to 6.7)
Category	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**
Malignant neoplasms	47	1.2	(0.8 to 1.5)	15	1.0	(0.5 to 1.6)	13	1.2	(0.6 to 2.1)	19	1.3	(0.8 to 2.0)
Respiratory system	13	1.2	(0.6 to 2.0)	1	0.7	(0.2 to 2.1)	2	0.7	(0.1 to 2.5)	8	2.0	(0.9 to 3.9)
Digestive organs	12	1.1	(0.6 to 1.9)	3	0.7	(0.2 to 2.2)	4	1.4	(0.4 to 3.6)	5	1.2	(0.4 to 2.9)

Source: Ott et al., 1996.

Table 7-8. Summary of results for selected cancers from follow-up studies of chemical manufacturing and processing workers exposed to TCDD

		Total cohorts				Subcohorts with high exposure, long latency, or both			
Cancer	Study	Observed deaths	Expected deaths	Relative risk	95% Confidence interval	Observed deaths	Expected deaths	Relative risk	95% Confidence interval
Connective and soft tissue cancers	Fingerhut (1991)	4	1.2	3.3	1.1 - 8.0	3	0.3	10.0	2.5 - 27.3
	Manz (1991)	0	0.4[a]	0.0	0.0 - 7.5	0	0.1[a]	0.0	0.0 - 30.0
	Zober (1990)	0	0.1[a]	0.0	0.0 - 30.0	0	0.0[a]	0.0	0.0 - 99.9
	Total	4	1.7	2.4	0.7 - 5.7	3	0.4	7.5	1.9 - 20.4
Non-Hodgkin's lymphomas	Fingerhut (1991)	10	7.3	1.4	0.7 - 2.4	2	2.1	1.0	0.2 - 3.1
	Manz (1991)	3	2.4[a]	1.2	0.3 - 3.4	NA	NA	NA	NA
	Zober (1990)	0	0.6[a]	0.0	0.0 - 5.0	0	0.2[a]	0.0	0.0 - 15.0
	Total	13	10.3	1.3	0.7 - 2.1	2	2.3	0.9	0.1 - 2.9
Lung cancer	Fingerhut (1991)	89	80.1	1.1	0.9 - 1.4	40	28.8	1.4	1.0 - 1.9
	Manz (1991)	30	21.3	1.4	1.0 - 2.0	NA	NA	NA	NA
	Zober (1990)	6	5.6	1.1	0.4 - 2.2	3	1.2	2.5	0.6 - 6.8
	Total	125	107.0	1.2	1.0 - 1.4	43	30.0	1.4	1.1 - 1.9
Stomach cancer	Fingerhut (1991)	10	9.7	1.0	0.5 - 1.8	4	2.9	1.4	0.4 - 3.3
	Manz (1991)	12	9.9	1.2	0.7 - 2.1	NA	NA	NA	NA
	Zober (1990)	3	2.7	1.1	0.3 - 3.0	2	0.5	4.0	0.7 - 13.2
	Total	25	22.3	1.1	0.7 - 1.6	6	3.4	1.8	0.7 - 3.7
All cancers combined	Fingerhut (1991)	265	229.9	1.2	1.0 - 1.3	114	78.0	1.5	1.2 - 1.8
	Manz (1991)	93	75.2	1.2	1.0 - 1.5	34	23.9	1.4	1.0 - 2.0
	Zober (1990)	23	19.7	1.2	0.8 - 1.7	7	4.2	1.7	0.7 - 3.3
	Total	381	324.8	1.2	1.1 - 1.3	155	106.1	1.5	1.2 - 1.7

[a]Estimated as a proportion of expected deaths from all cancers combined (see text).
NA, not available.

Table 7-9. Relative risks of soft tissue sarcomas and malignant lymphomas in relation to phenoxy acid and chlorophenol exposures in five case-control studies in Sweden

Exposure category and measure	Malignant lymphoma Northern Sweden 1974-1978 (Hardell et al., 1981)	Soft tissue sarcoma Northern Sweden 1970-1977 (Hardell and Sandström, 1979)	Soft tissue sarcoma Southern Sweden 1974-1978 (Eriksson et al., 1981)	Soft tissue sarcoma Northern Sweden 1978-1983 (Hardell and Eriksson, 1988)	Soft tissue sarcoma Central Sweden 1978-1986 (Eriksson et al., 1990)
Not exposed to phenoxy acids or chlorophenols					
Cases	108	33	85	41[a]	171[b]
Controls	303	187	206	255[a]	179[b]
Exposed to phenoxy acids, chlorophenols, or both					
Cases	61	19	25	13[a]	47[b]
Controls	32	19	13	56[a]	33[b]
Relative risk (95% CI)	5.3 (3.3 - 8.7)	5.7 (2.7 - 11.8)	4.7 (2.3 - 9.5)	1.4 (0.7 - 2.9)	1.5 (0.9 - 2.4)
Exposed to phenoxy acids					
Cases	41	13	14	9	23
Controls	24	14	5	22	18
Relative risk (95% CI)	4.8 (2.8 - 8.3)	5.3 (2.3 - 12.2)	6.8 (2.4 - 19.4)	2.5 (1.1 - 5.9)	1.3 (0.7 - 2.6)
Exposed to 2,4,5-T					
Cases	29	11	7	NA	19
Controls	23	10	1	NA	11
Relative risk (95% CI)	3.5 (2.0 - 6.4)	6.2 (2.5 - 15.8)	17.0 (2.1 - 140.0)	NA	1.8 (0.8 - 3.9)
Exposed to chlorophenols					
Cases	50	7	11	4	15
Controls	35	6	8	34	3
Relative risk (95% CI)	4.0 (2.5 - 6.5)	6.6 (2.1 - 20.9)	3.3 (1.3 - 8.6)	0.7 (0.2 - 2.2)	5.2 (1.5 - 18.4)

[a]Assuming no joint exposure to phenoxy acids and chlorophenols.
[b]Computed from Table 3 in the original report (Eriksson et al., 1990) with the assumption of no phenoxy acid exposures among persons with low-grade chlorophenol exposures.
NA, not available.

Table 7-10. Relative risks of malignant lymphoma and soft tissue sarcomas in relation to phenoxy acid and chlorophenol exposures in three case-control studies in Sweden[a]

Cancer and study locale	Exposure category	Cases	Controls	Relative risk (95% confidence interval)
Malignant lymphoma, northern Sweden (Hardell et al., 1981; Hardell, 1981)[b]	Exposed to phenoxy acids, chlorophenols, or both	51	28	1.0
	Unexposed	49	145	5.4 (3.1 - 9.5)
Soft tissue sarcoma, southern Sweden (Eriksson et al., 1981)[c]	Exposed to phenoxy acids, chlorophenols, or both	14	8	1.0
	Unexposed	17	39	4.0 (1.4 - 11.3)
Soft tissue sarcoma, central Sweden (Eriksson et al., 1990)[d]	Exposed to phenoxy acids	22	15	1.0
	Unexposed	33	51	2.3 (1.0 - 5.0)

[a]Restricted to persons who worked in the occupational categories in which these exposures predominantly occur.
[b]Analysis restricted to persons employed in agriculture, forestry, or the wood products industry.
[c]Analysis restricted to persons employed in agriculture or forestry.
[d]Analysis restricted to persons employed in agriculture, horticulture, or forestry.

Table 7-11. Mantel-Haenszel odds ratios for soft tissue sarcoma among persons exposed to all dioxins, TCDD, and dioxins other than TCDD in four case-control studies involving 434 cases and 948 controls[a]

Substance and variable	No exposure	Exposure < 1 yr[b]		Exposure ≥ 1 yr	
		Latency 5 - 19 yr	Latency ≥ 20 yr	Latency 5 - 19yr	Latency ≥ 20 yr
All dioxins					
No. of cases	352	24	34	3	21
No. of controls	865	22	52	0	9
OR	1.0	2.4		6.4	
90% CI	--	1.7 - 3.4		3.5 - 12	
TCDD					
No. of cases	352	18	22	1	5
No. of controls	865	14	25	0	2
OR	1.0	3.0		7.2	
90% CI	--	2.0 - 4.5		2.6 - 20	
Other dioxins					
No. of cases	352	6	12	2	16
No. of controls	865	8	27	0	7
OR	1.0	1.7		6.2	
90% CI	--	0.98 - 2.9		2.9 - 13	

[a]OR denotes odds ratio and CI confidence interval.
[b]All subjects were exposed for at least 1 day. Data for latency periods were combined to determine the odds ratios.

Source: Hardell et al., 1991.

Table 7-12. Relative risks of soft tissue sarcomas, non-Hodgkin's lymphomas, and Hodgkin's disease in relation to phenoxy acid and chlorophenol exposures in two case-control studies in southern Sweden

Authors, study period	Cancer	Exposure	Relative risk (confidence interval)[a]
Olsson and Brandt, 1978-1981 (Olsson and Brandt, 1988)	Non-Hodgkin's lymphomas	Phenoxy acids	1.3 (0.8 - 2.1)
		Chlorophenols	1.2 (0.7 - 2.0)
Persson et al., 1964-1986 (Persson et al., 1989)	Non-Hodgkin's lymphomas	Herbicides	4.9 (1.3 - 18)
	Hodgkin's disease	Herbicides	3.8 (0.7 - 21)
Wingren et al., 1975-1982 (Wingren et al., 1990)	Soft tissue sarcomas	Unspecified chemical work, potential exposure to phenoxy herbicides or chlorophenols	1.6 (0.8 - 3.3)

[a]Confidence intervals are 95% in the Olsson and Brandt study and 90% in the other two studies.

Table 7-13. Relative risks of non-Hodgkin's lymphomas in relation to farm use of 2,4,5-T in case-control studies in Kansas, eastern Nebraska, Iowa, and Minnesota

Occupational category	Exposure category and measure	Kansas (Hoar et al., 1986)		Eastern Nebraska (Zahm et al., 1990)		Iowa and Minnesota (Cantor et al., 1992)	
		Cases	Controls	Cases	Controls	Cases	Controls
All subjects	Exposed	3	18	13	27	25	48
	Unexposed	167	930	188	696	597	1,197
	Relative risk	0.9		1.8		1.0	
	95% confidence interval	0.3 - 3.2		0.9 - 3.5		0.6 - 1.7	
Farmers	Exposed	3	18	13	27	25	48
	Unexposed	130	644	134	512	331	650
	Relative risk	0.8		1.8		1.0	
	95% confidence interval	0.2 - 2.8		0.9 - 3.7		0.6 - 1.7	
Exposed farmers and unexposed nonfarmers	Exposed	3	18	13	27	25	48
	Unexposed	37	286	54	184	266	547
	Relative risk	1.3		1.6		1.1	
	95% confidence interval	0.4 - 4.6		0.8 - 3.4		0.6 - 1.8	

Sources: Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992.

Table 7-14. Relative risks of soft tissue sarcomas and non-Hodgkin's lymphomas in relation to phenoxyacetic acid and chlorophenol exposure in a case-control study in western Washington State, 1981-1984

Exposure measure	Soft tissue sarcomas	Non-Hodgkin's lymphomas
Estimated potential for phenoxyacetic acid exposure[a]		
Low	0.6 (0.3 - 1.1)	0.9 (0.6 - 1.3)
Medium	1.0 (0.6 - 1.7)	0.9 (0.7 - 1.3)
High	0.9 (0.4 - 1.9)	1.2 (0.8 - 1.9)
Any	0.8 (0.5 - 1.2)	1.1 (0.8 - 1.4)
Estimated potential for chlorophenol exposure[a]		
Low	0.9 (0.5 - 1.6)	1.0 (0.7 - 1.3)
Medium	0.9 (0.6 - 1.5)	0.9 (0.7 - 1.2)
High	0.9 (0.5 - 1.8)	0.9 (0.9 - 1.4)[b]
Any	1.0 (0.7 - 1.5)	1.0 (0.8 - 1.2)

[a]The reference category had no estimated potential for exposure (relative risk 1.0 by definition).
[b]Either the point estimate or the lower confidence limit appears to have been a typographical error in the original report. (On a logarithmic scale, the point estimate should be centered between the two confidence limits.)
Source: Woods et al., 1987.

Table 7-15. Relative risks of soft tissue sarcomas and non-Hodgkin's lymphomas in relation to potential exposure to phenoxy acids and chlorophenols in case-control studies in New Zealand

Measure	Soft tissue sarcomas		Non-Hodgkin's lymphomas (1978-1981) (Pearce et al., 1987)
	First study (1976-1980) (Smith et al., 1983, 1984)	Second study (1981-1982) (Smith and Pearce, 1986)	
Cases	82	51	183
Controls	92	315	338
Phenoxy acids			
Any potential exposure			
Cases	21	NR	44
Controls	19	NR	72
Relative risk (95% CI)	1.3 (0.7 - 2.7)	NR	1.2 (0.8 - 1.8)
Probable or definite exposure >1 day, >5 years before cancer registration			
Cases	17	6	29
Controls	13	46	50
Relative risk (95% CI)	1.6 (0.7 - 3.5)[a]	0.8 (0.3 - 1.9)	1.1 (0.7 - 1.8)
Chlorophenols			
Any potential exposure			
Cases	8	NR	21
Controls	7	NR	27
Relative risk (95% CI)	1.3 (0.5 - 3.8)	NR	1.5 (0.8 - 2.7)
Potential exposure >1 day, >5 years before cancer registration			
Cases	8	NR	20
Controls	6	NR	27
Relative risk (95% CI)	1.6 (0.5 - 4.7)	NR	1.4 (0.8 - 2.6)

[a]Among farmers, 3.0 (1.1-8.3); controlling for farming by standardization, 1.9 (0.8-4.5).
CI, confidence interval; NR, not reported.

Table 7-16. Relative risks of soft tissue sarcomas in relation to phenoxy acid exposure in case-control study in northern Italy, 1981-1983

		Men		Women	
Category	Measure	Unexposed	Possibly or certainly exposed	Unexposed	Possibly or certainly exposed
Living	Cases	21	2	16	5
	Controls	54	8	53	7
	Relative risk	1.0	0.6	1.0	2.4
	(95% confidence interval)	NA	(0.1 - 3.3)	NA	(0.7 - 8.5)
Deceased	Cases	13	1	6	4
	Controls	17	6	7	6
	Relative risk	1.0	0.2	1.0	0.8
	(95% confidence interval)	NA	(0.0 - 2.0)	NA	(0.1 - 4.1)
Total	Cases	34	3	22	9
	Controls	71	14	60	13
	Relative risk	1.0	0.4	1.0	1.9
	(95% confidence interval)	NA	(0.1 - 1.7)	NA	(0.7 - 5.0)
Total, farmers only	Cases	12	3	5	9
	Controls	12	14	8	13
	Relative risk	1.0	0.2	1.0	1.1
	(95% confidence interval)	NA	(0.0 - 0.9)	NA	(0.3 - 4.5)

NA, not applicable.

Source: Vineis et al., 1986.

Table 7-17. Relative risks for selected cancers from follow-up studies of paper and pulp mill workers

Cancer	Study	Observed deaths	Expected deaths	Relative risk	95% confidence interval
Non-Hodgkin's lymphomas	Robinson (1986)	12	8.9	1.3	0.7 - 2.3
	Jäppinen (1987)	2	3.5	0.6	0.1 - 1.9
	Henneberger (1989)	4	3.8	1.1	0.3 - 2.5
	Total	18	16.2	1.1	0.7 - 1.7
Lung cancer	Robinson (1986)	50	62.1	0.8	0.6 - 1.1
	Jäppinen (1987)	78	62.6	1.2	1.0 - 1.5
	Henneberger (1989)	25	28.0	0.9	0.6 - 1.3
	Total	153	152.7	1.0	0.8 - 1.2
Stomach cancer	Robinson (1986)	17	13.8	1.2	0.7 - 1.9
	Jäppinen (1987)	24	28.8	0.8	0.5 - 1.2
	Henneberger (1989)	5	4.2	1.2	0.4 - 2.6
	Total	46	46.8	1.0	0.7 - 1.3
All cancers combined	Robinson (1986)	160	211.5	0.8	0.6 - 0.9
	Jäppinen (1987)	196	203.8	1.0	0.8 - 1.1
	Henneberger (1989)	97	87.9	1.1	0.9 - 1.3
	Total	453	503.2	0.9	0.8 - 1.0

Table 7-18. Relative risks for selected cancers among adults exposed to TCDD in Seveso, Italy, in contaminated areas B and R

Cancer	Males OBS	Males RR	Males 95% CI	Females OBS	Females RR	Females 95% CI
Region B						
All malignancies	76	1.1	0.9 - 1.4	36	0.8	0.6 - 1.1
Trachea, bronchus, lung	18	1.1	0.7 - 1.8	0	---	---
Hepatobiliary	5	1.8	0.7 - 4.4	5	3.3	1.3 - 8.1
Liver	4	2.1	0.8 - 5.8	0	---	---
Hematopoietic system	8	2.1	1.0 - 4.3	6	1.9	0.8 - 4.4
Non-Hodgkin's lymphoma	3	2.3	0.7 - 7.4	1	0.9	0.1 - 6.4
Lymphoreticulosarcoma	3	5.7	1.7 - 19.0	1	2.3	0.3 - 16.9
Hodgkin's disease	1	1.7	0.2 - 12.8	1	2.1	0.3 - 15.7
Multiple myeloma	2	3.2	0.8 - 13.3	2	5.3	1.2 - 22.6
Leukemia	2	1.6	0.4 - 6.5	2	1.8	0.4 - 7.3
Myeloid leukemia	1	2.0	0.2 - 14.6	2	3.7	0.9 - 15.7
Region R						
All malignancies	447	0.9	0.9 - 1.0	318	0.9	0.8 - 1.1
Trachea, bronchus, lung	96	0.8	0.7 - 1.0	16	1.5	0.8 - 2.5
Hepatobiliary	11	0.5	0.3 - 1.0	12	0.9	0.5 - 1.7
Liver	3	0.2	0.1 - 0.7	2	0.5	0.1 - 2.1
Connective & soft	6	2.8	1.0 - 7.3	2	1.6	0.3 - 7.4
Non-Hodgkin's lymphoma	12	1.3	0.7 - 2.5	10	1.2	0.6 - 2.3
Lymphoreticulosarcoma	4	1.1	0.4 - 3.2	6	1.7	0.7 - 4.2
Multiple myeloma	1	0.2	0.0 - 1.6	2	0.6	0.2 - 2.8
Myeloid leukemia	5	1.4	0.5 - 3.8	2	0.5	0.1 - 2.1
Genitourinary organs	75	1.0	0.8 - 1.3	106	1.1	0.9 - 1.3
Breast	1	1.2	0.1 - 10.2			

Source: Bertazzi et al., 1993.

Table 7-19. Standard mortality ratios (SMRs) for selected cancers among adults exposed to TCDD in Seveso, Italy, in contaminated areas B and R

Cancer- cause of death	OBS	Males SMR	95% CI	OBS	Females SMR	95% CI
Region B						
All malignancies	104	1.1	0.9- 1.3	48	0.9	0.7-1.2
Trachea, bronchus, lung	40	1.2	0.9- 1.7	2	0.5	0.1-1.8
Pleura	3	5.3	1.1- 15.5	-	-	-
Hepatobiliary	4	0.6	0.2- 1.5	4	1.1	0.3-2.9
Liver	4	0.6	0.2- 1.7	3	1.3	0.3- 3.8
Rectum	7	2.9	1.2- 5.9	2	1.3	0.1- 4.5
Lymphohemepoietic	12	2.4	1.2- 4.1	7	1.8	0.8-3.7
Non-Hodgkin's lymphoma	2	1.5	0.2- 5.3	0	0	0-3.0
Lymphatic	2	2.9	0.3- 10.6	-	-	-
Hodgkin's disease	2	1.5	0.2- 5.3	2	6.5	-
Multiple myeloma	1	1.1	0- 6.2	4	6.6	1.8- 16.8
Leukemia	7	3.1	1.3- 6.4	1	0.6	0- 3.1
Myeloid leukemia	3	3.3	0.7- 9.6	-	-	-
Region R						
All malignancies	607	0.9	0.9- 1.0	401	0.9	0.8- 1.1
Trachea, bronchus, lung	208	0.9	0.8- 1.1	35	1.1	0.8- 1.5
Esophagus	30	1.6	1.1- 2.3	5	0.9	0.3- 2.2
Hepatobiliary	35	0.7	0.5- 1.0	25	0.8	0.5- 1.3
Liver	31	0.7	0.5- 1.0	12	0.6	0.3- 1.1
Connective and soft	4	2.1	0.6- 5.4	0	0	0- 2.4
Non-Hodgkin's lymphoma	10	1.1	0.5- 2.0	8	0.9	0.4- 1.7
Lymphohemopoietic	27	0.8	0.5- 1.2	29	1.0	0.6- 1.4
Bone	2	0.5	0.1- 1.7	7	2.4	1.0- 4.9
Multiple myeloma	5	0.8	0.3-1.9	5	1.0	0.3- 2.3
Myeloid leukemia	4	0.6	0.2- 1.6	4	0.6	0.2- 1.6
Genitourinary organs	73	1.0	0.8- 1.3	65	1.1	0.8- 1.4
Breast	-	-	-	67	0.8	0.6- 1.0

Source: Bertazzi et al., 1997, 1998.

Table 7-20. Standard mortality ratios (SMRs) for selected cancers among males and females exposed to TCDD in Seveso, Italy, in contaminated areas A and B combined

Cancer- cause of death	OBS	Males SMR	95% CI	OBS	Females SMR	95% CI
Region A&B Combined*						
All malignancies	166	1.1	1.0–1.3	83	0.9	0.7–1.1
Trachea, bronchus, lung	64	1.3	1.0–1.6	5	0.7	0.3–1.7
Pleura	3	5.3	1.1–-15.5	-	-	-
Hepatobiliary	6	0.5	0.2–1.0	7	1.0	0.5–2.2
Liver	6	0.5	0.2–1.1	6	1.3	0.6–2.9
Rectum	9	3.8	1.2–4.6	3	1.1	0.4–3.5
Lymphohemopoietic	15	1.7	1.0–2.8	13	1.8	1.1–3.2
Non-Hodgkin's lymphoma	3	1.2	0.4–3.9	4	1.8	0.7–4.9
Lymphatic	2	1.6	0.4–6.8	-	-	-
Hodgkin's disease	2	2.6	0.6–10.9	2	3.7	0.9–16.0
Multiple myeloma	1	0.6	0.1–4.3	4	3.2	1.2–8.8
Leukemia	9	2.1	1.1–4.1	3	1.0.6	0.3–3.0
Myeloid leukemia	5	3.4	1.3–8.4	1	-	0.1–5.1

Source: Bertazzi et al., 2001a*.

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
12 plants producing chemicals contaminated with TCDD	5,172	Current serum TCDD level (lipid adjusted) n = 253 Mean = 233 ppt	Total cancer SMR = 115 (102-130) Unspecified sites SMR = 162 (104-241)	<u>Strengths</u> High power, multiple sites (plants) exposure data, dose-response relationship, in vivo exposure information <u>Weaknesses</u> Possible confounding: smoking, other agents such as asbestos. Only 2 plants of 12 sampled for exposure data	Fingerhut et al., 1991
	1,520	>1 year exposed and >20 years latency, 95 sampled = 462 ppt	Total cancer SMR = 146 (121-176) Resp. system SMR = 142 (103-192)		Steenland et al., 1999
		Highest exposed group > 20,200 cumulative exposure score (concentration × fraction of day exposed × contact level × years exposed)	Total cancer = 1.60 (1.2-1.8) Lung cancer SMR = 1.65		
			All cancers / Trachea, bronchus, lung		
	Not provided	<1 yr, mean = 111ppt 1-<5 yr, mean = 413 ppt 5 - 15 yr, mean = 738 ppt ≥15 yr, mean = 2218 ppt	102 (75-133) / 96 (56-147) 165 (119-198) / 26 (73-192) 138 (97-186) / 146 (79-232) 115 (68-175) / 156 (71-272)	Possible nondifferential misclassification of exposure could underestimate true risks.	Aylward et al., 1996
German factory workers who produced phenoxy herbicides	1,189 men 399 women	Current adipose tissue TCDD levels used to obtain cumulative exposure during years when working	All cancer SMR = 1.41 (1.2-1.7) Lung cancer SMR = 1.51 (1.1-2.1)	<u>Strengths</u> Generally increasing risk with dose. Good evidence of in vivo exposure to TCDD congeners. Actual measurements from blood serums. Smoking apparently not a confounder	Becher et al., 1998 Becher et al., 1996 Flesch-Janys et al., 1998
	689 men	<u>Medium and low</u> 11 sampled Mean = 83 Median = 60 ppt	Nonsignificant exposure >20 years SMR = 1.54 (0.8-2.7)	<u>Weaknesses</u> Measurements are current. Possible misclassification of exposure by TEQ quartile	Manz et al., 1991
	459 men	<u>High</u> 37 sampled Mean = 296 ppt Median = 137 ppt	All cancer exposure duration ≥ 20 years SMR = 2.54 (1.1-5.0)		
	Blood fat 275 workers	Highest TCDD quartiles > 2,503 ng/kg - years	Total cancer SMR 1.73 (1.2-2.4)		
		Highest TEQ quartile >5217.7 ng/kg years	Total cancer SMR = 1.64 (1.2-2.3)		

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin (continued)

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
Uncontrolled decomposition reaction on 11/17/53 resulting in exposure to TCDD in trichlorophenol production unit	243	Full group- measurement of blood lipid TCDD+ duration of exposure to obtain dose n = 138	Total cancer SMR = 1.2 (0.8-1.7)	Strengths In vivo exposure assessment. 40-year follow-up Weaknesses Possible synergistic effect with smoking, small size of cohort	Ott and Zober, 1996 Zober et al., 1990
	108	<0.1 ug/kg body weight	SMR = 0.8 (0.4-1.6)		
	66	<1.00 0.1 to 0.99 ng/kg body weight	SMR = 1.2 (0.5-2.3)		
	69	≥1.00 ug/kg body weight	SMR = 1.6 (0.9-2.6)		
	<69	≥1.00 ug/kg body weight + ≥20 years latency body weight	SMR = 1.97 (1.05-3.36) Lung cancer = 3.06 (1.12-6.66)		
	127 with chloracne and erythema	≥20 years latency	SMR = 2.01 (1.22-3.15)		
Phenoxy herbicide manufacturing and preparation accident, 1963	140 exposed in accident	Current measurements mean = 96.3 ppt serum TCDD, extrapolated to 1,841.8 ppt serum TCDD max at time of accident, n =14	Malignant neoplasms RR = 1.7 (1.1-2.7)	Strengths Current in vivo TCDD serum lipid measurements. Wide range of exposure and adequate latency, dose response relationship	Bueno de Mesquita et al., 1993 Hooiveld et al., 1998
	259 exposed compared with 482 nonexposed workers	Medium exposure, extrapolated range (7.7 to 124.1 ppt) at time of accident (lipid adjusted)	Malignant neoplasms RR = 5.0 (2.2-11.5)	Weaknesses Small cohort, lack of power	
	242 exposed compared with 482 nonexposed workers	High exposure, extrapolated range (124.2 to 7,307.5 ppt) at time of accident (lipid adjusted)	Malignant neoplasms RR = 5.6 (2.5 - 12.7)		
	549 exposed compared with 482 nonexposed	Exposed but not in accident. 244.1 ppt extrapolated, n = 17	RR = 4.1 (1.8-9.0) adjusted		

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
Chemical explosion of phenoxy herbicide factory in Seveso, Italy, July 1976	Zones A, B, and R	Exposure as measured by blood serum. TCDD ranged as high as 56,000 ppt in one child Geometry means were as follows:	Significant excess risks in males without regard for latency	<u>Strengths</u> Relatively pure exposure to TCDD. Its distribution in the environment was measured. This exposed population stable. In vivo plasma TCDD serum available on a large number of subjects. Biases and confounding not likely to explain the unusual RRs	Caramaschi et al., 1981 Bertazzi et al., 1989b, 1992, 1993, 1997, 1998, 1999, 2001a Landi et al., 1996, 1998 Pesatori et al. 1993, 1999
	A-Zone N=862 population	A-53.2 ppt (N=7) plasma TCDD current 230.0 ppt extrapolated to time of accident	No significant findings	<u>Weaknesses</u> Time lapsed since measurement of exposure. Small size of population in most heavily exposed region. Small numbers of deaths from which to measure risks. Possible misclassification of exposure. 20 year follow-up is too short	
	B-zone N=6,647 population	B-11.0 ppt (N=51) plasma TCDD current 47.5 ppt extrapolated to time of accident	*<u>Zone A and B</u> Total cancer RR = 1.10 (0.9–1.2) *Males* Total cancer RR=1.1 (1.0-1.3) Respiratory cancer RR=1.3 (1.0-1.6) Lymphohematopoietic RR=1.7 (1.0–2.8) Leukemia RR=2.1 (1.1-4.1) *Females (etc.)* Myeloma RR=3.2 (1.2–8.8)		
	R-zone N=42,831 population	R-4.9 ppt (N=52) plasma TCDD current 200 cases of chloracne were reported	**<u>Zone R</u> *Males* Esophagus RR=1.6 (1.1-2.3) **<u>Zone R</u> *Females* Bone - RR=2.5 (1.0-4.9) No separated finding yet		

*Bertazzi et al., 2001a.
**Bertazzi et al., 1997, 1998.

Table 7-22. TCDD concentrations in the blood of selected residents in the zones contaminated after the Seveso, Italy, industrial accident in 1976[a]

Study area	Lipid-adjusted plasma concentration	
	Number of Subjects	Median
Zone A	296 (1976-1977) 7 (1993-1994)	447.0 ppt 73.3 ppt
Zone B	80 (1976-1977) 51 (1993-1994)	94.0 ppt 12.4 ppt
Zone R	48 (1976-1977)	48 ppt
Reference Zone	52 (1993-1994)	5.5 ppt

[a]Adapted from Bertazzi et al., 2001a.

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