FINAL REPORT

LITERATURE REVIEW
ON THE HUMAN HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO THE HERBICIDES 2,4,5-T AND 2,4-D, AND DIOXINS

PREPARED FOR
THE DEPARTMENT OF HEALTH, GOVERNMENT OF WESTERN AUSTRALIA

August 2003
Weed eradication programs undertaken by the Agricultural Protection Board (APB) involved the use of 2,4-D and 2,4,5-T in the Kimberley region of Western Australia. People involved in the spraying during the 1970s and 1980s have reported suffering from ill health as a result of exposure to the herbicides (Harper, 2002).

In response to this, the present review was commissioned by an Expert Medical Panel (EMP) for the Department of Health, Western Australia to provide information on the scientific evidence of associations between exposure to the herbicides 2,4,5-T and 2,4-D as well as the co-contaminant 2,3,7,8-TCDD and adverse health effects, including signs and symptoms of disease, diagnosed disease or death from any cause.

The objectives of this review were to:
- Provide a synthesis of existing authoritative reviews investigating adverse health effects in humans from exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD.
- Identify and critically evaluate new literature, published since the last update of the Key Review (i.e. 2002), investigating human health effects from exposure to 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D.
- Provide an evaluation on the overall strength of evidence of the association of specific health endpoints and exposure to the compounds of interest, including, where possible, an indication on what type and extent of exposure this evidence is based on.
- Identify and summarise literature describing patterns of signs and symptoms of disease, illness and death in humans from exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

The Key Reviews considered and summarised for this report were performed by the International Agency for Research on Cancer (IARC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR, 1998), the U.S. Environmental Protection Agency (U.S. EPA, 2000c), the World Health Organization (WHO/IPCS, 2002), and the National Academy of Sciences (NAS, 2002). Eighteen updates to these Key Reviews were identified from the scientific literature and evaluated using defined criteria. The total evidence accumulated in the scientific literature was assessed with regards to a number of defined adverse health endpoints. An overall evaluation on the strength of association between exposure to the compounds of interest and each adverse health endpoint was made, based on the total available epidemiological and toxicological evidence and according to set criteria. In addition, literature describing patterns of signs and symptoms of disease or death were summarised independently of the Literature Update. These were selected using a separate set of criteria and summarised in this review.

The following lists the outcomes of the overall evaluation on the strength of evidence of association between exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD and each investigated adverse health endpoint. The health outcomes where an ESTABLISHED CAUSAL LINK exists was Chloracne. Health outcomes where a PROBABLE CAUSAL LINK exists included Total Cancer, Soft Tissue Sarcoma and Non-Hodgkin’s Lymphoma. Health outcomes where a POSSIBLE CAUSAL LINK exists included Laryngeal Cancer, Lung Cancer, Prostate Cancer, Hodgkin’s Disease, Multiple Myeloma, Chronic Lymphoid Leukaemia, Immune System Disorders, Diabetes, and Lipid, Lipoprotein Disorders and Porphyria Cutanea Tarda. Health outcomes where INSUFFICIENT EVIDENCE exists to make a classification included Hepatobiliary Cancer, Cancers of the Head and Neck, Bone Cancer, Skin Cancer (melanoma and nonmelanoma), Testicular Cancer, Urinary Bladder Cancer, Renal Cancer, Leukaemia (other than CLL), Neurobehavioral Disorders, Respiratory Disorders, Male Reproductive Disorders, Thyroid Homeostasis, Circulatory Disorders, and Gastrointestinal Disorders. Health outcomes where NO CAUSAL LINK is established included Gastrointestinal Cancer and Brain Tumours.

Forty-seven studies describing patterns of disease, signs, symptoms or death were identified from the scientific literature using defined criteria and summarised into disease groups according to exposure dose, type and duration. The patterns observed in the exposed individuals and groups showed a wide range of possible signs and symptoms that may be associated with the exposure to 2,4,5-T and/or 2,4-D and/or 2,3,7,8-TCDD. The most frequently observed signs and symptoms in all long-term exposure groups related to gastrointestinal, cognitive, motor-sensory, neuropsychiatric and skin disorders and diseases. Generally similar signs and symptoms were observed in individuals or groups that were exposed to the compounds of interest for relatively short periods of time. Signs and symptoms reported from acute exposure (mainly poisoning) differed from long-and short-term exposure disease categories mainly with respect to greater frequency of circulatory, respiratory and hematologic disorders and conditions. However, due to a number of limitations regarding the study design of descriptive case series, case reports or medical surveys, the frequent lack of exposure information, broad symptom definitions and different approaches taken, an evaluation on the causal link of the observed health outcomes and exposure to these compounds cannot be made.
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**Acronyms, Abbreviations and Definitions**

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<th>Definition</th>
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<tr>
<td>2,4,5-T</td>
<td>2,4,5-trichlorophenoxyacetic acid</td>
</tr>
<tr>
<td>2,4,5-TCP</td>
<td>2,4,5-trichlorophenol</td>
</tr>
<tr>
<td>2,4-D</td>
<td>2,4-dichlorophenoxyacetic acid</td>
</tr>
<tr>
<td>95% CI</td>
<td>Confidence Interval, the interval of numerical values within which one can be 95% confident the population value being estimated lies</td>
</tr>
<tr>
<td>Agent Orange</td>
<td>Herbicide mixture of 2,4,5-T and 2,4-D (approximately 1:1) used in the Vietnam conflict for defoliation purposes</td>
</tr>
<tr>
<td>APB</td>
<td>Agricultural Protection Board</td>
</tr>
<tr>
<td>ATSDR</td>
<td>The United States Department of Health and Human Services – Agency for Toxic Substances and Disease Registry (Toxicological Profile for Chlorinated Dibenzo-p-Dioxins 1998)</td>
</tr>
<tr>
<td>bw</td>
<td>Body weight</td>
</tr>
<tr>
<td>Case reports, case histories or case series</td>
<td>Descriptive studies that usually lack conclusive evidence. They generally arise from a clinical occurrence of a disease or illness and a suspicion that the concurrence of exposure and occurrence of the disease or illness may be related.</td>
</tr>
<tr>
<td>Case Studies</td>
<td>Case histories, case series and case reports summarised in this report</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>Epidemiological studies that compare groups of people with and without a specific disease in relation to their individual retrospective exposures. Case-control studies provide an estimate of relative risk as the measure of association (e.g. studies of leukaemia in a cohort).</td>
</tr>
<tr>
<td>Cohort studies or follow-up studies</td>
<td>Epidemiological studies measuring individual exposures and determine disease or illness in a study population and follow up these individuals prospectively. Cohort studies provide an estimate of relative risk as the measure of association (e.g. Ranch Hand studies, agricultural workers).</td>
</tr>
<tr>
<td>Correlation or environmental studies</td>
<td>Epidemiological studies investigating populations (e.g. Seveso) and the measure of disease is related to a measure of exposure of the population to the chemical of concern. Individual exposure is unknown or not documented, hence a causal relationship is often difficult to infer.</td>
</tr>
<tr>
<td>Cross-sectional studies</td>
<td>Epidemiological studies that measure absence or presence of disease and exposure at one particular time. Also called prevalence studies.</td>
</tr>
<tr>
<td>Dioxin</td>
<td>Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans</td>
</tr>
<tr>
<td>EDC</td>
<td>Endocrine Disrupting Chemicals</td>
</tr>
<tr>
<td>EMP</td>
<td>Expert Medical Panel</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>Key Review</td>
<td>Authoritative reviews on health effects from exposure to phenoxy herbicides and/or dioxins, including NAS, IARC, US EPA, ATSDR and WHO/IPCS</td>
</tr>
<tr>
<td>Literature</td>
<td>Literature published since 2002 and reporting on human health effects from exposure to 2,4,5-T, 2,4-D and dioxins</td>
</tr>
<tr>
<td>Longitudinal studies</td>
<td>Epidemiological studies that measure absence or presence of disease and exposure of an individual or group of individuals over a period of time</td>
</tr>
<tr>
<td>MCPA</td>
<td>2-methyl-4-chlorophenoxyacetic acid</td>
</tr>
<tr>
<td>NAS</td>
<td>The National Academy of Science (Veterans and Agent Orange Update 2002)</td>
</tr>
<tr>
<td>ng</td>
<td>Nanogram (1×10⁻⁹ gram)</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio, a statistical technique used in case-control (Trohoc) studies to determine the risk of exposure to a factor on development of a certain characteristic or disease state. OR is an estimation of RR. Estimation of the magnitude or strength of the association or relationship observed in the study.</td>
</tr>
<tr>
<td>PCDD</td>
<td>Polychlorinated dibenzo-p-dioxins</td>
</tr>
<tr>
<td>PCDF</td>
<td>Polychlorinated dibenzofurans</td>
</tr>
<tr>
<td>pg</td>
<td>Picogram (1×10⁻¹² gram)</td>
</tr>
<tr>
<td>ppb</td>
<td>Parts per billion (e.g. pg/g (picogram per gram))</td>
</tr>
<tr>
<td>ppt</td>
<td>Parts per trillion (e.g. pg/g (picogram per gram))</td>
</tr>
<tr>
<td>Ranch Hand</td>
<td>Vietnam Veterans that were involved in Operation Ranch Hand (spraying of phenoxy herbicides)</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk, a statistical technique used in follow-up (Cohort) studies to determine the risk associated with exposure to a certain factor on disease state development. RR estimates how many times greater the risk of disease development is in patients exposed to a certain factor compared to those who are not. Estimation of the magnitude or strength of the association or relationship observed in the study. If the CI surrounding the RR contains 1, then it is not statistically significant.</td>
</tr>
<tr>
<td>Serum TCDD concentration</td>
<td>2,3,7,8-TCDD concentration measured in blood serum; all concentrations are given on a lipid basis unless noted otherwise</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardised mortality (morbidity) ratio, The ratio of the number of events observed in the study group or population to the number that would be expected if the study population had the same specific rates as the standard population, multiplied by 100.</td>
</tr>
<tr>
<td>TCDD</td>
<td>Tetrachlorodibenzodioxin, used in this review to refer to 2,3,7,8-tetrachlorodibenzodioxin</td>
</tr>
</tbody>
</table>
TEF  Toxic Equivalency factor (WHO) – toxicity of a compound relative to that of 2,3,7,8-TCDD (Van den Berg et al., 1998)

TEQ  Toxic Equivalency defined as the concentration of a compound multiplied by its toxic equivalency factor (TEF) (Van den Berg et al., 1998)

US EPA The United States Environment Protection Agency (Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds 2000)

WA Western Australia

BACKGROUND

1 INTRODUCTION

Weed eradication programs undertaken by the Agricultural Protection Board (APB) involved the use of 2,4-D and 2,4,5-T in the Kimberley region of Western Australia. People involved in the spraying during the 1970s and 1980s have reported suffering from ill health as a result of exposure to the herbicides.

In October 2001, the Minister for Agriculture commissioned an investigation into the concerns of APB workers employed during 1975 and 1985 under the weed eradication program in the Kimberley. This investigation identified 321 former APB workers and 13 other individuals with alleged exposure to the chemicals (Harper, 2002). Of the 90 participants, 60 were of Australian Indigenous heritage. Demographics, self-reported health concerns, work conditions and health effects were recorded. Age of participants at the time of the interview ranged from 29 to 65, employment with the APB ranged from one calendar year (47%) up to 4-8 years (13%). With respect to exposure, the majority (85%) reported exposure during 3-6 months per year on a daily basis (74%). The interviews indicated that personal protective clothing was rarely worn amongst sprayers and the majority of workers believed the spray to be mildly toxic, harmless or had no understanding of its toxicity. A range of past and current symptoms and health problems were reported which included the nervous system, skin, constitutional, gastrointestinal, musculoskeletal, reproductive, respiratory, psychological, urogenital, cardiovascular, endocrine, cancer and immunological (Harper, 2002). Mortality amongst APB workers was investigated and preliminary results indicate 26 confirmed deaths with malignancy representing the most frequent cause (34%) (Harper, 2002).

Based on this investigation, (Harper, 2002) concluded that ill health of 13 and 14 former spray workers was probably and possibly associated with exposure to the herbicides, respectively. A set of recommendations were provided in the report, seven of which were predicated on a causal association between exposure to the herbicides and illness. These were referred to an expert medical panel (EMP) for evaluation and advice. This review was commissioned by the EMP for the Department of Health, Western Australia to provide information on the scientific evidence of associations between exposure to the herbicides 2,4,5-T and 2,4-D as well as the co-contaminant 2,3,7,8-TCDD and adverse health effects, including signs and symptoms of disease, diagnosed disease or death from any cause.

2 GENERAL TOXICOLOGY

In general, the phenoxy herbicides 2,4,5-T and 2,4-D are not considered particularly toxic since relatively high concentrations are required to observe health effects. Chlorophenoxy herbicides as a group have been classified in Group 2B by IARC, i.e. limited evidence for carcinogenicity in humans and less than sufficient evidence for carcinogenicity in experimental animals (IARC, 1987).

2,4-dichlorophenoxyacetic acid (2,4-D) is a systemic herbicide used in a wide variety of applications. The World Health Organization has classified 2,4-D as “moderately hazardous” (WHO, 1996). Tissue uptake of 2,4-D is considered poor and a rapid metabolism could partially explain its low toxicity. At high doses administered to laboratory animals, 2,4-D has been associated with effects such as behavioural effects, muscle weakness and incoordination, neurotoxicity, alterations in brain development and thyroid hormone imbalances (NAS, 2002). 2,4-D has been found to have effects on some hormones, cellular components involved in the development and functioning of brain cells and some enzymes and transporters, calcium and energy metabolism. The relationship of any of these effects to human disease outcomes is unknown (NAS, 2002).

2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was introduced in the 1960s for use as a herbicide (IARC, 1997). The main intermediate in the production of 2,4,5-T is 2,4,5-trichlorophenol (TCP). Depending on temperature control and purification efficiency, 2,4,5-T is contaminated with 2,3,7,8-TCDD at a wide range of concentrations (generally in the low ppm to high ppt range, with more recently produced batches typically contaminated to the lower end of the spectrum). Similar to 2,4-D, the limited data available suggests 2,4,5-T to be relatively non-toxic. 2,4,5-T is absorbed after oral exposure, however, dermal absorption is considerably slower. Animal laboratory studies have indicated fetotoxicity, retarding growth, cleft palate and weak genotoxicity in some animals at high concentrations. However, these results are not consistent amongst other animal species. 2,4,5-T has been found to alter cellular metabolism, affect cholinergic transmission and the tyrosine kinase receptor, and disrupt apoptosis. The relevance of these effects to humans is unknown (NAS, 2002).

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two groups of persistent organic pollutants, comprising a total of 210 compounds, and are often collectively referred to as “dioxins”. In the contemporary environment, dioxins are ubiquitously distributed and virtually all organisms are exposed to some “background” level of dioxins. PCDD/Fs can be formed by numerous processes including the production of synthetic chemicals, thermal, photochemical and biochemical processes. Due to their high acute toxicity in animals, their carcinogenic potency and range of health effects that have been reported from animal studies, dioxins (PCDD/Fs) are perhaps the most studied chemicals to which humans are exposed. Among this class, the vast majority of the published literature focuses on 2,3,7,8-tetrachlorodibenzodioxin (TCDD). 2,3,7,8-TCDD is classified as a Group 1 carcinogen, i.e. there is limited evidence for carcinogenicity in humans but sufficient evidence for carcinogenicity in experimental animals, and strong evidence in exposed humans that 2,3,7,8-TCDD acts through a relevant mechanism of carcinogenicity (IARC, 1997). Dioxins are hydrophobic, lipophilic compounds and are absorbed well into the body. 2,3,7,8-TCDD mean half-life estimates in humans are approximately 7 years, however,
a wide range of half-lives have been reported from different individuals and different exposure doses. In addition to carcinogenic effects, numerous non-cancer effects have been observed in various animals after exposure to 2,3,7,8-TCDD, such as weight loss (wasting syndrome) and liver necrosis at high doses. The most sensitive endpoint of 2,3,7,8-TCDD exposure in animals is the immune system, however, immune system effects vary among and within species. In animals, 2,3,7,8-TCDD has been shown to affect numerous body systems, including the endocrine system and the nervous system, result in reproductive and developmental effects and effects on the cardiovascular system. Current scientific evidence indicates that most effects of 2,3,7,8-TCDD are a result of binding to the aryl hydrocarbon receptor (AhR), a protein that regulates gene expression. Since the AhR operates similar in humans compared to animals, adverse health effects in humans are generally biologically plausible. However, considerable differences in sensitivity to 2,3,7,8-TCDD are present between and among animal species and substantial uncertainties remain with respect to application of experimental results to humans.

3 PREVIOUSLY EXPOSED POPULATION GROUPS

This review focuses on epidemiological studies, investigating adverse health effects in individuals or groups of individuals that have been exposed to the phenoxy herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. The evaluation of associations between a particular adverse health endpoint and exposure to these compounds is often complicated by numerous confounding factors of the disease such as dietary habits, smoking, alcohol consumption, obesity etc. An additional difficulty in studies on exposure to dioxins is that these compounds occur ubiquitously in the environment. Hence control groups typically carry background body burdens of dioxins and other dioxin-like compounds (Remillard and Bunce, 2002c). Another important uncertainty in epidemiological investigations on associations between health outcomes and dioxin or other chemical exposure is the frequent lack of information on the individual exposure dose. In the majority of studies, investigations take place years after the last exposure has occurred. Hence, the serum lipid dioxin levels at time of exposure have to be extrapolated using the current serum concentrations. Post-exposure ranking of high-medium-low exposed cohorts based on such retrospective estimates may not necessarily reflect the situation at time of exposure, due to the individual variability of pharmacokinetic determinants such as half-life (Remillard and Bunce, 2002c).

The key exposure groups studied in epidemiological investigations and referred to in this review can be categorised into a) occupational exposure (e.g. herbicide applicators, chemical production workers), b) Environmental exposure (e.g. residents of contaminated areas and background exposure of the general population) and c) exposure during military service in Vietnam (e.g. veterans of the Operation Ranch Hand). In most studies, a particular exposure group was investigated independently or subsequently by several researchers. A wide range of exposure assessments was used among these studies, the main ones including job history (e.g. spraying of phenoxy herbicides, self-reported exposure or personnel records) and the presence of absence of chloracne. Both of these methods are imprecise and are subject to errors of the classification made, hence bias and chance may have been introduced. Internal serum TCDD analysis (and back extrapolation to the time of exposure) provides a better surrogate for exposure and dose, however, the majority of studies are lacking this information due to the relatively high costs involved in the analysis. Hence, some studies use a combination of the different exposure surrogates. The following provides an overview on the major studies that have investigated these exposure groups and which are referred to in this review. An overview on the internal serum TCDD concentrations assessed in these exposure groups is provided.

Herbicide Applicators

A number of studies have been carried out to determine adverse health effects in farmers, commercial pesticide applicators and other non-industrially exposed individuals involved in the spraying of chemicals contaminated with dioxins. The majority of these studies include individuals exposed to 2,4-D and/or 2,4,5-T, contaminated with 2,3,7,8-TCDD, however, detailed exposure information is often not available, and most applicators sprayed herbicides for a relatively short period of time. The few data available suggest that exposure to TCDD in such cohorts overall was likely to be considerably lower compared to production worker cohorts (IARC, 1997). Back-extrapolated serum TCDD levels in commercial 2,4,5-T applicators from New Zealand for example, indicated a contamination of approximately 300 ppt (lipid) at time of exposure (Smith et al. 1992a). Serum TCDD levels from Australian 2,4,5-T applicators who were spraying during 1965-1974 were estimated at 13-329 ppt at the time of exposure, whereas applicators spraying after 1974 were estimated to have had a serum TCD concentration of 2-19 ppt at time of exposure (Johnson et al., 1992a).

Chemical Production Workers

Adverse health effects in workers at plants which produced chemicals (mainly TCP and/or 2,4,5-T) contaminated with 2,3,7,8-TCDD have been studied by numerous researchers. The most extensive study on production workers exposed to these chemicals has been carried out by the U.S. National Institute for Occupational Safety and Health (NIOSH). The NIOSH cohorts included 5000 male workers that were likely to have been exposed to the chemicals from 12 US production plants (e.g. Monsanto-Nitro, West Virginia; Dow, Michigan), identified by personnel records from the plants or previous studies. Serum TCDD levels were determined from a subset of these workers and follow-up investigations were undertaken (by several investigators). Serum TCDD concentrations, extrapolated to the time of exposure, indicated an average concentration of 2000 ppt lipid (maximum 32,000 ppt lipid) (Fingerhut et al., 1991a), summarised in IARC (IARC, 1997)). The United States referent rates were used for comparison purposes.

Another production worker cohort studied includes 247 employees and clean-up workers (4 women) at the BASF TCP production plant in Germany (accident). Average serum TCDD levels extrapolated to time of exposure were approximately 400 ppt lipid (IARC), ranging from 1119 to 148 ppt lipid in workers with and without chloracne (Zober et al. 1994). Other production plants where herbicides,
A large-scale study involving more than 18000 production workers and herbicide sprayers (2,4,5-T, 2,4-D and MCPA) from 20 cohorts and 10 countries was carried out by IARC (Kogevinas et al., 1997; Saracci et al., 1991). Exposure was estimated from personnel records, work history and questionnaires and exposure to 2,3,7,8-TCDD was presumed from personnel records, work history and questionnaires and exposure to 2,3,7,8-TCDD was presumed for workers involved in the production or spraying of TCP, 2,4,5-T and related products and aggregated into different exposure groups.

### 3.1 Environmentally Exposed Groups

#### Accidental Exposure

Residents of Seveso in Italy were contaminated with 2,3,7,8-TCDD as a result of a TCP production reactor accident in 1976. The area affected by the chemical dispersal was divided into Zones A (TCDD ≤ 50 µg/m³), B and R (TCDD ≤ 5 µg/m³) depending on TCDD contamination in soil. All inhabitants from these zones were considered exposed. Measured serum TCDD levels ranged from 828 to 56000 ppt in Zone A in the year of exposure. Back-extrapolated serum TCDD levels to time of exposure (measured 16 years after the accident) were 334 and 111 in Zones A and B, respectively. Studies on health effects in Seveso inhabitants are carried out in regular intervals to the present day. Inhabitants of Zone A numbered approximately 750, Zone B 5000 and Zone R 30000 people.

Other accidentally exposed groups to environmental contamination with 2,4,5-T (and by-products of hexachlorophene) include residents of Missouri where contaminated waste oils were sprayed on various sites around the state for dust control. Residents in Taiwan and Japan were exposed to PCBs and PCDF in contaminated rice oil (referred to as Yusho and Yu-Cheng episodes, respectively). Even though rice oil did not contain 2,3,7,8-TCDD, the TCDD-like congeners are considered comparable in their mechanism of action to 2,3,7,8-TCDD. Median TEQ concentrations of rice oil samples were approximately 0.98 ng/kg (Masuda, 1996), summarised in (Päpke, 1998). Approximately 2000 people consumed the contaminated rice oil over a period of one year and TEQ concentrations in human tissue were 2230.2 ppt (analysed 1977 in fat), 184.6 ppt (analysed 1990 in blood), summarised in (Päpke, 1998). Similarly high concentrations were found in Yu-Cheng patients.

#### Background exposure

The ubiquitous occurrence of PCDD/Fs in the contemporary environment results in the exposure of virtually all organisms to these compounds. Due to their lipophilic, persistent nature, and their potential to biomagnify through the food chain, PCDD/Fs have been detected in human tissues worldwide. Typically, more than 90% of the human PCDD/F body burden are accumulated via food (Fuerst et al., 1992; U.S. EPA, 2000a). The term “general population” refers to people who are exposed to background levels of PCDD/Fs (i.e. levels that occur in an area without known point sources). With the elimination of localised high-risk groups, evaluation of background levels in the general population serves as a baseline for exposure and tissue concentrations and assists in identifying risks to humans with respect to the uptake of dioxins from occupational, accidental or environmental contamination.

U.S. estimates of the daily dioxin intake of the general population are in the range of 0.3 to 3.0 pg TEQ/kg body weight for adults (Schechter and Olson, 1997). Similar values have been reported from Canada, Germany, England and the Netherlands. This background exposure leads to average PCDD/F tissue concentrations of approximately 20-40 pg TEQ/g lipid. For example, the weighted mean PCDD/F concentrations in human blood from North America is 32.8 pg TEQ/g lipid, from Europe and Japan 42.9 pg TEQ/g lipid; 2,3,7,8-TCDD concentrations account for approximately 17% and 8% of the total TEQ blood concentrations, respectively (weighted mean = 5.5 and 3.4 pg/g lipid, respectively) (U.S. EPA, 2000a). Approximately 10% of the general population are estimated to have greater than three times the average background body burdens (U.S. EPA, 2000a).

PCDD/F concentrations in blood serum from the general population in New Zealand are towards the lower end compared to other industrialised countries, with a weighted mean of 12.4 pg TEQ/g lipid (range 5.05 to 26.7). 2,3,7,8-TCDD concentrations range from <1 to 7.0 pg/g lipid with a weighted mean of 2.0 in the general population of New Zealand (NZ MoE, 2001) (see Figure 1). Due to the potential of PCDD/Fs to accumulate in tissues over time, PCDD/F concentrations within the general population typically increase with increasing age group.

### 3.2 Vietnam Veterans

#### Veterans of Operation Ranch Hand

During the Vietnam conflict, a number of herbicide mixtures were sprayed to defoliate forests (inland and coastal) and destroy crops. A total of 49,268,937 litres of Agent Orange was sprayed in Vietnam from 1961 to February 1971 (Stellman et al., 2003). Applicators generally sprayed for only relatively short periods. Agent Orange, a mixture of 2,4,5-T and 2,4-D (1:1) was sprayed during 1965 to 1971 by members of the Air Force Operation Ranch Hand and the Army Chemical Corps. The majority of Agent Orange was applied using fixed winged aircraft, and only approximately 10-12% was sprayed by Army Chemical Corps on the ground using trucks and backpack spray units (or from helicopters). These cohorts, including individuals involved in aerial spraying and ground troops, have shown elevated serum TCDD levels with a median serum TCDD concentration of 12.4 ppt (n=888) in 1987 compared to 4.2 ppt in the comparison group (n=856). The highest serum TCDD levels, analysed in 1987, were found in non-flying personnel (median 23.6 ppt) (Wolfe et al. 1990). In 1988, serum TCDD concentrations from 10 men heavily exposed during the Vietnam War were reported by (Nygren et al. 1988) at 46.2 ppt (maximum 213 ppt).
A number of large-scale studies on health effects in Vietnam Veterans involved in the application and/or handling of Agent Orange were carried out over the years, including numerous follow-up investigations. The most extensive epidemiological studies were conducted by the United States Air Force, investigating effects in Air Force personnel who were involved in aerial spraying of the Operation Ranch Hand during 1962 and 1971 compared to Air Force personnel who served in south-east Asia during the same period. Cross-sectional medical studies were carried out at regular intervals from 1982, including extensive medical evaluations. Serum TCDD analysis indicate that amongst Vietnam veterans, members of the Operation Ranch Hand had significant levels of exposure to dioxins above background.

**Other Vietnam Veterans**

The Centers for Disease Control Vietnam Experience Study (CDC, 1988b) was designed as a multidimensional assessment of the health of Vietnam veterans. The study population was a random sample of men who enlisted in the United States Army from 1965 to 1971, whose military occupation was other than duty soldier and who enlisted for a single term of a minimum of 16 weeks active duty. Serum TCDD was analysed in 646 ground combat troop veterans (mean 4.2 ppt). No correlation was observed between serum TCDD and service in areas ranked by level of presumed intensity of spraying or between serum TCDD and self-reported exposure to Agent Orange. However, this study did not include Vietnam veterans who had served in Operation Ranch Hand, nor members of the Army Chemical Corps which also sprayed Agent Orange.

**Australian Vietnam Veterans**

Health effects in Australian Vietnam veterans have been investigated in a number of studies. Amongst these, the Australian Department of Veteran’s Affairs conducted a mortality study of more than 59000 Australian male and 484 female veterans (based on personnel data and vital statistics) compared to the Health Insurance Medicare database (Crane et al. 1997a). Self-reported health status of Australian Vietnam veterans compared to the Australian population were investigated by O’Toole et al. 1996a-c.

### Table 1. Overview on some epidemiological studies investigating human adverse health effects from exposure to the herbicides 2,4,5-T and 2,4-D and dioxins.

Adopted and changed from: (IARC, 1997).

<table>
<thead>
<tr>
<th>Reference p. 67 IARC</th>
<th>Cohort</th>
<th>Date(s) or duration of exposure</th>
<th>Date of sampling</th>
<th>No. of workers</th>
<th>Mean measured 2,3,7,8-TCDD blood concentration ppt (lipid)</th>
<th>Back-extrapolated to exposure date ppt (lipid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ott et al., 1993</td>
<td>BASF (Germany) production workers</td>
<td>1953 (accident)</td>
<td>1988-92</td>
<td>1.38</td>
<td>15.4 (geometric. mean)</td>
<td>~400 (geom. mean)</td>
</tr>
<tr>
<td>(Flesch-Janys et al., 1996; Flesch-Janys et al., 1995; Kogevinas et al., 1997)</td>
<td>Production worker, Boehringer-Ingelheim, Germany</td>
<td>13.1 years; mean of 5.4 years after exposure;</td>
<td>1985-94</td>
<td>48</td>
<td>84.1 (med.)</td>
<td>141 (3-2252) for total cohort</td>
</tr>
<tr>
<td>Mean of 11.0 years after employment</td>
<td>48</td>
<td>48.9 (med.)</td>
<td></td>
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<tr>
<td>(Fingerhut et al., 1991a; Fingerhut et al., 1991b)</td>
<td>Production worker, USA (NIOSH)</td>
<td>1987 (15-37 years after employment),</td>
<td>253 (from 2 of 12 plants)</td>
<td>233</td>
<td>~2000 (mean)</td>
<td>32000 (max.)</td>
</tr>
<tr>
<td>&gt;1 year exposed</td>
<td>119</td>
<td>418</td>
<td></td>
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<tr>
<td>(Hooiveld et al., 1996a; Hooiveld et al., 1996b)</td>
<td>Production worker, Netherlands</td>
<td>1955-1985 (factory A)</td>
<td>1993</td>
<td>48</td>
<td>22.9 (production geom.)</td>
<td>286 (geom.) (17-1160)</td>
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<td>87.2 (1963 accident, geom.)</td>
<td>1434 (geom.) (301-3683)</td>
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<tr>
<td><strong>Herbicide Applicators</strong></td>
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<tr>
<td>(Smith et al., 1992)</td>
<td>2,4,5-T sprayer, New Zealand</td>
<td>1953-88 (mean duration: 16 years)</td>
<td>1988</td>
<td>9</td>
<td>53.3</td>
<td>~300 (in 1970)</td>
</tr>
<tr>
<td>(Johnson et al., 1992b)</td>
<td>2,4,5-T sprayer, Victoria, Australia</td>
<td>Before 1965: 3-&lt;18; 1965-74: 2-34</td>
<td>13-329</td>
<td></td>
<td></td>
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<tr>
<td>Reference</td>
<td>Cohort</td>
<td>Date(s) or duration of exposure</td>
<td>Date of sampling</td>
<td>No. of workers</td>
<td>Mean measured 2,3,7,8-TCDD blood concentration ppt (lipid)</td>
<td>Back-extrapolated to exposure date ppt (lipid)</td>
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<tr>
<td>p. 67 IARC</td>
<td>Australia</td>
<td>After 1974: 2-&lt;17</td>
<td>2-19</td>
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<td><strong>Vietnam Veterans</strong></td>
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<tr>
<td>(Nygren et al., 1988)</td>
<td>US Vietnam Veterans (heavily exposed)</td>
<td>Late 1960s</td>
<td>1984-85</td>
<td>9</td>
<td>46.3 (arith.) ~180</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td>15.7 (geom.) ~60</td>
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<tr>
<td>(Wolfe et al., 1990a)</td>
<td>U.S. Ranch Hand veterans</td>
<td>Late 1960s</td>
<td>1987</td>
<td>888</td>
<td>12.4 (med.) ~50</td>
<td></td>
</tr>
<tr>
<td>(CDC, 1988b)</td>
<td>US Vietnam Veterans Ground combat troops</td>
<td>Late 1960s</td>
<td>1987</td>
<td>646</td>
<td>4.2 ± 2.3</td>
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<td><strong>Seveso residents</strong></td>
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<tr>
<td>(Mocarelli et al., 1990)</td>
<td>Population, Seveso accident, Italy</td>
<td>1976</td>
<td>1976</td>
<td>19 (Zone A)</td>
<td>828-56000</td>
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<tr>
<td>(Landi et al., 1996)</td>
<td>Population, Seveso accident, Italy</td>
<td>1976</td>
<td>1992-93</td>
<td>6 (Zone A)</td>
<td>61.5 (mean), 71.5 (median) 333.8 388.7</td>
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<td>82 (Zone B) 16.8 (mean), 12.5 (median) 111.4 77.6</td>
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<td>52 (outside) 5.3 (mean), 5.5 (median)</td>
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<tr>
<td><strong>Background exposure of the general population</strong></td>
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<tr>
<td>(NZ MoE, 2001)</td>
<td>New Zealand</td>
<td>Lifetime background exposure</td>
<td>550 (age 35-49)</td>
<td></td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>
The objective of this review is to identify, summarise and evaluate the published scientific literature on the evidence of associations between human exposure to the phenoxy herbicides 2,4,5-T and 2,4-D as well as dioxins (focusing on 2,3,7,8-TCDD) and adverse health effects. Endpoints of interest include acute and chronic signs and symptoms of disease and death. The purpose of this review is to provide a medical expert panel (EMP) with an overview on the current scientific evidence on associations between these chemicals and health effects in humans. The EMP advises the Western Australian Government on its response to recommendations made on the basis of a survey regarding concerns of Agricultural Protection Board (APB) workers, who have been involved in herbicide spraying in the Kimberley region between 1975 and 1985.

In undertaking this task, the following approaches have been designed to limit the scope of the review within the required time frame. A number of authorities and international agencies have provided extensive reviews and evaluations on the associations between adverse human health effects and exposure to the phenoxy herbicides 2,4,5-T and 2,4-D and/or dioxins. The present review provides a synthesis of these Key Reviews to ensure consideration of the total scientific evidence and to limit the extensive number of individual publications covering the investigation of human health effects from exposure to the compounds of interest. For explicit and detailed information of original studies, the key works can be referenced. Updates to these Key Reviews were identified and evaluated from the scientific literature using defined criteria. Literature Updates were assessed against the total evidence accumulated in the scientific literature (as synthesised by the Key Reviews) and an overall evaluation on the strength of association between exposure to the chemicals and specific adverse health effects was made. Health outcomes were divided within the review consortium and each individual provided a synthesis of Key Reviews, reviewed the relevant Literature Updates and assessed the strength of evidence of association between exposure and the particular health outcome reviewed. Regular meetings were held to ensure consistency amongst review sections and to provide the forum for discussion on evaluations. In addition, case reports and case series describing patterns of signs and symptoms of disease were summarised independently of the literature update. These were selected using a separate set of criteria and summarised in this review. Hence, the specific aims of this review were defined to:

- Provide a synthesis of existing authoritative reviews investigating adverse health effects in humans from exposure to the phenoxy herbicides of interest and dioxins.
- Identify and critically evaluate new literature, published since the last update of the Key Review (i.e. 2002), investigating human health effects from exposure to 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D.
- Provide an evaluation on the overall strength of evidence of the association of specific health endpoints and exposure to the compounds of interest, including, where possible, an indication on what type and extent of exposure this evidence is based on.
- Identify and summarise literature describing patterns of signs and symptoms of disease, illness and death in humans from exposure to the phenoxy herbicides and/or dioxins.

Considering the specific APB cohort details (i.e. majority of adult male employees), health outcomes specific to children and women were not considered in detail. Evaluation outcomes from the most recent Key Review on these endpoints were summarised separately. Selection criteria and methodology are fully documented in this report.
1 FRAMEWORK AND WORKING PROCEDURE

Based on the objective and aims of this review, the framework of this report was designed to allow an overview on the various adverse health effects that have been associated with human exposure to the phenoxy herbicides 2,4-D and 2,4,5-T, and 2,3,7,8-TCDD.

The overall framework of this review was discussed at an inaugural meeting with the EMP and was structured into different sets of diseases or conditions that have been associated with human exposure to the chemicals of interest. The individual health endpoints were divided among the working group individuals for review. Each individual working group member provided an overview on the disease or condition, a synthesis of each Key Reviews and a summary and evaluation of the Literature Updates included, as well as an overall conclusion regarding the total accumulated strength of evidence of the association regarding the endpoint under investigation. The working group met at weekly intervals to discuss the outcomes.

Normative data was sourced from the Australian Institute of Health and Welfare or the Australian Bureau of Statistics. If no data was available from these authorities for a particular disease or condition, a search on the scientific literature was performed to identify national surveys or reports.

A separate section was provided for case histories and case reports describing patterns of symptoms. Since such descriptive studies mostly lack ascertainment of the association between symptoms and exposure, an evaluation on the strength of evidence of such studies was not undertaken.

All studies included in this review are summarised in the section “Literature Update Summaries” describing in detail the study design, methodology used, findings and evaluation outcomes. Exposure doses and type of exposure, if available from the studies were reported. The full publications are provided in Appendix 2. A short summary of studies excluded, as well as the rationale for exclusion, is provided in Appendix 3. Methodology used to identify, select and evaluate studies is fully documented below.

2 SYNTHESIS OF KEY REVIEWS

This review provides a summary of five authoritative reviews (Key Reviews) on studies investigating human health effects and exposure to dioxins, 2,4,5-T and 2,4-D. Conclusions drawn by these reviews regarding the association between a particular health endpoint and exposure to the compounds investigated are summarised for each Key Review. If a formal evaluation was undertaken, the outcomes are presented. In providing this information, wording was kept as close to the original review as possible.

Where reported by the Key Reviews it was noted whether the conclusion and evaluation was drawn from studies investigating groups exposed to relatively high or low concentrations. Since most of the human evidence is based on the total findings of a variety of exposure groups (i.e. a wide range of exposure concentrations) and the majority of studies lack internal dose assessments, conclusions based on one particular exposure group where the extent of exposure was known are rare.

Similarly, where reported by the Key Reviews it was noted whether the conclusion and evaluation was drawn from studies investigating groups exposed to the herbicides 2,4,5-T and 2,4-D or 2,3,7,8-TCDD, or mixtures thereof. Since exposure to 2,4,5-T mostly and exposure to 2,4-D potentially involved some exposure to the co-contaminant 2,3,7,8-TCDD, and since most of the human evidence is based on groups exposed to a mixture of these, the distinction of whether a particular health effect observed was due to one or a combination of these compounds is mostly not possible.

In an attempt to provide more information on what type and extent of exposure the conclusion and evaluation of the Key Review may have been based, the studies considered by each Key Review were reported, categorised into occupationally exposed chemical workers (i.e. mostly relatively high exposure to herbicides including 2,4,5-T, 2,4-D and 2,3,7,8-TCDD, and potentially other chemicals), occupationally exposed herbicide sprayers (i.e. potentially high exposure to various herbicides including 2,4,5-T and 2,4-D and 2,3,7,8-TCDD), residents of Seveso (ranging from relatively low to high exposure to 2,4,5-T and 2,3,7,8-TCDD), other residents of contaminated areas (i.e. potentially high exposure but often ranging from low to high exposure to various compounds including dioxins and/or PCBs), background populations (i.e. mostly low exposure to dioxins and PCBs and other compounds), Vietnam veterans (i.e. mostly relatively low exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD) or Vietnam veterans of the Operation Ranch Hand (generally higher exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD compared to other Vietnam veterans). More detailed information on the type and extent of exposure and a description of these main cohorts are provided in the section “Background”.

The following provides an overview on the Key Review considered for this report:

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
“Monographs on the Evaluation of Carcinogenic Risk to Humans Volume 69 Polychlorinated Dibenzo-para-Dioxin and Polychlorinated Dibenzo-p-dioxins”. IARC examines relevant biological and epidemiological information in order to assess the strength of evidence on the carcinogenicity of dioxins in humans. Among epidemiological studies, cohort, case-control and correlation (i.e. ecological) studies as well as case-series and case-reports were considered. An overall evaluation of the evidence for carcinogenicity arising from human and experimental animal data is provided.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
“Toxicological Profile for Chlorinated Dibenzo-p-Dioxins”. ATSDR provides an overall perspective of the toxicology of PCDDs, including epidemiological studies. The epidemiological studies reviewed include those with study populations known to reside or work in environments with...
above-background levels of PCDDs and related compounds (accidental, occupational, residential exposure, including pesticide use)

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
“Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds”. US EPA reviews toxicological studies on adverse health effects, including mechanisms of action, pharmacokinetics and animal laboratory studies. Epidemiological studies on cancer and non-cancer effects among persons exposed to 2,3,7,8-TCDD and other PCDD/Fs are reviewed with emphasis placed on studies with exposures to 2,3,7,8-TCDD (mainly manufacture and use of 2,4,5-T, TCP, hexachlorophene, also 2,4-D). Studies investigating occupational (e.g. herbicide application, production workers), military (e.g. Vietnam veterans) and Environmental (e.g. Seveso) exposures have been included in the review and assessment. Only follow-up and case-control studies have been considered for cancer effects. In addition, case reports and other clinical observations were included in non-cancer effect assessments.

WORLD HEALTH ORGANIZATION 2002
“International Programme on Chemical Safety Global Assessment of the State-of-the-Science of Endocrine Disrupters”. WHO/IPCS provides an assessment of the current state-of-the-science relative to environmental endocrine disruption in humans, experimental studies, and wildlife species. The assessment focuses on peer-reviewed scientific literature that demonstrate or hypothesise associations between environmental exposure and adverse outcomes via mechanisms of endocrine disruption.

NATIONAL ACADEMY OF SCIENCES 2002
“Veterans and Agent Orange Update”. NAS summarises the strength of scientific evidence concerning the association between herbicide exposure during Vietnam service and a set of diseases or conditions suspected to be associated with such exposure. In addition to exposure of Vietnam veterans, other cohorts potentially exposed to 2,4,5-T, 2,4-D and dioxins were included in the review and evaluation (e.g. herbicide sprayers, production workers, Seveso residents). Case studies that were lacking a control or comparison group were generally not considered. Strength of evidence evaluation is based on the total accumulated evidence and biologically plausible mechanisms.

3 LITERATURE UPDATES
Additional studies, providing an update of the literature published since 2002 and not included in the most up to date Key Review i.e. (NAS, 2002) were identified using the search strategies outlined below.

3.1 DATABASES SEARCHED
Databases searched included health and medical sciences databases (MEDLINE, PREMEDLINE, EMBASE, ERIC, TOXNET), occupational health and safety databases (HSELINE, MHIDAS, RILOSH, NIOSHTIC) and environmental sciences databases (SCIENCE DIRECT, CAMBRIDGE SCIENTIFIC ABSTRACTS, SCIRUS, SCIFINDER).

3.2 SEARCH TERMS
Search terms included a combination of terms identifying the chemicals of interest (2,4,5-T, 2,4-D and dioxins) and a variety of health outcomes, as listed below:

Chemicals: CAS registry numbers for each compound, phenoxy herbicides, chlorophenoxyacetic acid, 2,4-D, 2,4,5-T, dioxin, TCDD, tetrachlorodibenzodioxin, furan.

Health outcomes: health, effects, sign, symptom, disease, dysfunction, disorder, death, chronic, acute, cancer, tumour, sarcoma, melanoma, lymphoma, myeloma, leukaemia, reproduction, birth defect, fertility, stillbirth, birth weight, pre-term birth, neurobehavioral, cognitive, neuropsychiatric, neuropathy, chloracne, porphyria, respiratory, diabetes, lipid disorder, gastrointestinal, liver toxicity, digestive, circulatory.

The searches were limited by year (since 2002). The results of all searches were imported into a reference database (ISI ResearchSoft EndNote Version 5.0). Duplicates were eliminated using the software function. Literature identified in this manner totalled 589 publications.

3.3 CRITERIA FOR CONSIDERING STUDIES
All peer-reviewed papers, reports, books and book chapters were considered. Conference abstracts/papers were considered providing they included Methodology, Results and Discussion. A total of 589 papers were identified using the above search strategies. To determine the relevance of papers for this review, all abstracts were read and assessed against a set of exclusion/inclusion criteria (Table 2). Where abstracts were not available from the database, the full publication was obtained unless the title was clearly indicative of non-relevance. The following criteria were used to select publications from the databases:
Table 2. Criteria for inclusion/exclusion of publications for Literature Updates

<table>
<thead>
<tr>
<th></th>
<th>Included studies</th>
<th>Excluded studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>Epidemiological studies, including case-control, cohort, pooled analysis, meta-analysis, cross-sectional and longitudinal studies</td>
<td>Reviews, experimental, theoretical and animal studies, correlation studies, case reports, case histories and case series</td>
</tr>
<tr>
<td><strong>Effects investigated</strong></td>
<td>Signs, symptoms of disease, including acute, chronic, death</td>
<td>Biochemical effects and effects specific to women and children</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>Exposure to substances known to contain 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD and dioxin-like compounds</td>
<td>Exposure to undefined or unidentified mixtures of harmful toxicants, where contamination with 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD and dioxin-like compounds is unknown</td>
</tr>
<tr>
<td><strong>Methods/outcomes</strong></td>
<td>All studies reporting some measure of effect</td>
<td>Studies not reporting measures of effects</td>
</tr>
<tr>
<td><strong>Year of publication</strong></td>
<td>2002 to present</td>
<td>Publications prior to 2002 and publications included in the Key Reviews</td>
</tr>
</tbody>
</table>

Based on the abstract, 534 publications could be excluded from the literature update database. Exclusion of these was mainly based on study type (i.e. no epidemiological investigation) and effects investigated (i.e. biochemical and specific to women and children). For the remaining potentially relevant 55 publications, a copy of the full publication was obtained for further, detailed evaluation of relevance. A total of 17 papers matched the inclusion criteria and were included in this review. A detailed summary and evaluation of these papers is provided in the section “Literature Updates”. The remaining 38 papers were excluded based on the remaining exclusion criteria (18 reviews, 1 commentary, 6 letters, 1 correlation study, 3 mixtures of undefined chemicals, 3 without measures of effect, 3 case series/reports and 1 was included in NAS review). A short summary of these 38 excluded papers, and a statement on the rationale for exclusion is provided in Appendix 3.

### 3.4 Evaluation of Literature Updates

All studies that met the inclusion criteria were assessed for the potential of bias, confounding and chance. With respect to bias, classification of exposure, disease and confounders as well as selection of study subjects (e.g. definition and validation of exposure, number of participants, selection of control groups) were examined for the potential of leading to stronger or weaker associations than in fact exist. With respect to confounders, studies were examined for addressing, and the approach to minimise, potential erroneous outcomes due to associations between the disease and other factor(s) that may influence its prevalence.

In evaluating the strength of evidence provided by a particular study, the following aspects of publications were considered:

- Study design: definition of study population, disease and exposure
- Methodology: controlling of confounders and other variables that can influence the outcomes (e.g. use of matched control groups, statistical adjustments for variables), number of subjects included, medical validation of disease, symptom or cause of death
- Reporting: clearance of presentation of methodology, study design, data on which conclusions are based, reporting of exposure estimates
- Outcomes: statistically evaluated measure of effect

Strong evidence for an association (or alternatively for no association) would hence be provided by a study that showed statistically significant outcomes (or alternatively non-significant outcomes), defined a large study population for which internal exposure was assessed and which was controlled for known confounders. Further, validation of the endpoint investigated was undertaken to rule out bias and chance, statistical tools used were appropriate, and the outcomes discussed were clearly presented.

In contrast, weak evidence for an association would be provided by any study that either showed statistically non-significant outcomes or borderline significance of the association and was limited by one or more of the above criteria. Alternatively, weak evidence would be provided with statistically significant results which were limited by the above criteria. A strong statistical significance (e.g. high odds ratios and narrow confidence intervals) would require more or more severe limiting criteria to explain the outcome.

### 4 Overall Evaluation of Strength of Evidence

After this assessment of individual literature updates, an evaluation was made concerning the overall strength of evidence of a causal link (or no causal link) between the chemicals 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD and the health endpoint investigated. For this, the total accumulated evidence was considered (i.e. studies reviewed by the Key Reviews and Literature Updates) and the following aspects were considered for causality:

- Strength of associations in all available studies
- Consistency of results among different studies
- Presence of dose-response and temporal relationships
- Biological plausibility

Based on these criteria for causality, an overall evaluation was undertaken for each specific endpoint investigated. The following classification was used to determine the overall strength of evidence:
**Established Causal Link**

By established causal link, we mean that, while not all doubt has been removed, there is good epidemiological and toxicological evidence that exposure to 2,3,7,8-TCDD, 2,4-D or 2,4,5-T results in significantly increased risks of developing the disease, cause of death or symptom. Further, the observed associations are unlikely to be due to chance, bias or confounding, and that the putative causal link is biologically plausible, is temporally correct and shows dose-response effects, or similar or analogous effects in experimental animals or in vitro models. It is similar to the NAS classification of sufficient evidence of an association, to IARC classification Group One and to the US EPA classification “proven”.

**Probable Causal Link**

By probable causal link, we mean that there is epidemiological and toxicological evidence that exposure to 2,3,7,8-TCDD, 2,4-D or 2,4,5-T results in significantly increased risk of developing that disease, cause of death or symptom, although chance, bias and confounding remain as alternative explanations for the observed association. The putative causal link it is biologically plausible, is temporally correct and similar or analogous effects in experimental animals or in vitro models. It is similar to the NAS of limited or suggestive evidence of an association, to IARC classification Group 2A and to the US EPA classification “probable”.

**Possible Causal Link**

By possible causal link, we mean that there is weak epidemiological and toxicological evidence that exposure to 2,3,7,8-TCDD, 2,4-D or 2,4,5-T results in significantly increased risk of developing that disease, cause of death or symptom, but chance, bias and confounding have not been controlled. The putative causal link it is biologically plausible, is temporally correct and similar or analogous effects in experimental animals or in vitro models. It is similar to the NAS of limited or suggestive evidence of an association, to IARC classification Group 2B and to the US EPA classification “possible”.

**Insufficient Evidence**

By insufficient evidence to make a classification, we mean that the available epidemiological and toxicological evidence is not sufficient to allow a classification to be made. This is similar to Group 3 of the IARC or Inadequate/Insufficient of the NAS system of classifying diseases.

**Evidence of No Causal Link**

By evidence of no causal link, we mean that, while not all doubt has been removed, there is epidemiological and toxicological evidence that exposure to 2,3,7,8-TCDD, 2,4-D or 2,4,5-T does not result in significantly increased risk of developing that disease, cause of death or symptom. Alternatively, the putative causal link is not biologically plausible, and that similar or analogous effect has not been observed in experimental animals or in vitro models. It is similar to the NAS of sufficient evidence of no association, to IARC classification Group Four and to the US EPA classification “not carcinogenic”.

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Table 3 provides an overview on the different classifications used by IARC, US EPA and NAS and to which of the present criteria they approximate:

<table>
<thead>
<tr>
<th>This review</th>
<th>IARC</th>
<th>US EPA</th>
<th>NAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established causal link</td>
<td>Group 1</td>
<td>Proven</td>
<td>Sufficient evidence</td>
</tr>
<tr>
<td>Probable causal link</td>
<td>Group 2A</td>
<td>Probable</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td>Possible causal link</td>
<td>Group 2B</td>
<td>Possible</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td>Insufficient causal link</td>
<td>Group 3</td>
<td>Further research required (inadequate)</td>
<td>Inadequate or Insufficient evidence</td>
</tr>
<tr>
<td>Evidence of no causal link</td>
<td>Group 4</td>
<td>Not carcinogenic</td>
<td>Sufficient evidence of no association</td>
</tr>
</tbody>
</table>

5 **Case Studies**

Case histories, case reports and case series reporting the patterns of disease, signs, symptoms and death observed after exposure to the phenoxy herbicides and/or dioxins were identified using the following strategies:

5.1 **Databases Searched**

Databases searched for all search terms included health and medical sciences databases (MEDLINE, PREMEDLINE, EMBASE, ERIC, TOXNET), occupational health and safety databases (HSELINE, MHIDAS, RILOSH, NIOSHTIC) and environmental sciences databases (SCIENCE DIRECT, CAMBRIDGE SCIENTIFIC ABSTRACTS).

5.2 **Search Terms**

A preliminary search using similar search terms as used for the Literature Updates (in combination with a set of signs and symptoms, rather than diagnosed diseases) identified mainly case reports describing the patterns of disease, signs and symptoms after poisoning incidences. A new search strategy was developed that allows the identification of case series and case histories describing patterns of disease, signs and symptoms after acute or long-term exposure to concentrations leading to chronic or transient acute disease, signs or symptoms. The main difficulty was to achieve a balance between the identification of the majority of such studies and the large number of studies returned by the databases. After several tests, using a variety of combinations of search terms, validated against known studies that have to be returned by the database, the combination of terms listed below were used. In addition, citations from included studies were scanned for potentially relevant papers and, if not identified by the search strategy, were included for consideration.
**Chemicals:** CAS registry numbers for each compound, phenoxy herbicides, chlorophenoxyacetic acid, 2,4-D, 2,4,5-T, dioxin, TCDD, tetrachlorodibenzo-dioxin, furan.

**Study group:** Seveso OR BASF OR Vietnam OR Ranch Hand OR occupational OR accidental OR applied OR applied OR applicator OR applicators OR application OR sprayed OR sprayer OR sprayers OR spraying OR cohort OR cohorts OR NIOSH OR farmer OR farmers OR farming OR agricultural OR agriculture OR forestry OR railroad OR employees OR employee OR worker OR workers OR manufacture OR manufacturer OR production

**Study design:** case report OR case reports OR case history OR case histories OR case study OR case studies OR case series OR population survey OR population surveys OR health survey OR health surveys OR health description OR health descriptions OR health evaluation OR health evaluations OR self-reported OR health outcome OR health outcomes OR medical survey OR medical surveys OR medical surveillance OR medical report OR medical reports OR medical history OR medical histories OR health status OR health complaint OR health complaints OR pattern of disease OR patterns of disease OR pattern of symptoms OR symptoms OR symptom

**Health outcomes:** Health effect OR health effects OR sign OR signs OR symptom OR symptoms OR disease OR diseases OR death OR deaths OR chronic OR acute OR ill OR illness OR mortality OR syndrome OR syndromes OR cognitive OR neuropsychiatric OR psychiatric OR neuropathy OR motor OR coordination OR skin OR disorder OR disorders OR dysfunction OR dysfunctions OR health complaint OR health complaints OR health condition OR Anxiety OR appetite OR weight OR weight loss OR behaviour OR behavioural OR consciousness OR chloride OR circulation OR confusion OR coordination OR cramp OR cramps OR depression OR dermatitis OR distressed OR dizzy OR dizziness OR drowsy OR drowsiness OR dyspnoea OR exhaustion OR health problems OR health problem OR fatigue OR sick OR sickness OR rash OR gastritis OR hepatitis OR hirsutism OR hostility OR indigestion OR insomnia OR irritable OR irritability OR irritation OR itching OR libido OR memory OR mental OR mood OR morale OR nausea OR numbness OR oedema OR pain OR paranoia OR personality OR phobia OR suicide OR violence OR weakness OR weight loss OR diarrhoea OR vomiting OR shortness of breath OR infertility OR blurred OR premature birth OR miscarriage OR impotence OR stiffness OR bleeding OR cough OR anxiety OR sweating OR anorexia OR asthma OR joint swelling OR foetal death OR sun sensitivity OR balance OR fainting OR infection OR seizures OR disorientation OR hair loss OR panic OR ulcer OR vision OR tingling OR immunological OR nervous OR constitutional OR gastrointestinal OR musculoskeletal OR reproductive OR respiratory OR circulatory OR psychological OR urogenital OR cardiovascular OR endocrine OR cancer OR tremor OR heart attack OR fear OR concentration OR headache OR neurotic OR encephalopathy OR acidosis OR intoxication.

The results of all searches were imported into a reference database (ISI ResearchSoft EndNote Version 5.0). Duplicates were eliminated using the software function. Literature identified in this manner totalled 796 publications.

### Table 4. Criteria for inclusion/exclusion of publications for Case Studies

<table>
<thead>
<tr>
<th></th>
<th>Included studies</th>
<th>Excluded studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study type</td>
<td>Descriptive studies including case reports, case histories, case series,</td>
<td>Experimental, theoretical and animal studies</td>
</tr>
<tr>
<td></td>
<td>population surveys, medical reports</td>
<td></td>
</tr>
<tr>
<td>Effects investigated</td>
<td>Patterns of signs and symptoms of disease, including acute, chronic, death</td>
<td>Biochemical effects, effects specific to women</td>
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<tr>
<td></td>
<td></td>
<td>and children and studies investigating one</td>
</tr>
<tr>
<td></td>
<td></td>
<td>particular disease or condition</td>
</tr>
<tr>
<td>Exposure</td>
<td>Exposure to compounds known to contain 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD</td>
<td>Exposure to mixtures that included other,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>undefined harmful toxicants</td>
</tr>
<tr>
<td>Methods/outcomes</td>
<td>Self-reported outcomes and medical histories, descriptions of signs, symptoms of</td>
<td>Studies that do not describe patterns of</td>
</tr>
<tr>
<td></td>
<td>disease</td>
<td>disease, signs or symptoms</td>
</tr>
<tr>
<td>Year of publication</td>
<td>1960 to present (depending on electronic database limitations)</td>
<td></td>
</tr>
</tbody>
</table>

Based on the abstract, 609 publications could be excluded from the case study database. Exclusion of these was mainly based on the study type (i.e. no health effects investigated) and effects investigated (i.e. investigation of one particular disease or condition). For the remaining potentially relevant 187 case histories, a copy of the full publication was obtained for further, detailed evaluation of relevance. A total of 47 papers matched the inclusion criteria and were included. A detailed summary and discussion of these studies is provided in the section “case studies”. The remaining 140 papers were excluded based on the above exclusion criteria.
LITERATURE UPDATE SUMMARY AND EVALUATION

18 papers matched the inclusion criteria defined for Literature Updates and were evaluated for this review. Of these, the majority (N=11) investigated exposure to 2,4,5-T and/or 2,4-D (including the co-contaminant 2,3,7,8-TCDD) and 7 papers investigated exposure to mixtures of PCDD/Fs and/or PCBs and were included due to the similar mechanism of action of these compounds compared to 2,3,7,8-TCDD. The majority of exposure groups studied in the Literature Updates (N=6 and N=6, respectively) included environmentally and occupationally exposed cohorts, 3 papers included military exposure during the Vietnam conflict. The study design of Literature Updates was dominated by cohort studies (N=13) investigating a variety of endpoints, including cancer (N=5), neurobehavioral disorders (N=5), circulatory disorders (N=4), diabetes (N=4), lipid and lipoprotein disorders (N=4), immunological disorders (N=3), respiratory disorders (N=3), chloracne (N=2), Gastrointestinal and renal disorders (N=1) and skin disorders (N=1).

A detailed summary of study design, exposure, methods and outcomes of each Literature Update and summarises the evaluation undertaken by the reviewers are provided below. The evaluation is based on the potential of bias, confounding and chance as well as the quality of data reported and the statistical strength of association observed (see section “Methodology”).

The majority of Literature Updates reviewed provided outcomes that were limited by statistical power, study design or methodology (including control for confounding, bias and chance) and/or reporting quality to varying degrees. A major limitation of most studies was the lack of adequate exposure assessments. A copy of each paper has been provided in Appendix 2 for further reference.

(Baccarelli et al., 2002) Immunologic effects of dioxin: new results from Seveso and comparison with other studies.

Study design: cohort study investigating immunologic effects

Study group: Seveso residents (N=62) from the most highly contaminated zones A (N=55) and B (N=7) and residents (N=59, frequency matched by sex, decade of age, cigarette smoking status) from the surrounding non-contaminated area (non-ABR zone).

Exposure: Environmental (accidental) acute exposure to 2,4,5-T and 2,3,7,8-TCDD during 1976 industrial accident.

Dose: current serum TCDD reported in quintiles: 1.2-3.5 ppt (N=21); 3.6-6.0 ppt (N=21); 6.1-9.3 ppt (N=23); 9.4-20.0 ppt (N=22); 20.1-89.9 ppt (N=22).

Methods: randomly sampled subjects and verified residence at recruitment; questionnaire and personal interview; collection of a detailed personal medical history and medication use; determination of serum TCDD concentration; quantification of plasma immunoglobulins IgA, IgG and IgM, and complement components C3 and C4; all analysis performed blinded to subject’s exposure status; considered confounding factors (age, sex, smoking status, body mass index, consumption of domestic livestock and poultry, alcohol consumption, acute and chronic medical conditions and current medication use).

Statistics: nonparametric tests for group comparisons; simple and multiple regression analysis to assess correlations between variables; multiple regression models adjusted for confounding factors.

Results: Significant decrease in IgG levels in exposed subjects with increasing serum TCDD concentration (r = -0.35, p = 0.0002; slightly more pronounced in females (r=-0.39, p=0.003, N=53) than males (r=-0.33, p=0.02, N=56)). Medium IgG concentration decreased from 1526 mg/dl in quintile 1 (serum TCDD<3.5ppt) to 1163 mg/dl in quintile 5 (serum TCDD 20.1-89.9 ppt) (test for difference between groups, p=0.002). Consistently lower IgG in subjects from zone A (1142 mg/dl.; p=0.01) and zone B (1294 mg/dl.; p=0.03) than subjects from non-contaminated area (1403 mg/dl.). Serum TCDD was not significantly correlated with IgM, IgA, C3. Weak positive association of C4 with serum TCDD, but not significant after adjusting for some confounding factors.

Conclusion: The possible long-term immunologic effects of 2,3,7,8-TCDD, coupled with the increased incidence of lymphatic tumours in the area of the accident and the conflicting results in the literature warrant further investigation.

Evaluation: Study based on relatively small random sample of acutely exposed resident population but well designed with matched control, detailed assessment of personal medical history and laboratory test validation of conditions. Includes dose measurement and adjustment for confounding. Overall, this study provides good evidence for an association between decreased IgG levels and exposure to 2,3,7,8-TCDD, however, no IgG levels found in this study approached levels of those typically observed in patients with antibody immunodeficiency disorders (less than or equal to 350 mg/dL).

(Crump et al., 2003) Meta-analysis of dioxin cancer dose response for three occupational cohorts

Study design: Cohort study (meta-analysis) investigating total cancer mortality


Exposure: Occupational exposure to 2,4,5-T, TCP and 2,3,7,8-TCDD (and potentially other chemicals) from chemical production.

Dose: acute and long-term exposure; Cumulative serum TCDD or TEQ concentration: 180, 988, 3416 and 10425 ppt-year (Quartiles, Hamburg cohort), 605 19614, 55645 and 150454 ppt-year (Quartiles, BASF cohort), 260, 402, 853, 1895, 4420, 12125 and 59838 ppg-year (Septiles, NIOSH cohort).

Methods: Meta-analysis to estimate the lifetime average daily TEQ intakes corresponding to an increase of 0.1, 0.05 and 0.01, in the lifetime probability of mortality from cancer (ED_{0.1}, ED_{0.05} and ED_{0.01}); converted reported dose data to cumulative serum concentrations; modelling of dose-response assuming that SMR depends linearly on cumulative serum TCDD concentration and using cumulative TCDD lagged 15 years (estimated using a first-order elimination process)
Statistics: statistical modelling of cancer dose-response based on an amalgam of cumulative serum TEQ; meta-analysis of combined data from the 3 cohorts was accomplished via the combined likelihood of the three data sets reported, use of likelihood ratio tests to test hypothesis and calculation of confidence intervals using the profile likelihood method. All hypothesis tests of individual parameters were two sided.

Results: A linear model provided adequate fit to the data (p=0.29), producing a baseline SMR estimate of 100(17 (95% CI, 104-130) and predicting that each ppt-year of cumulative lipid TEQ increased the relative risk by 6.3×10^{-6} (95% CI, 8.8×10^{-7}-1.3×10^{-5}). The model with variable baseline and using a 15-year lag time predicted ED_{90} = 475 pg/kg/day (95% CI, 223-3401), ED_{95} = 231 pg/kg/day (95% CI, 109-1653) and ED_{99} = 45 pg/kg/day (95% CI, 21-324). A statistically significant (p=0.02) trend was found in total cancer mortality with increasing dioxin exposure. The analysis did not support that the human evidence for dioxin carcinogenicity is limited to populations with very high exposures. The trend tests show an increase in total cancer at cumulative TEQ serum levels that would result in a lifetime (70 years) intake of 7 pg TEQ/kg body weight/day (cumulative TEQ = 3988 ppt-years), with no increase at 6 pg/kg body weight/day (cumulative TEQ = 3605 ppt-years).

Conclusion: Overall, the available dose-response assessments for dioxin and cancer indicate that dioxin TEQ exposures within roughly 3-fold of current background levels may be carcinogenic. US EPA estimates that current lifetime human exposures to dioxins average approximately 1 pg/kg/day (99% percentile: 3 pg/kg/day). The proximity of food borne dioxin exposure levels to those associated with cancer argues for careful consideration of both the cancer mechanism and the upper ranges of long-term average exposures for dioxins.

Evaluation: detailed exposure assessment, complex statistical analysis of three occupational cohorts with detailed information on testing of hypothesis and reporting of statistical data, considered background exposure in analysis and lag time for cancer mortality. No evaluation of the likelihood that confounding lifestyle factors or occupational exposures to other chemicals may have been responsible for the observed responses in the individual data used, however, responses of workers exposed to different TEQ concentrations were effectively compared to background SMR as an estimated parameter. This study uses the best assessments of exposure in available occupational studies to consider all cancer risk. Overall, it provides some evidence for an increased risk in total cancer with increased serum TEQ.

(Dwyer et al., 2002) Hypertension and serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and hypertension in the air force veterans of the Vietnam war

Study design: cohort study investigating hypertension

Study group: Male Veterans of Operation Ranch Hand unit (N=2101) and a comparison group (N=1436) of Air Force veterans who served in South East Asia during the same period, matched by age, race and military occupation. The same cohort was used for other studies (e.g. (Wolfe et al., 1990b)).

Exposure: Exposure to 2,4,5-T, 2,4-T and 2,3,7,8-TCDD from spraying of Agent Orange during military service in Vietnam (1962-1971).

Dose: serum TCDD (in 1987, 1992 or 1997) in Ranch Hand veterans (Median: 11.6 ppt, Quintile 1: 0.4-5.35 ppt, Quintile 2: 5.38-9.10 ppt, Quintile 3: 9.19-16.4 ppt, Quintile 4: 16.47-35.50 ppt, Quintile 5: 35.5-617.8 ppt) and in comparison group (Median: 3.9 ppt, Quintile 1: 0.30-2.40 ppt, Quintile 2: 2.42-3.42 ppt, Quintile 3: 3.43-4.39 ppt, Quintile 4: 4.40-5.75 ppt, Quintile 5: 5.76-54.8 ppt).

Methods: Physical examinations were carried out in 1982, 1985, 1987, 1992 and 1997 as part of the Air Force Health Study using personal interviews on history of medical diagnosed hypertension (ICD 401) and verification by medical record viewing; grouping of veterans in each cohort according to quintiles of serum TCDD (analysed in 1987, 1992 or 1997); adjusted for confounding factors (body mass index at end of service, quantity of cigarette smoking, alcohol consumption per year, age at end of service, race, military occupation (officer, enlisted flyer, enlisted ground crew), serum lipids (total cholesterol, HDL cholesterol, triglycerides), family history of hypertension and family history of stroke in first degree relatives).

Statistics: relative risk of hypertension was estimated in the 2nd, 3rd, 4th and 5th quintile in the comparison group and all quintiles in the Ranch Hand veterans relative to the 1st quintile in the comparison group; all analysis were stratified by year of birth in 5-year intervals and analysis were performed two sided.

Results: No difference was observed with respect to the risk of hypertension between the Ranch Hand and comparison cohorts (RR = 1.02, 95% CI, 0.90-1.16; p=0.76). Body mass index was significantly associated with hypertension. The relative risk of hypertension by quintile serum TCDD were significantly increased in the 2nd, 3rd, 4th and 5th quintiles in the Ranch Hand and comparison group after adjustment for confounding factors. Serum TCDD was significantly and adversely related to the risk of hypertension within each of the two cohorts. This relation was not explained by confounding factors, although all of these contributed significantly to the model.

Conclusion: Although no significant difference was found between cohorts, serum TCDD was significantly associated to the risk of hypertension within each of the two cohorts. A possible explanation was suggested as metabolic factors that are causal in the development of hypertension and for which serum TCDD is indicative.

Evaluation: This study was reported in conference proceedings, however, provided enough detailed information for inclusion in this review. The study controlled for confounding factors and used a relatively large study population. Even though the comparison group was not spraying herbicides, serum TCDD results indicate that some had been exposed to dioxins above that of the general background. Although the internal dose was determined by serum TCDD analysis, these are up to 10 years apart and may therefore introduce errors in the quintile exposure grouping. All quintiles above the 5.35 ppt showed significant associations between serum TCDD and hypertension, with increasing relative risk with increasing serum TCDD quintile. Overall, this study provides some evidence that hypertension may be positively related to serum TCDD concentration, even at relatively low levels.

(Hardell et al., 2002) Exposure to pesticides as risk factor for NHL and Hairy Cell Leukemia: pooled analysis of two Swedish case-control studies
Study design: Pooled analysis of two case control studies investigating non-Hodgkin’s lymphoma (NHL) and hairy cell leukaemia (HCL), respectively.

Study group: Swedish population group of males with NHL (N=404) and HCL (N=111) and matched (for age, gender, country) control group (N=741 and 400, respectively).

Exposure: Recalled exposure to range of herbicides (including 2,4,5-T and 2,4-D), pesticides, fungicides, impregnating agents and organic solvents. Minimum exposure one day with lag of one year.

Dose: unknown; assessment of years and total number of days for exposure to various agents was used as surrogate for dose.

Methods: Pooled analysis of two earlier studies one on NHL and one on HCL. Studies were male, population based with cases identified from cancer registry and controls from population registry. Exposure data was ascertained by questionnaire with telephone interviewer supplementation (blinded to ca/co). Dose-response was investigated by comparing high (greater than median number of days exposed) and low (smaller than median number of days exposed) dose exposures divided by the median exposure time in days. Deceased cases were included in NHL study (matched by deceased controls to minimise recall bias), only living cases were included in HCL study.

Statistics: Conditional logistic regression analysis for matched studies, including univariate and multivariate analysis. Adjustments were made for study, study area and vital status. Risk estimates for different pesticides used only subjects with no pesticide exposure as unexposed.

Results: An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, however only a marginal increase in risk was reported for low exposure to 2,4-D + 2,4,5-T (Total OR = 1.48 (95% CI, 0.99-2.20); low exposure OR = 1.87 (95% CI, 1.08-3.20); high exposure OR = 1.20 (95% CI, 0.68-2.08)). No dose-response was observed for 2,4,5-T + 2,4-D, the highest OR was seen when first exposure occurred 10-20 years before diagnosis (10-20 years OR = 2.87 (95% CI, 0.81-11); 20-30 years OR = 1.87 (95% CI, 0.98-3.53); >30 years OR = 1.15 (95% CI, 0.67-1.93)). This trend was significant in phenoxyacetic acids as a group (2,4,5-T +2,4-D including MCPA). For 2,4,5-T + 2,4-D the risk was highest for exposure 1-10 years prior to diagnosis, whereas no increased risk was seen for those with last exposure >10 years fro the time of diagnosis (1-10 years OR = 4.31 (95% CI, 1.12-21); 10-20 years OR = 1.85 (95% CI, 0.90-3.78)). Exposure to phenoxyacetic acids during different decades from the 1940s to 1980s showed increased risks during recent decades (1940s OR = 1.46 (95% CI, 0.37-5.23); 1950s OR = 1.44 (95% CI, 0.91-2.62); 1960s OR = 1.68 (95% CI, 1.10-2.55); 1970s OR = 2.37 (95% CI, 1.42-3.95); 1980s OR = 3.25 (95% CI, 1.53-7.07).

Conclusion: the etiology of NHL is multifactorial and further studies should consider immunotoxic effects by the studied chemicals as well as tumour induction period and interaction with virus infection.

Evaluation: Potential for recall bias, although farmers as occupation did not increase the risk, indicating that the outcomes are not explained merely by misclassification of exposure. Observational bias was minimised by blinded data gathering and analysis. Adjustments were made for vital status and geographical area to minimise heterogeneity between study designs. However, confounding factors were not addressed and therefore remain as potential alternative explanations. The use of years of recalled exposure as surrogate for dose and exposure is extremely limiting and may have introduced errors in the classifications of exposure, duration and latency of exposure. Overall, this study provides some evidence for a marginal association between exposure to 2,4,5-T + 2,4-D and NHL and HCL, the strength of evidence is limited by potential chance and bias.

(Hoppin et al., 2002) Chemical predictors of wheeze among farmer pesticide applicators in the agricultural health study

Study design: Cohort study investigating wheeze

Study group: farmers (N=20468) in Iowa and North Carolina, mostly male

Exposure: occupational exposure to a variety of pesticides (N=40) including 2,4-D

Dose: unknown; self-reported annual pesticide use and frequency of application was used as surrogate for dose

Methods: recruitment of farmers enrolled in the Agricultural Health Study (N=52000). Questionnaires on demographics, farming practices, medical history, frequency of wheeze, quantity and type of pesticides used and frequency of pesticide application (days). Only subjects that have applied pesticides and reported wheeze during the last year were included. Statistics: exposures were evaluated using a base logistic regression model controlling for age, state, smoking history and asthma-atory (eczema or hay fever). Dose-response modelling of chemical specific exposures using application frequency categories. To address confounding by multiple exposures, models were developed that included chemicals commonly applied together and chemical application methods used.

Results: Eleven pesticides were significantly associated with wheeze when evaluated for ever use, of these, all 10 for which dose-response models were constructed had significant tests for trend (p<0.05). 2,4-D application was not significantly associated with wheeze (OR = 0.99; 95% CI, 0.99-1.11; p = 0.46) and no dose-response was observed.

Conclusion: The associations observed, although small, suggest an independent role for specific pesticides in respiratory symptoms of farmers.

Evaluation: large study population, but potential for recall and selection bias. The use of self-reported frequency of pesticide use as surrogate for dose and exposure frequency is extremely limiting (no information on active ingredient concentration, solvents or other ingredients) and may have introduced chance with respect to the exposure classifications. No comparison group was included. The exclusion of farmers that have applied pesticides prior to the year before the study limits the detection of potential latency effects. Overall, this study suggests that wheeze is not associated with exposure to 2,4-D, however the strength of evidence is extremely limited by potential chance and bias.

(Ingel and Prikhozhan, 2002) Relationship between emotional stress in female residents of Chapaevsk and toxicological and genetic values

Study design: cohort study investigating emotional stress

Study group: Three cohorts of females of Chapaevsk, Russia: “Zavod” - female factory workers where contact with dioxins was possible (N=15; average age was 32.9 +/- 3.9 years); “Titovka” - females living in Titovka (N=16; average age was 30.8+-4.0 years) who never had occupational contact with dioxins but who lived near the factory; “Nagornyi” – females (N=14; average age was 32.7+-/-3.7
years) who have never had any occupational contacts with dioxins and lived in the area with insignificant amount of polychlorinated biphenyl’s in environment.

**Exposure**: Occupational and environmental exposure to dioxins and PCBs.

**Dose**: not reported

**Methods**: Serum dioxin analysis from 4-6 females per cohort. Investigated level of chromosome aberrations in cells of peripheral blood and severity of stress. The severity of stress was estimated via 5 standard psychological questionnaires to determine psychological depression, restlessness, overfatigue, state of health, activity, mood and interpersonal relationships. Some characteristics of lifestyle were taken into account such as the amount of children in the family, estimated income per a member of the family, peculiarities of the diet, living conditions and the presence of hereditary and occupational diseases.

**Statistics**: limited information (standard statistics to determine correlations)

**Results**: Psychological testing of Chapaevsk females found that the three cohorts differed by the degree of stress. The highest severity of stress was observed in females occupationally exposed to dioxins. Significant differences (p<0.05) were found for overfatigue, statue of health and interpersonal relationships between Titovka and Zavod and for overfatigue and state of health between Nagornyi and Zavod. Restlessness did not differ between the cohorts. The influence of income on the severity of stress was found only for the group never having occupational exposure to dioxins (Nagornyi). Significant correlations were observed for restlessness, overfatigue and mood, while no correlation with age and other characteristics of quality of life on severity of stress was observed. Serum dioxins concentration was significantly correlated with the severity of stress (level of psychological depression and severity of overfatigue) (p < or = 0.001) and levels and spectra of chromosomal aberrations in peripheral blood cells (p < or = 0.05, p < or = 0.01 in different tests).

**Conclusion**: exposure to dioxins can cause stress and be one of the reasons of high level of genetic disorders of Chapaevsk females. The severity of stress can be used as an indicator of the general toxic situation and also for the estimation of the personal sensitivity of human genome to genotoxic factors in the environment.

**Evaluation**: The influence of social and economic factors were addressed and internal dose was determined, however, only in a few individuals of the cohort. The study is limited by the relatively small number in each cohort. Overall, this study provides evidence of a positive correlation between exposure to dioxins and emotional stress; however, the statistical power is limited by the small number of individuals included.

**Reference**: (Kelly et al., 2002) Assessment of health effects in New York City firefighters after exposure to polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-furans (PCDFs): the Staten Island Transformer Fire Health Surveillance Project

**Study design**: cohort study investigating a range of health outcomes

**Study group**: male firefighters and clean-up personnel (N=60) in New York

**Exposure**: Exposure to PCBs and PCDFs during an electrical transformer fire in 1998

**Dose**: serum PCB averaged 2.92 ppt (± 1.96), PCDD/F TEQ averaged 39.0 ppt (± 21.5), protective clothing was worn during the fire and cleanup

**Methods**: Comprehensive medical examinations (N=58) using questionnaires and physical examination (electrocardiogram, body weight, body fat, pulmonary functions, urine and blood analysis including glucose, cell counts, liver enzymes, lipid profiles). Pre-exposed baseline information (12-15 months) was available except for pulmonary functions. Follow-up examinations were undertaken 9 months post exposure. Serum PCB (N=58, 2-3 weeks after exposure) and PCDD/F (N=48, 2 months after exposure) analysis were undertaken.

**Statistics**: Analysis of covariance for comparison of pulmonary functions and serum levels at different points in time. Spearman’s correlation to assess significant correlations for rank-ordered variables on serum measures and continuous variables on serum measures. Wilcoxon’s signed-ranks test to assess comparisons between 2 samples.

**Results**: Initial symptoms were reported by 55% of firefighters (skin irritation/itching, neurologic complaints, respiratory complaints) none of which were incapacitating or prolonged in duration. None had chloracne. Diastolic and systolic blood pressures were within normal values in all participants. Electrocardiograms and pulmonary functions were within normal limits in all participants. 12% showed evidence of minimal obstructive airway disease, 14% of minimal small airway flow limitations. All subjects had normal urinalysis, serum chemistry and cell counts. Several had post exposure liver function tests and lipid profiles that were elevated compared with post exposure values. No significant correlations were observed between serum PCB and either symptom scores. Multiple regression analysis of serum PCB levels was not significant for SGOT, SGPT, GGTP and cholesterol but significantly correlated to triglycerides (p=0.002). No significant association was found for these variables when compared to the pre exposure data. At follow up, all subjects remained symptom free and had normal examination results.

**Conclusion**: All fire fighters had no short-term health effects; protective clothing worn provided adequate protection from high exposure potential.

**Evaluation**: This study only investigates short-term health effects (follow ups are planned). The strength of this study is the availability of pre exposure detailed medial histories. The exposure has been assessed individually, however, with respect to dioxin levels, a delay of 3 months occurred post exposure. Since concentrations are relatively low in most participants, this may have resulted in the lack of detection of exposure of some individuals (73% had significantly decreased PCB levels 9 months post exposure). No information is provided whether confounding factors have been controlled and the small sample size limits the statistical power. Overall, this study provides weak evidence that short-term health effects are not associated with acute exposure to relatively low concentrations of PCBs and PCDFs.

**Reference**: (Michalek et al., 2003a) Serum dioxin and psychological functioning in U.S. Air Force Veterans of the Vietnam War.

**Study design**: cohort study investigating psychological functioning

**Study group**: male Vietnam veterans (N = 1,109) of operation Ranch Hand and a matched (age, race, occupation)
comparison group of other U.S. Air Force veterans (N = 1,493) who served in Southeast Asia during the same period (1962-1971), and who participated in the U.S. Air Force Health Study. The same cohort was used for other studies (e.g. (Wolfe et al., 1990b)).

**Exposure:** military exposure to Agent Orange herbicide containing 2,3,7,8-tetrachlorodibenzo-p-dioxin

**Dose:** median and range dioxin level (ppt) based on the 1992 analysis: comparison (4.0; 0-10), background (5.7; 0-10), low (14.9; 10-26), high (45.7; 18-618).  

**Methods:** Dioxin exposure was assessed using blood samples collected and analysed for dioxin concentrations in 1987 and 1992. Back extrapolation of initial dioxin dose (if currently above 10ppt) using constant half-life of 8.7 years. Each veteran was then assigned to one of four exposure categories according to current level and back extrapolated initial dioxin level: comparison (TCDD$_{current} \leq 10$ ppt), background (current $\leq 10$ ppt), low (current $> 10$ ppt; initial $\leq 94$ ppt), high (current $> 10$ ppt; initial $\geq 94$ ppt). For psychological Assessment subjects were administered the Minnesota Multiphasic Personality Inventory (MMPI) in 1982 and 1985 and the Millon Clinical Multiaxial Inventory (MCMI) in 1987 and 1992.

**Statistics:** logistic regression to compute point estimate of odds ratio and associated 95% CI of having an elevated MMPI or MCMI. Ranch Hand veterans with background, low and high exposures were each contrasted with the comparison group. Adjustments were made for age, race, rank, marital status and combat exposure level.

**Results:** Ranch Hand veterans with higher dioxin levels showed some difficulties in anxiety, somatization, depression, and a denial of psychological factors. However, those with background levels also showed indications of emotional distress, primarily in emotional numbing and lability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or behaviours.

**Conclusion:** Few consistent psychological abnormalities are associated with dioxin exposure and Vietnam veterans.

**Evaluation:** This represents a well designed study with large cohorts, although the relatively low sample size in the high category may have limited statistical power. Adjustments were made for all known confounders. The main limitation of the study rests with the uncertainties regarding the categorisation of exposure based on serum dioxin concentrations up to 26 years after the exposure has ceased and the back extrapolation using one compartment, steady state pharmacokinetic modelling, in particular with respect to the comparison and background groups. Overall, this study provides good evidence that compared to other veterans of war, cohorts of the operation Ranch Hand are not experiencing significantly higher psychological problems.

**Reference:** (Mo et al., 2002) A study about the skin and general disease pattern of the Vietnam Veterans exposed to dioxin

**Study design:** cohort study investigating a range of conditions and diseases

**Study group:** Koreans Vietnam veterans (N=332) who visited one hospital

**Exposure:** military exposure to Agent Orange

**Dose:** unknown

**Methods:** clinical evaluation, physical examination, medical history, serum and urine chemistry, electrocardiogram, electrodiagnostic study, roentgenographic study and dermatologic evaluation.

**Statistics:** not reported

**Results:** The prevalence of hypertension (12.0%), hyperlipidemia (6.9%), diabetes mellitus (5.7%), liver disease (4.5%) and peripheral neuropathy (1.2%) of subjects was not significantly higher compared to the general population. The prevalence of xerotic eczema (3.9%), seborrheic dermatitis (3.9%), psoriasis vulgaris (0.9%), photoallergic dermatitis (0.6%) and chronic urticaria (0.3%) was not significantly elevated compared to the general population.

**Conclusion:** The prevalence of systemic diseases is not higher in Korean veterans compared to the general population. No appropriate comparison group was available for comparisons of dermatological diseases.

**Evaluation:** This study has a number of limitations, including the lack of exposure data, a biased sampling of subjects, the lack of a matched comparison group and the lack of reporting on the statistical evaluations undertaken. Overall, this study does not provide evidence on associations between the investigated health effects and exposure to Agent Orange.

**Reference:** (Pelclova et al., 2002) Lipid metabolism and neuropsychological follow-up study of workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin.

**Study design:** cohort study (case series) investigating lipid metabolism, neuropsychological functioning

**Study group:** former male production and clean-up workers (N=12) with history of illness post exposure. The same cohort was used for other studies (e.g. (Pelclova et al., 2001)).

**Exposure:** Occupational exposure during herbicide production (butylester of 2,4,5-T contaminated with 2,3,7,8-TCDD) during 1965-1968 in the former Czechoslovakia (uncontrolled decomposition reaction), exposure lasted 10 days to 23 months.

**Dose:** mean estimated TCDD serum at time of intoxication was back extrapolated to 5000 ppt (256 ppt in 1996, range 14-760 ppt)

**Methods:** 12 former workers were given medical examinations (35 years post-exposure). Blood cholesterol and triglycerides were measured; the common carotid artery was examined by ultrasound and the intima-media thickness (IMT) measured. Findings were compared with TCDD serum levels from 1996. Neuropsychological and ophthalmological examination, eight tests were employed to assess neuropsychological effects. Subjects were follow-up examined for chloracne and duration of cases compared with 2,3,7,8-TCDD plasma levels in 1996.

**Statistics:** Spearman’s correlation coefficient to measure association between two quantitative variables. Fisher exact test to measure the association between two categorical variables. Paired data was compared using McNemara test, Student’s two-sample t-test or one-way ANOVA with Duncan’s test.

**Results:** Elevated plasma lipids were observed. Hyperlipidaemia was statistically more frequent in patients with higher serum TCDD (p=0.03); Positive correlations were observed between the serum TCDD and triglycerides (p=0.02) and cholesterol (p=0.01). Results with respect to circulatory and vision disorders are presented descriptive only and have been included into the case history section of this review (1 subject required surgery for acute stenosis of carotid artery; 7 had atherosclerotic plaques in the carotid arteries. An increased mean intima-media thickness was
observed. Eight persons had sclerotic degenerative changes at the ocular fundus). Neuropsychological findings were assessed as normal only in three persons with lower 2,3,7,8-TCDD plasma levels. Significant correlations of some neuropsychological impairment with serum TCDD levels were observed only in the 1996 examination. Only 2 subjects (1st and 3rd most exposed) still presented signs of chloracne 35 years after exposure. A statistically significant association between serum TCDD and patients with and without chloracne in 2001 was found (p=0.03)

**Conclusion**: The authors conclude that hyperlipidaemia, atherosclerotic plaques, increased IMT, ischaemic heart disease and neuropsychological disturbances were frequent in this group of former 2,3,7,8-TCDD workers. Hyperlipidaemia may have played an important role in the prevalence of a number of these disorders.

**Evaluation**: The levels of triglycerides and cholesterol in workers with high serum TCDD are considerably higher compared to background levels and are amongst the highest reported compared to other exposed cohorts. However, the low number of subjects in this study and lack of a matched control group limits the study considerably. Cholesterol and triglyceride correlations to serum TCDD indicate a dose-response relationship, however, it is not clear whether potential confounding factors were controlled. Neuropsychological findings were only significant in a 1996 examination. Overall, this study presents only weak epidemiological evidence for a relationship between exposure to 2,3,7,8-TCDD and lipid or lipoprotein disorders as well as neuropsychological functioning.

**Reference**: (Remillard and Bunce, 2002b; Remillard and Bunce, 2002c) Use of Haber’s Rule to estimate the risk of diabetes from background exposures to dioxin-like compounds (full paper) & Consideration of a link between dioxins and diabetes (conference paper)

**Study design**: pooled study using previously reported data

**Study group**: unexposed comparison groups (N=258) used for previous studies on chemical workers.

**Exposure**: Environmental background exposures of the general population

**Dose**: The referent group serum TCDD levels were 7 pg/g lipid (TEQ = 35 pg/g; n=259).

**Methods**: Modelling of previously reported epidemiological data (chemical workers exposed to herbicides contaminated with 2,3,7,8-TCDD and matched control groups) where average TCDD serum levels were known.

**Statistics**: Development of a model using Haber’s Rule (states that the product of concentration and time of exposure is constant) to estimate whether the referent’s lifetime 35 ppt of TEQ may represent a significant exposure in the context of chronic toxicology.

**Results**: Background exposure to PCDD/Fs (35 ppt TEQ) is not a significant risk factor for individuals that have been occupationally or accidentally exposed (contribution <1% of diabetes risk). Present levels of dioxins in the general population are unlikely to constitute an important risk factor for type II diabetes.

**Conclusion**: The authors conclude that present background exposure to dioxins is not a significant risk factor for type II diabetes in individuals who have not been occupationally or accidentally exposed.

**Evaluation**: The study gives no direct information on risk in exposed populations but rather investigates the contribution of background dioxins levels to the risk of diabetes in referent groups. A number of assumptions were made in this study, most importantly the assumption that Harber’s Rule applies to a link between dioxin exposure and diabetes. Overall, this modelling approach provides some supporting evidence that low, background dioxin exposure may not be associated with significantly increased diabetes risk.

**Reference**: (Revich et al., 2002) Effects of dioxins in the development of malignant tumours and disorders of reproductive health of the population

**Study design**: cohort study (with some aspects of a correlation study, i.e. unit of analysis are populations rather than individuals) investigating cancer mortality and reproductive health outcomes

**Study group**: Population of Chapaevsk (87000); comparison population groups were from Samara area (regional area) and general Russian population

**Exposure**: the town of Chapaevsk is characterized by increased level of dioxins in the environment. No individual exposure data given in this article.

**Dose**: unknown; residency in Chapaevsk was used as surrogate for exposure and dose. A previous study (Revich et al., 2001) has investigated serum TEQ concentrations in Chapaevsk residents and found elevated levels in women (mean TEQ 42 ppt; mean TCDD 23 ppt), female workers (mean TEQ 412 ppt; mean TCDD 81 ppt) six residents living 1-3 km from the chemical plant (mean TEQ 75 ppt; mean TCDD 46 ppt), four residents living 5-8 km from the chemical plant (mean TEQ 25 ppt; mean TCDD <2.5 ppt).

**Methods**: The health status of the Chapaevsk population (82 thousand people) was investigated by analysing of medical records (1994-1998). The specific association of dioxins with cancers and reproductive disorders determined.

Statistics:

**Results**: Mortality caused by malignant tumours is statistically higher than the expected values. The relative risk for men of the following specific cancers was reported:

- General morbidity 1.9 (95% CI, 1.8-2.1), mortality 1.8 (95% CI, 1.6-1.9); Cancer of the oesophagus morbidity 1.9 (95% CI, 0.9-3.6), mortality 1.7 (95% CI, 0.7-3.3); Stomach cancer morbidity 1.9 (95% CI, 1.5-2.4), mortality 1.7 (95% CI, 1.3-2.2);
- Colon cancer morbidity 1.6 (95% CI, 0.9-1.9), mortality 1.3 (95% CI, 0.8-2.2); Retinal cancer morbidity 1.6 (95% CI, 1.1-2.4), mortality 1.5 (95% CI, 1.0-2.4); Laryngeal cancer morbidity 2.3 (95% CI, 1.2-3.8); Liver and gall tract cancer morbidity 4.3 (95% CI, 2.9-6.2); Lung cancer morbidity 3.3 (95% CI, 2.9-3.7), mortality 3.1 (95% CI, 2.6-3.5); Bone cancer morbidity 2.3 (0.8-5.0), mortality 2.1 (95% CI, 0.9-4.4); Urinary bladder cancer morbidity 3.6 (95% CI, 2.6-4.9);
- Urogenital cancer morbidity 2.6 (95% CI, 1.7-3.6); Leukaemia mortality 1.5 (95% CI, 0.8-2.7); Lymphoma cancer morbidity 1.1 (95% CI, 0.4-2.3); Renal cancer morbidity 1.2 (95% CI, 0.7-2.0); Hemoblastosis morbidity 1.1 (95% CI, 0.6-1.6).

Changes in the reproductive health of residents were observed with high incidence of spontaneous abortions, preterm births, genital disorders (cryptorchidism, phimosis, hypospadia, delayed sexual development), male to female sex ratios was 1.03 over 16 years.

**Conclusion**: The mortality caused by malignant tumours in Chapaevsk is statistically higher than the expected values.
Changes in the reproductive health of residence were observed.

**Evaluation:** This study borders on being an environmental study, but includes a comparison cohort and may also be seen as similar to the studies at Seveso, where exposure to dioxins occurred in the general population. Data was obtained from medical records, however detailed information on the methodology was not provided. No attempt was made to categorise the population into different exposure groups (e.g. workers, or location relative to chemical plant). The study would also benefit from more discussion of patterns of migration and emigration to and from the town, as substantial amounts of either could have the effect of biasing results towards the norm. It is also possible that there was exposure to other chemicals in Chapaevsk that could confound the observed effects. There are other factors, such as cigarette smoking and alcohol consumption, which may have been elevated in this town and could have affected mortality. Due to lack of individual exposure date, caution is required when predicting causal relationships from population studies. Overall, this study does not control bias or confounding, and chemical exposure is not assessed. It can therefore only provide weak evidence of an association of the cancer mortality and morbidity or adverse reproductive health associated with exposure to dioxins.

**Reference:** (Sweeney et al., 2002) Cancer in Humans related to exposure to chemicals contaminated with 2,3,7,8 TCDD: The NIOSH studies

**Study design:** Pooled analysis of one cross-sectional, one baseline and follow-up morbidity studies investigating total cancer morbidity

**Study group:** workers (total N=5172) from 12 US chemical plants (NIOSH cohort) including participants from a Baseline Morbidity Study (N=5172) (Fingerhut et al., 1991a), an Update Study (N=5132) (Steenland et al., 1999) and a cross-sectional study (N=5132 and N=3538 for workers with detailed exposure) (Piacitelli et al., 2000).

**Exposure:** Occupational exposure during production of TCP, 2,3,4-T, hexachlorophene or production of Agent Orange formulation for a period of 2 to 35 years between 1942 and 1984. Individual exposure varied but many workers exposed to 2,3,7,8-TCDD-contaminated chemicals on a daily basis for up to 20 years

**Dose:** serum TCDD concentrations in 273 living cohort members (mean: 220 ppt, median: 70 ppt, range: 2-3400 ppt) and 79 referents (mean: 7 ppt, median: 6 ppt, range: 2-20 ppt)

**Methods:** Cancer mortality studies consisted of a baseline mortality study (N=5172) published in 1991. The U.S. population was used for comparison. An updated study in 1999 included a 6-year follow-up (N=5132), with a defined exposure cohort (N=3538) who had sufficient detailed records to estimate 2,3,7,8-TCDD exposure. Cross-sectional morbidity study (1987-88) focussed on outcomes other than cancer and included reproductive outcomes and serum exposure data. Life table analysis, using the U.S. population for comparison, were conducted for these cohorts. Cumulative exposure scores were categorised into septiles.

**Results:** The Baseline Mortality Study (1991) reported a significant increased mortality for all cancers in the entire cohort (SMR = 1.15; 95% CI, 1.02-1.30) and for workers with more than 1 year employment and 20 years latency (SMR = 1.46; 95% CI, 1.21-1.76) but no significant increase in specific cancer. The Update Study (1999) reported significant increase in all cancers for the entire cohort (SMR=1.13; 95% CI, 1.02-1.25). Mortality from all cancers was not statistically significantly higher than expected except for cancers of the larynx (SMR=2.22; 95% CI, 1.06-4.08) and bladder (SMR=1.99; 95% CI, 1.13-3.23), the latter most likely a result of exposure to 4-aminobiphenyl at one plant. Statistically significantly increased total cancer mortality was observed in the two highest cumulative-exposure septime groups (SMR=1.68; 95% CI, 1.19-2.30). Significantly increased total cancer mortality and mortality from lung cancer was observed in the defined exposure cohort (p=0.02 and p=0.05, respectively). The trend test for lung cancers was also statistically significant using log cumulative exposure and a 15-year lag.

**Conclusion:** A general, dose-related increase in mortality exists from all cancers and does not appear to be related to an excess in any single type of cancer. The highest rate of cancer was most evident in workers at the highest exposure categories. These results suggest that overall cancer mortality was influenced by high, long-term 2,3,7,8-TCDD exposure.

**Evaluation:** this article represents a short paper published in conference proceedings. The study uses previously published results from the NIOSH cohort, which have been well designed (although only briefly described in the paper) and use relatively large sample sizes. The main limitation of the study is the relatively limited knowledge on the exposure of individuals and the categorisation of exposure based on either serum TCDD from a subgroup of workers and job details. Overall, this study provides good evidence that increased overall cancer mortality is associated with relatively high (acute or long-term) exposure to dioxins.

**Reference:** (Thomke et al., 2002) Cranial nerve function in workers exposed to polychlorinated dioxins and furans.

**Study design:** cohort study investigating cranial nerve function

**Study group:** male workers (N=35 males) at a pesticide plant producing 2,4,5-T with chloracne compared to workers (1 female, 85 males) without chloracne

**Exposure:** occupational exposure to 2,4,5-T (and 2,3,7,8-TCDD contaminant), exposure occurred 2-36 years prior to examination and lasted from more than 1 year in 92 workers and less than 1 year in 29 workers

**Dose:** serum TEQ concentrations in 28 workers with (median: 871 ppt, range: 160-14178 ppt) and 86 workers without (median: 230; range: 0-6066 ppt) chloracne; back extrapolated 2,3,7,8-TCDD levels in workers with (median: 203 ppt; range: 22-11777 ppt) and without (median: 113 ppt; range: 0-4023 ppt); presence and absence of chloracne was used as a surrogate for dose

**Methods:** Clinical and neurophysiological examinations (visual and brainstem auditory evoked potentials (VEP & BAEP, blink reflex) performed by trained neurologists; serum dioxin analysis and back extrapolation of initial 2,3,7,8-TCDD concentration using one compartment first-order pharmacokinetic model.

**Statistics:** not described
Results: BAEP abnormalities were more frequent in workers with chloracne than those without chloracne, but this was not significantly significant (p<0.15). VEP abnormalities were seen in one worker with and two without chloracne. Clinically visual functions were normal except in one worker, who was amaurotic since birth. Blink reflex abnormalities without corresponding clinical findings were observed in two patients without chloracne. In conclusion.

Conclusion: severe exposure to PCDD/F is not followed by clinical signs of cranial nerve dysfunction but may create an increased risk to develop subclinical dysfunction of the hair cells in the organ of the cochlear nerve as indicated by a more than twofold increase in the frequency of abnormal BAEP findings in workers with chloracne.

Evaluation: this study is limited by the use of absence or presence of chloracne as a surrogate for exposure. Although serum dioxin concentrations have been analysed in some workers, the data was not examined (probably due to the resulting low sample number) in that respect. The use of chloracne as a surrogate for exposure may introduce errors, in

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Reference: (Van Den Heuvel et al., 2002) Immunologic biomarkers in relation to exposure markers of PCBs and dioxins in Flemish adolescents (Belgium).

Study design: cohort study investigating changes in humoral or cellular immunity or respiratory complaints

Study group: Adolescents born in 1980-1983 and who resided in Hoboken (adjacent to chemical and other industry; N=58), Wilrijk (adjacent to chemical and other industry; N=42) and Peer (rural countryside; N=100).

Exposure: Environmental exposure to various chemicals including PCBs and dioxins

Dose: analysis of serum marker PCBs (0.99 and 1.67 nmol/L in girls and boys, respectively) and CALUX (0.15 and 0.16 pg/mL serum in girls and boys, respectively) measurements were used as surrogate for dose

Methods: Examination was undertaken by school physicians (medical history, allergic complaints during past year). Questionnaires were administered to assess lifestyle, dietary habits, smoking, drinking habits, intake of medications and social class of parents. Blood was collected to assess for indicator PCBs and CALUX TEQ. Immune phenotyping, and determination of serum immunoglobulins were performed.

Statistics: dichotomous classifications to code for the presence of allergic diseases and positive allergic tests were used. Student’s t-test and Fisher’s exact test were used to compare means and proportions between girls and boys. Confounding variables were identified by stepwise multiple regression or logistic regression. Dose-effect relations were calculated using multiple linear regression or logistic regression.

Results: the eosinophil count was negatively and independently correlated with serum dioxin-like chemical concentration (p=0.009). Monocytes tended to decrease with increasing serum TEQ (p=0.055). A negative, borderline significant correlation was observed between the number of NK cells and serum TEQ (p=0.05). No significant association was observed between other lymphocyte phenotypes and serum TEQ. Dioxin-like activity was negatively correlated with serum IgE (p=0.02) but positively correlated with IgA (p=0.05). A negative correlation was found between IgG levels and the concentration of the combined marker PCBs (p=0.009). After adjustment for sex and family history of hay fever, serum TEQ were negatively associated with the odds of having a positive RAST for house dust mites (OR=0.68; p=0.01), cat dander (OR=0.63; p=0.03) and grass pollen (OR=0.70; p=0.02). A history of upper airway allergy was negatively associated with serum TEQ (OR=0.66; p=0.02). A negative association was observed between the odds of bronchial wheezing and serum TEQ (OR=0.25; p=0.03), however this was not the case after adjustment for family history of hay fever and/or asthma. A negative association was found between medical treatment for asthma and serum TEQ (OR=0.58; p=0.005) and a positive association existed between ever having asthma and serum PCB concentration (OR=2.12; p=0.05). The odds of suffering hay fever increased with higher serum PCB concentrations (OR=1.63; p=0.04), however, this was not the case after correction for sex.

Conclusion: Biomarkers of internal exposure to dioxin-like compounds were related to biomarkers of the immune status. The effects of exposure to dioxin-like compounds in adolescents were associated with a lower prevalence of allergic diseases.

Evaluation: This study uses represents an extensive assessment of immunologic biomarkers and their association with exposure to dioxin-like compounds. The biomarkers used for exposure include all Ah-receptor mediating compounds, which provides a better understanding of effects from exposure to such chemicals as a whole, however, it is therefore not possible to determine which of the observed effects may be associated with exposure to 2,3,7,8-TCDD. Potential confounders were assessed and controlled, but the study may be limited by the relatively low sample size. Overall, this study provides some evidence that exposure to dioxin-like compounds may result in alterations of the immune status.

Reference: (Watanabe et al., 2002) Health effects of low dose exposure of polychlorinated dibenzo-p-dioxins, dibenzofurans and coplanar PCB among Japanese residents.

Study design: cohort study investigating a range of disorders and conditions

Study group: 294 male and 291 female residents from 17 areas (general population) aged between 40-60 (volunteers)

Exposure: Background exposure to dioxins and PCBs

Dose: serum dioxin and PCB TEQ mean: 23.8 ppt (SD=15.8), TCDD mean: 1.8 ppt (SD=1.9)

Methods: Life habits (dietary habits, smoking, alcohol consumption, residential and work environment, physical activity, past history of disease and treatments, reproductive history) and dietary habits were collected using questionnaires and checked by trained dieticians. Blood analysis was undertaken for peripheral blood tests and blood chemistry studies (including total cholesterol, HDL-cholesterol, triacylglycerol). For immunologic biomarkers, T lymphocytes (CD3, CD4, CD8) were measured. NK activity and natural killer cell activity was determined. Blood serum dioxin and PCB analysis was undertaken.
Statistics: Correlation analysis between dioxin and PCB and various variables. Linear regression and logistic analysis were used for evaluation of effects of dioxins (p<0.05, significant)

Results: Dioxin and PCB concentration was correlated with profession (higher in farmers). GOT, GPT, triglycerol, total bilirubin, CPK and albumin were positively correlated with dioxin and PCB body burden in males. Total protein, alkaline phosphatase, triglycerol and calcium were positively correlated with dioxin and PCB body burden in females. Amylase was negatively correlated in both sexes. An inverse correlation with dioxin and PCB body burden was found for NK cell marker and NK activity. Testosterone and androstenedione showed a negative association with dioxin levels. Past history of hypertension, diabetes mellitus and hyperlipidemia were significantly correlated with dioxin and PCB body burden (with increased odds ratios). Diabetes only showed a marginal association.

Conclusion: A body burden of 5 ppt body weight may be a risk level for various conditions and diseases

Evaluation: This study was reported in conference proceedings as a short paper and only presents preliminary results. Although statistical evaluation has been performed, limited results are presented without detailed information on significance. The questionnaire includes a range of questions regarding potential confounding factors, however, the authors do not discuss if and how they controlled for these. Exposure data are obtained using blood serum PCB and dioxin concentrations. Overall, in its preliminary form, this study does not provide detailed information to assess the potential for bias and confounding and can therefore only provide minimal information for an association between the investigated health outcomes and exposure to dioxins and PCBs.

Reference: (Zhu et al., 2002) Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers

Study design: Case control study investigating risk factor profiles of sinonasal and nasopharyngeal cancer

Study group: Males with sinonasal cancer (N=70) and nasopharyngeal cancer (N=113) from a previous population-based case control study on Vietnam veterans (TSCCSG, 1990), compared to 1,910 community-based controls.

Exposure: A variety of risk factors were investigated, including exposure to pesticides such as 2,4,5-T

Dose: unknown

Methods: The study used data from a previous population-based case control study on Vietnam veterans and focused on cases reported to have sinonasal or nasopharyngeal cancer by the U.S. cancer registries and confirmed by study pathologists. Controls were selected by random digit dialling. Although most information was collected via the telephone, some were completed in person, and in 18.6% of the sinonasal cancers and 10.6% of the nasopharyngeal cancers the subject had died, and the questionnaire was completed by next-of-kin. None of the comparisons had next of kin questionnaires.

Statistics: Polytomous logistic regression was used to simultaneously compare 2 groups of cases. A forward approach was used in which a variable having an OR confidence interval excluding 1 and with most significant likelihood test entered the model at each step. Effects of interview quality were tested by repeating the analysis only using subjects with good interviews.

Results: Based on 3 cases being exposed, for sinonasal cancer an adjusted odds ration of 5.9 (95 % CI, 2.2, 37.4) was found “for exposure to herbicides containing 2,4,5-T”. The odds ratio for nasopharyngeal cancer was close to unity, but this was based on exposure of a single case.

Conclusion: The authors conclude that except for smoking and chlorophenol exposure, which are associated with both sites, the risk factor profiles may differ between sinonasal and nasopharyngeal cancers. The relatively high odds ratios for exposure to 2,4,5-T may be, despite the low sample size, implicative and noteworthy for further research. Caution should be taken in the interpretation of the results.

Evaluation: Unfortunately, “exposure to herbicides contained 2,4,5-T” is not defined within the study and no exposure assessment information was available. There is the possibility that there is some recall bias. Overall, this study adds to the evidence that there is an association between 2,4,5-T and sinonasal cancer, and not nasopharyngeal cancer. However, the small number of exposed cases, the wide confidence intervals, the possibility of recall bias, and the use of next-of-kin questionnaire for some cases but for no controls means that this study can only provides weak evidence for the possible relationship between 2,4,5-T and these tumours.
1  TOTAL CANCER

Overview
Cancer is a major cause of death in Australia. Each year, about 345,000 new cases of cancer are diagnosed in Australia, of which about 270,000 are non-melanocytic skin cancers. Excluding these, there were 77,666 new registrable cancer cases and 34,089 deaths due to cancer in 1996. Australian males have a 1:3 and females a 1:4 chance of developing cancer in their lifetime. The most common registrable cancers in 1996 were: colorectal (10,998 new cases), prostate (10,055); breast (9706); melanoma (7761); lung (7621) and: non-Hodgkin's lymphoma (3105).

As with most epidemiological studies, human evidence on associations between cancer and exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD are often limited by the lack of adequate exposure data. Most studies rely solely on interviews and questionnaires of work history as surrogate for exposure classifications, thereby limiting the strength of evidence by bias and chance. In addition, some studies are often limited to investigating cancer endpoints after only 10 or less years post exposure. This limits the possibilities of detecting cancers that may require a latency period of up to 30 years.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
IARC considered studies on cancer in occupationally exposed cohorts (including 10 publications on 2,4,5-T and/or 2,4-D exposure of NIOSH, BASF; IARC and other chemical worker cohorts, 8 publications on herbicide applicators and other occupationally exposed cohorts), environmentally exposed groups (4 publications on Seveso cohorts), Vietnam veteran studies (1 publication on Ranch Hand cohorts) and 24 case-control studies.

IARC notes that the human epidemiological evidence was not consistent for all studies, but did suggest a generalised excess of all cancer mortality without any site specificity in four highly exposed herbicide production cohorts (based on 5 studies) with well-documented exposure (total SMR = 1.4 (95% CI, 1.2-1.6). Epidemiological review from the most highly 2,3,7,8-TCDD exposed populations provided strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. There is evidence in some studies for a dose-response effect, however the data are not available for some of the larger studies. The overall findings are unlikely to be due to chance or confounding, although confounding cannot be ruled out. It is highlighted that the general population is exposed to levels far lower than those experienced by the industrial populations.

IARC concludes that 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor. This receptor is highly conserved in an evolutionary sense and functions the same way in humans and experimental animals. Tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimes in bioassays.

In its evaluation, more weight has been given by IARC to studies with direct 2,3,7,8-TCDD measurements and to studies involving heavy exposure to herbicides likely to be contaminated with 2,3,7,8-TCDD. Based on the evidence provided by the reviewed studies, IARC’s evaluation on the carcinogenicity of 2,3,7,8-TCDD states that there is limited evidence in humans for the carcinogenicity of 2,3,7,8-TCDD and that there is sufficient evidence in experimental animals for the carcinogenicity of 2,3,7,8-TCDD. Overall, 2,3,7,8-TCDD was classified as CARCINOGENIC TO HUMANS (GROUP 1).

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
ATSDR considered studies on cancer occupationally exposed groups (including 8 publications on cohorts with 2,4,5-T and/or 2,4-D exposure of NIOSH, BASF and other chemical worker cohorts, and 12 publications on herbicide sprayer cohorts), environmentally exposed groups (2 publications on Seveso cohorts), Vietnam veteran studies (3 publications on Ranch Hands and CDC cohorts) and 7 case-control studies.

ATSDR notes that the major weakness in most studies reviewed is the lack of adequate exposure data and concomitant exposure to other compounds. From its review, ATSDR conclude that the available epidemiological data suggest that 2,3,7,8-TCDD may be a human carcinogen. Statistically significant increases in risks for all cancers were found in highly exposed workers with longer latency periods. The estimated SMRs in these exposure groups were low, however, they were consistent across studies with the highest exposures. It was highlighted that the evidence for site-specific cancers is weaker, with some data suggesting a possible relationship between soft-tissue sarcoma, non-Hodgkin’s lymphoma, or respiratory cancer with 2,3,7,8-TCDD exposure. Overall, based on results of the epidemiology studies and the animal studies evaluated, ATSDR concludes that the 2,3,7,8-TCDD MAY BE A HUMAN CARCINOG.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
US EPA considered studies on cancer occupationally exposed groups (including 13 publications with 2,4,5-T and/or 2,4-D exposure of NIOSH, BASF; IARC and other chemical worker cohorts, 6 herbicide sprayers, 4 pulp and paper mill worker), environmentally exposed groups (10 publications on the Seveso cohort), Vietnam veteran publications (4 publications on the Ranch Hand cohort) and 16 case-control studies.

US EPA notes that the strongest evidence that exposure to 2,3,7,8-TCDD leads to an increased risk of generalised cancers at multiple sites is derived from four occupational cohorts and Seveso residents. These studies provide evidence of in vivo exposure to 2,3,7,8-TCDD with actual measurements of 2,3,7,8-TCDD serum levels in individuals, or their surrogates positively correlated with significantly increased risks of cancer mortality. Other studies report little or no increased risk of cancer. These generally suffer from
one or more deficiencies that render them not relevant to provide information that could assist in determining the carcinogenicity of dioxins.

US EPA concludes that, although there are uncertainties associated with the epidemiological evidence that could have influenced the risk estimates rendering the data “limited”, the overall weight of evidence from the epidemiological studies suggests that the generally increased risk of overall cancer is more likely than not due to exposure to 2,3,7,8-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 2,3,7,8-TCDD to be a multisite, multisex, and multispecies carcinogen with a mechanistic basis.

In their evaluation, based on the weight of all of the evidence (human, animal, mode of action), 2,3,7,8-TCDD meets the stringent criteria that allows EPA and the scientific community to accept a causal relationship between 2,3,7,8-TCDD exposure and cancer hazard (U.S. EPA, 2000b), and is characterised as a HUMAN CARCINOGEN.

WORLD HEALTH ORGANIZATION 2002
WHO/IPCS considered site specific hormonally influenced cancers (breast cancer, endometriosis, testicular cancer, prostate cancer and thyroid cancer) rather than total cancer. From its review, WHO/IPCS concluded that although there is biological plausibility and some experimental evidence that EDCs may contribute to hormonally influenced human cancer, the current state of the science has not provided clear evidence for a causal link. It is highlighted that further research should focus on the assessment of exposure to endocrine disruptors during critical periods of human development. No separate evaluation outcomes were provided.

NATIONAL ACADEMY OF SCIENCES 2002
NAS investigates a range of site specific cancers rather than total cancer. These are summarised in the following sections. No conclusions or separate evaluation outcomes were provided by NAS regarding total cancer outcomes.

Literature Updates
A meta-analysis of dioxin cancer dose response was performed by (Crump et al., 2003) using three cohorts of chemical production workers. The workers were exposed to 2,4,5-T, its co contaminant 2,3,7,8-TCDD, 2,4-D (and other pesticides). The study utilised the detailed exposure assessments, categorised into quartiles or septiles by the original studies (and converted them to cumulative serum TCDD concentrations). A statistically significant (p=0.02) trend was found in total cancer mortality with increasing dioxin exposure. The results indicated that dioxin carcinogenicity is not limited to populations with very high exposures. The trend tests showed an increase in total cancer at cumulative TEQ serum levels that would result in a lifetime (70 years) intake of 7 pg TEQ/kg body weight/day (cumulative TEQ = 3988 ppt-years). The dose-response assessments carried out for dioxin and cancer suggest that dioxin TEQ exposures within approximately 3-fold of current background levels may be carcinogenic. The authors considered background exposure and lag time for cancer mortality. Possible confounding by individual factors (e.g. life style habits and exposure to other chemicals) could not be controlled, however, was addressed as a total using the modelling approach. Overall, the use of serum TCDD as a dose surrogate and an increased sample size through data pooling, in combination with the demonstrated dose-response relationship and significant increased risks provide strength to the reported association between cancer and exposure to dioxins.

A cohort study by (Revich et al., 2002) investigated the development of malignant tumours in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have demonstrated elevated serum dioxin concentrations), however, it uses a comparison group from the regional area. The results showed a statistically higher mortality caused by malignant tumours compared to the expected values. The relative risk for men of cancer morbidity and mortality showed relatively high odds ratios and narrow confidence intervals with 1.9 (95% CI, 1.8-2.1) and 1.8 (95% CI, 1.6-1.9), respectively. This was not the case for females, however. Important limitations of this study include the use of residency as a surrogate for exposure without more detailed information, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, although a significant association was observed between cancer morbidity and mortality in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

A pooled analysis of a cross-sectional, baseline and a follow-up morbidity study (Sweeney et al., 2002) investigated cancer mortality in chemical plant workers who were exposed to 2,4,5-T, 2,4-D and the co-contaminant 2,3,7,8-TCDD (and other pesticides) for a period of 2 to 35 years. Serum TCDD concentrations in 273 living cohort members were used as an exposure surrogate (mean 220 ppt in workers and 7 ppt in referents). Subject exposure was correlated and classified according to their job history. A general, dose-related increase in mortality was observed from all cancers and did not appear to be related to excess in any specific type of cancer. The results showed statistically significantly increased total cancer mortality in the two highest cumulative-exposure septile groups (SMR=1.68; 95% CI, 1.19-2.30). The highest rate of cancer was most evident in workers at the highest exposure categories. The authors concluded that these results suggest that overall cancer mortality was influenced by high, long-term 2,3,7,8-TCDD exposure. Overall, the study uses well-designed (although only briefly described in the paper) previously published results from the NIOSH cohort and has the advantage of relatively large sample sizes. The main limitation of the study is the relatively limited knowledge on the exposure of individuals and the categorisation of exposure based on serum TCDD from a living subgroup of workers and job details. Hence, the relatively high SMR is somewhat limited by the introduction of chance.
Biological Plausibility

NAS (NAS, 2002), IARC (IARC, 1997) and US EPA (U.S. EPA, 2000c) provide a comprehensive summary and update of biological plausibility of 2,3,7,8-TCDD, 2,4,5-T and 2,4-D carcinogenicity. Animal studies have shown that 2,3,7,8-TCDD can cause cancers or act as tumour promotor, however, the mechanism of action is not established to date. The effect of 2,3,7,8-TCDD on a variety of growth regulation, hormone systems and other cellular process regulating factors may influence tumour formation. Studies to date indicate complex hormonal interactions may be involved in 2,3,7,8-TCDD-induced carcinogenesis. Animal studies have found the incidence of cancer varies at multiple sites rather than an increase in site-specific cancers in 2,3,7,8-TCDD-treated animals. The findings in human epidemiology studies of occupationally exposed individuals suggest an increased risk of generalised cancers at multiple sites. The consistency of this finding as corroborated by animal studies suggests 2,3,7,8-TCDD is acting as a multisite, multispecies carcinogen. This finding of increased risk at multiple sites in exposed humans appears to be theoretically plausible, given there is a body of evidence about the mechanism of dioxin action and the fundamental level at which this class of compounds appears to act on gene expression and cellular regulation in target tissues. The IARC have stated that the “lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution”. The mechanistic basis of 2,3,7,8-TCDD cancer induction remains to be elucidated.

Many phenoxy herbicides, particularly 2,4-D have been under review by the EPA during the last decade, primarily because of inconsistencies in reported animal studies (Charles et al., 1996) as well as a body of epidemiological evidence that suggested a relationship between exposure to these chemicals and development of cancer (reviewed by (Munro et al., 1992)). However, equivocal results and outdated methodologies in some of these studies highlight that conclusions on carcinogenicity of these herbicides should be interpreted with caution. With a few exceptions (e.g. at high concentrations), the available evidence indicates both 2,4-D and 2,4,5-T are not genotoxic and are not being considered potential human carcinogens.

1.1 GASTROINTESTINAL TRACT TUMOURS

Overview

Gastrointestinal tract tumours include colon cancer, rectal cancer, stomach cancer and pancreatic cancer. Bowel cancer is the second most common cause of cancer-related death (after lung cancer) affecting 6% of population in western industrialised countries (3% of whom die). The colon and rectum are parts of the body’s digestive system, which remove nutrients from food and store waste until it passes out of the body. Together, the colon and rectum form the large intestine (or large bowel). The colon represents the first 6 feet of the large intestine, and the rectum the last 8-10 inches. Cancer that begins in the colon is called colon cancer, and cancer that begins in the rectum is called rectal cancer. Cancers affecting either of these organs may also be called colorectal cancer. Australian normative data on this type of cancer is provided in Appendix 1.

Risk factors for gastrointestinal cancers include age, family history of the same form of cancer, some disease of the affected organ and dietary factors. Gastrointestinal cancers are most common in people over 50 and associated with diets high in fat and calories and low in fibre. Cigarette smoking is considered a risk for pancreatic cancer and possibly stomach cancer. Infection with bacterium Helicobacter pylori also increases the risk of stomach cancer and colon cancer can develop with other conditions, such as ulcerative colitis, a chronic inflammation of the bowel.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
IARC reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. Gastrointestinal tumours were investigated in 5 publications on occupationally exposed cohorts (including 2,4,5-T exposure of BASF, NIOSH, IARC, other chemical worker cohorts and herbicide sprayers), 2 publications on environmentally exposed groups (Seveso residents), 1 study on Vietnam veterans (Ranch Hands), and one case control study. In the 5 most highly exposed occupational cohort studies, gastrointestinal cancers did not show significant standard mortality ratios (overall SMR = 1.2 (95% CI, 0.9-1.5). No evaluation was undertaken with regards to an association between exposure to dioxins and gastrointestinal cancers in particular. For more detailed information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998

ATSDR considered studies with focus on total cancer. Few studies on specific site cancers are mentioned in the review and, no evaluation was undertaken with regards to an association between exposure to dioxins and gastrointestinal cancers in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides evidence for an association between cancer and exposure to 2,3,7,8-TCDD. The key evidence for this association is derived from 2,4,5-T (and other herbicide production) cohorts and the Seveso cohorts, exposed to relatively high concentrations of 2,3,7,8-TCDD. The results of the Literature Updates were consistent in this finding, however, were limited by confounding, bias or chance to varying degrees. The putative causal link is biologically plausible and dose-response and analogous effects were demonstrated in experimental animals. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that a PROBABLE CAUSAL LINK exists between total cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

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conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
Studies considered by WHO/IPCS were limited to specific site hormonally influenced cancers (breast cancer, endometriosis, testicular cancer, prostate cancer and thyroid cancer). For information on WHO/IPCS’s review on these cancers, see section 1 “Total Cancer” and section 1.10 testicular cancer. No review or evaluation was undertaken with regards to an association between EDC and gastrointestinal cancers.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed two additional studies for its 2002 Update, including a cohort study investigating an occupationally exposed cohort (2,4-D production) and residents of Chapaevsk, Russia exposed to a mixture of industry emissions (including dioxins). Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of BASF, NIOSH and other chemical worker cohorts, paper mill workers and agricultural workers), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that these studies generally show relative risks close to unity and do not provide evidence of any increased risk. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE EVIDENCE OF NO ASSOCIATION between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and gastrointestinal cancers.

Literature Updates
A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including rectal and colon cancers in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed statistically weak but significantly increased morbidity in male residents from rectal cancer OR = 1.6 (95% CI, 1.1-2.4) and borderline elevated rectal cancer mortality 1.5 (95% CI, 1.0-2.4), respectively. These results were not significant for females. Morbidity and mortality from colon cancer were not significant in males OR = 1.6 (95% CI, 0.9-1.9) and 1.3 (95% CI, 0.8-2.2), respectively, nor females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data.

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides no evidence of an association between gastrointestinal cancers and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Update indicated increased rectal cancer morbidity, however, due to its considerable limitations this study can provide little evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, however, animal studies do not support associations with gastrointestinal cancers specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is EVIDENCE OF NO CAUSAL LINK between gastrointestinal cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.2 HEPATOBILIARY CANCER

Overview
Hepatobiliary cancers include cancer of the liver and the intrahepatic bile duct. Known risk factors for these types of cancers include chronic infection with hepatitis B or C virus and exposure to aflatoxin and vinyl chloride. An increase of hepatobiliary cancer with increasing age occurs in the general population and is greater in men than women. Misclassification of metastatic cancers as primary liver cancer can lead to overestimating of deaths due to liver cancer. Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to hepatobiliary cancers. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”. 

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
US EPA reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. No specific review or evaluation was undertaken by US EPA with respect to gastrointestinal cancers. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to gastrointestinal cancers specifically no animal studies have found an increased incidence after exposures to the chemicals of interest (NAS, 2002).
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and hepatobiliary cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to hepatobiliary cancers. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and hepatobiliary cancers.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed one additional study for the 2002 Update, investigating residents of Chapaevsk, Russia exposed to a mixture of industry emissions (including dioxins). Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of BASF, IARC, NIOSH and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that these studies provide inadequate evidence to link herbicide exposure to hepatobiliary cancer. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and hepatobiliary cancers.

Literature Updates
A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including hepatobiliary cancers in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed statistical significantly increased morbidity in male residents from liver and gall tract cancer morbidity 4.3 (95% CI, 2.9-6.2). These results were not significant for females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and lifestyle habits cannot be ruled out. Overall, although a significant association was observed between liver and gall tract cancer morbidity in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to hepatobiliary cancers specifically high doses of 2,3,7,8-TCDD showed significant increases in the incidence of neoplasia in the liver, hepatocellular carcinomas and toxic hepatitis in rats and mice of both sexes.

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence for an association between hepatobiliary cancers and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Update indicated increased morbidity from liver and gall tract cancers, however, due to its considerable limitations this study can provide little evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, and animal studies do support associations with liver cancers specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE to evaluate whether and association exists between hepatobiliary cancers and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.3 Cancers of the Head and Neck
Overview
Cancers of the head and neck are a group of malignancies involving the tongue, salivary gland, gum, floor of mouth, other and unspecified parts of mouth, oropharynx, nasopharynx, hypopharynx as well as other sites within the lip, oral cavity and pharynx (including ICD 10 Codes C01 to C14). Australian normative data on this type of cancer is provided in Appendix 1.

As with cancer of the respiratory tract, cigarette smoking is a known risk factor for cancers of the head and neck and exposure to other compounds such as nickel, chromium, wood dust, formaldehyde, salt-preserved foods are confounding for some of the cancers of the head and neck. Most studies have not been able to control for this confounding influence. There also appears to be a synergistic effect with alcohol consumption and these types of cancer and genetic factors may play a role in some types.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
IARC reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. Cancers of the head and neck were investigated in 1 publication on occupationally exposed cohorts (including phenoxy herbicide exposure) and a case control study on nasal and nasopharyngeal cancer. No
evaluation was undertaken with regards to an association between exposure to dioxins and cancers of the head and neck in particular. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and cancers of the head and neck in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with regards to cancers of the head and neck. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and cancers of the head and neck.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed one additional study for the 2002 Update, investigating residents of Chapaevsk, Russia exposed to a mixture of industry emissions (including dioxins). Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC and other chemical worker cohorts, paper and pulp mill workers and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that these studies provide only sparse information to link herbicide exposure to nasopharyngeal cancers. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and nasopharyngeal cancers.

Literature Updates
A case control study by (Zhu et al., 2002), investigated risk factors between sinonasal and nasopharyngeal cancers in Vietnam veterans. A variety of risk factors were investigated, including exposure to 2,4,5-T. Unfortunately, “exposure to herbicides contained 2,4,5-T” was not further defined within the study and no exposure assessment information was available. Cancers were identified using the U.S. cancer registries and confirmed by study pathologists. Controls were selected by random digit dialling. Based on 3 cases exposed, for sinonasal cancer an adjusted odds ration of 5.9 (95 % CI, 2.2; 37.4) was found “for exposure to herbicides containing 2,4,5-T”. The odds ratio for nasopharyngeal cancer was close to unity, but this was based on exposure of a single case. The authors conclude that the relatively high odds ratios for exposure to 2,4,5-T may be, despite the low sample size, implicative and noteworthy for further research. There is the possibility that there is some recall bias. Overall, this study suggests that there is an association between 2,4,5-T and sinonosal cancer, and not nasopharyngeal cancer. However, the small number of exposed cases, the wide confidence intervals, the possibility of recall bias, and the use of next-of-kin questionnaire for some cases but for no controls means that this study can only provides limited evidence for the possible relationship between 2,4,5-T and these tumours.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to cancers of the head and neck specifically, no animal studies have found an increased incidence of nasopharyngeal cancer (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence for an association between cancers of the head and neck and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Update indicted an association between 2,4,5-T and sinonasal cancer, however, due to its limitations this study can provide little evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, however, animal studies do not support associations with cancers of the head and neck specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE to evaluate whether and association exists between cancers of the head and neck and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.4 LARYNGEAL CANCER
Overview
Laryngeal cancer is a malignant disease that arises from the tissue of the larynx (or “voice box”). The most common type is a squamous cell carcinoma. The tumour is related to cigarette smoking. Laryngeal cancer is much less common than lung cancer, so it is more difficult to make meaningful observations about laryngeal cancer. The tumour is more common in men than woman. Australian normative data on this type of cancer is provided in Appendix 1.

Cigarette smoking often confounds studies of the relationship between herbicides and dioxin and laryngeal cancer. Although most studies have been unable to control for cigarette smoking, several reviews have concluded that it is likely that many of the observations of populations exposed to herbicides could have resulted from smoking alone. Other risk factors include alcohol consumption, gastroesophageal reflux, human papilloma virus, a weakened immune system and occupational exposure to asbestos and some chemicals and dusts (NAS, 2002).
Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to laryngeal cancers. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and laryngeal cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to laryngeal cancers. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDC and laryngeal cancers.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed two additional studies for the 2002 Update, including a study of Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins) and an investigation of Swedish lumberjacks exposed to phenoxyacetic herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of BASF, IARC, NIOSH and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts)

NAS concludes that these studies provide only limited evidence to link herbicide exposure to laryngeal cancer. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE EVIDENCE of an association between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and laryngeal cancers.

Literature Update

A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including laryngeal cancers in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed statistical significantly increased mortality in male residents from laryngeal cancer mortality 2.3 (95% CI, 1.2-3.8). Significantly lower laryngeal cancer mortality was observed in females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, although a significant association was observed between laryngeal cancer mortality in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

A pooled analysis of a cross-sectional, baseline and a follow-up morbidity study by (Sweeney et al., 2002) investigated cancer mortality, including laryngeal cancer in chemical plant workers who were exposed to 2,4,5-T, 2,4-D and the co-contaminant 2,3,7,8-TCDD (and other pesticides) for a period of 2 to 35 years. Serum 2,3,7,8-TCDD concentrations in 273 living cohort members were used as exposure surrogate (mean 220 ppt in workers and 7 ppt in referents). Subject exposure was correlated and classified according to their job history. A general, dose-related increase in mortality was observed from all cancers and did not appear to be related to excess in any specific type of cancer. Mortality was statistically significantly higher than expected for cancers of the larynx (SMR=2.22; 95% CI, 1.06-4.08). The results also showed statistically significantly increased total cancer mortality in the two highest cumulative-exposure seperte groups (SMR=1.68; 95% CI, 1.19-2.30). The highest rate of cancer was most evident in workers at the highest exposure categories. The authors concluded that these results suggest that overall cancer mortality was influenced by high, long-term 2,3,7,8-TCDD exposure. Overall, the study uses well-designed (although only briefly described in the paper) previously published results from the NIOSH cohort and has the advantage of relatively large sample sizes. The main limitation of the study is the limited knowledge on the exposure of individuals and the categorisation of exposure based on serum 2,3,7,8-TCDD from a living subgroup of workers and job details. Hence, the observation is limited by the potential for chance.

Biological Plausibility

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to laryngeal cancer, it should be noted that there is an important argument of analogy. The larynx is very closely related in embryology, anatomy and function to the bronchus and the lower respiratory tract. Most of the aetiological factors that have been found to be of importance in lung cancer have also been found to be of aetiological significance in laryngeal cancer. However, no animal studies have found an increased incidence of laryngeal cancer associated with exposure to 2,3,7,8-TCDD and phenoxy herbicides (NAS, 2002).

Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides only weak evidence for an association between laryngeal cancers and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. The relative rarity of this cancer results in wide confidence intervals and not all studies show consistency in trend. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Updates suggest
an association between laryngeal cancer and exposure to dioxins and/or 2,4,5-T and 2,4-D, however, due to their limitations these study cannot provide strong evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, however, animal studies do not support associations with laryngeal cancers specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK of an association between laryngeal cancers and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.5 LUNG CANCER

Overview

Lung cancer is a malignant disease of the tissues of the lung. In Australian males, it is the most common cause of death from cancer. There are several different histological types of lung cancer, with approximately 40% adenocarcinomas, 25% small cell carcinomas and 15% epidermoid or large cell carcinoma. The main types of lung cancer are identified collectively as bronchogenic carcinoma, or carcinoma of the lung. The lung is often a site for the development of metastatic cancer. Australian normative data on this type of cancer is provided in Appendix 1.

A number of risk factors are known to be associated with lung cancers, including cigarette smoking, exposure to asbestos, chromium, nickel, aromatic hydrocarbons and radioactive ores. The American Cancer Society estimated approximately 90% of male lung cancer incidences to be due to tobacco smoking. Epidemiological studies on dioxin- and/or phenoxy herbicide-exposed populations have often not controlled for cigarette smoking or other confounders.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997

IARC reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. Specific cancers reviewed in more detail are limited to STS, lung cancer, NHL, haematopoietic tumours, colon and nasopharyngeal/nasal cancers. Lung cancers were investigated in 7 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, other chemical worker cohorts and herbicide sprayers), 3 publications on environmentally exposed groups (Seveso residents), and 1 study on Vietnam veterans (Ranch Hands).

In the 5 most highly exposed occupational cohort studies, lung cancers showed statistically elevated standard mortality ratios (overall SMR = 1.4 (95% CI, 1.1-1.7)). The findings were evaluated as being unlikely due to chance and that these lung cancer results are not the result of confounding by cigarette smoking, although the strength of the association is low. IARC concluded that epidemiological data from 5 occupationally exposed cohort studies provide strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. For more detailed information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998

ATSDR considered studies with focus on total cancer. Few studies on site specific cancers are mentioned in the review and, no evaluation was undertaken with regards to an association between exposure to dioxins and lung cancer in particular, although in its conclusion, ATSDR states that some epidemiology studies of highly exposed workers with long latency periods suggest a possible relationship between 2,3,7,8-TCDD exposure and respiratory cancers. For more detailed information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000

US EPA reviewed studies with focus on evaluating the evidence of an association of all cancers, rather than each particular cancer site. Specific site cancers reviewed in more detail were limited to STS, NHL and lung cancer. Lung cancer was investigated in 13 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, BASF and other chemical worker cohorts), 2 publications on environmentally exposed groups (Seveso residents and Yusho patients), and 1 study on Vietnam veterans (Ranch Hands).

US EPA concludes that both the Yusho patients and the most highly exposed occupational cohorts show a significant risk of lung cancer. No further evaluation was undertaken with respect to lung cancer specifically. For more detailed information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and lung cancer.

NATIONAL ACADEMY OF SCIENCES 2002

NAS reviewed three additional studies for the 2002 Update, including a study of Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins), an investigation of a Dow Chemical Company cohort who were involved in the manufacture of 2,4-D and an investigation of Swedish lumberjacks exposed to phenoxyacetic herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of BASF, IARC, NIOSH and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that evidence remains inconclusive but suggestive regarding an association between exposure to at least one of the chemicals of interest and lung cancer. Absence of data on smoking and other confounding factors limits the usefulness of the currently available studies. The key evidence for an association is based on the NIOSH cohort, which experienced some of the highest 2,3,7,8-TCDD exposures of any population studied. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE EVIDENCE of an association between exposure to at least one of the
chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and lung cancer.

**Literature Update**

A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including lung cancer in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed statistically significantly increased morbidity and mortality in male residents from lung cancer morbidity 3.3 (95% CI, 2.9-3.7) and 3.1 (95% CI, 2.6-3.5), respectively. These results were also significant for females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, although a significant association was observed between lung cancer mortality and morbidity in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

A pooled analysis of a cross-sectional, baseline and a follow-up morbidity study by (Sweeney et al., 2002) investigated cancer mortality, including laryngeal cancer in chemical plant workers who were exposed to 2,4,5-T, 2,4-D and the co-contaminant 2,3,7,8-TCDD (and other pesticides) for a period of 2 to 35 years. Serum TCDD concentrations in 273 living cohort members were used as exposure surrogate (mean 220 ppt in workers and 7 ppt in referents). Subject exposure was correlated and classified according to their job history. A general, dose-related increase in mortality was observed from all cancers and did not appear to be related to excess in any specific type of cancer. The results also showed statistically significantly increased total cancer mortality in the two highest cumulative-exposure septime groups (SMR=1.68; 95% CI, 1.19-2.30). The highest rate of cancer was most evident in workers at the highest exposure categories. Significantly increased total cancer mortality and mortality from lung cancer was observed in the defined exposure cohort (p=0.02 and p=0.05, respectively). The trend test for lung cancers was also statistically significant using log cumulative exposure and a 15-year lag. The authors concluded that these results suggest that overall cancer mortality was influenced by high, long-term 2,3,7,8-TCDD exposure. Overall, the study uses well-designed (although only briefly described in the paper) previously published results from the NIOSH cohort and has the advantage of relatively large sample sizes. The main limitation of the study is the limited knowledge on the exposure of individuals and the categorisation of exposure based on serum TCDD from a living subgroup of workers and job details. Hence, the observation is limited by the potential for chance.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to lung cancer, there is evidence of increased incidence of squamous-cell carcinoma of the lung in rates exposed to high concentrations of 2,3,7,8-TCDD, although the relevance to human exposure is not clear. Mechanistic studies support a role of 2,3,7,8-TCDD as a promoter in the carcinogenic process and lung tissue has been found to have high concentrations of the Ah receptor that mediates 2,3,7,8-TCDD effects. In addition, CYP1A1 and CYP1A2 have been shown to be expressed in human lung biopsies (NAS, 2002).

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides only weak evidence for an association between lung cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Updates indicate that such an association exists, however, due to their limitations or relatively wide confidence intervals, these studies can only provide weak evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, and animal studies support associations with lung cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a **POSSIBLE CAUSAL LINK** of an association between lung cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

### 1.6 Bone Cancer

**Overview**

Bones are a common site for secondary, metastasised tumours, whereas primary bone cancers are rare and among the least frequent types of cancer. Australian normative data on this type of cancer is provided in Appendix 1.

The incidence of bone cancer in herbicide/dioxin exposed cohorts is typically low resulting in difficulties of interpreting results. Risk factors for adults include exposure to ionising radiation in treatment for other cancers and a history of other, non-cancer bone diseases (NAS, 2002).

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

No specific review or evaluation was undertaken with respect to bone cancer. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and bone cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

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U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to bone cancers. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDC and bone cancer.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed one additional study for the 2002 Update, investigating Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins). Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Ranch Hand and other veteran cohorts)

NAS concludes that these studies provide little information to link herbicide exposure to bone cancer. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT information to determine if an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and bone cancer.

Literature Updates
A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including bone cancer in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed no statistically increased morbidity or mortality in male residents from bone cancer 2.3 (0.8-5.0), mortality 2.1 (95% CI, 0.9-4.4), respectively. These results were also not significant for females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, although a significant association was observed between bone cancer mortality and morbidity in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to bone cancer, no animal studies have reported increased incidences of bone cancer from exposure to dioxins or phenoxy herbicides to date (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides only little evidence for an association between bone cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The result of the Literature Update indicate that such an association exists, however, due to its considerable limitations, this study can not provide strong evidence for such associations. The putative causal link of non-specific cancer is biologically plausible, however, no animal studies support associations with bone cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE to evaluate whether and association exists between bone cancer and exposure 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.7 SOFT-TISSUE SARCOMAS
Overview
Soft tissue sarcoma (STS) arises in the soft somatic tissues that occur within and between organs. Soft tissue sarcoma is a relatively rare condition and because of the diverse characteristics of soft tissue sarcoma accurate diagnosis and classification can be difficult. There exists inconsistency in studies considering the potential effects of herbicide and dioxin exposure and soft tissue sarcoma. This inconsistency may be due to variations in exposure assessment and in the predominant phenoxyacetic acid herbicide used in a geographic area. Issues of confounding by other exposures and assessment of exposure as well as potential for study bias need consideration. Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
IARC reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. Specific cancers reviewed in more detail are limited to STS, lung cancer, NHL, haematopoietic tumours, colon and nasopharyngeal/nasal cancers. STS was investigated in 5 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, other chemical worker cohorts and herbicide sprayers), 2 publications on environmentally exposed groups (Seveso residents), 1 study on Vietnam veterans (Ranch Hands) and 10 case control studies.

In the 5 most highly exposed occupational cohort studies, the overall SMR for STS was approximately 4.7. A trend of increasing risks with increasing exposure in these cohorts was found, and although confidence limits are broad, the test for trend gave p values of 0.04 for STS. A similar trend was also observed in the Seveso cohort, but only in the zone which overall had the lowest exposure. IARC concluded that epidemiological data from 5 occupationally exposed cohort studies provide strong evidence of increased risks for all cancers combined, along with less strong evidence of...
increased risks for cancers of particular sites. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and STS in particular, although in its conclusion, ATSDR states that some epidemiology studies of highly exposed workers with long latency periods suggest a possible relationship between 2,3,7,8-TCDD exposure and STS. For more detailed information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA reviewed studies with focus on evaluating the evidence of an association of all cancers, rather than each particular cancer site. Specific site cancers reviewed in more detail were limited to STS, NHL and lung cancer. STS was investigated in 14 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, BASF, other chemical worker cohorts and herbicide applicators), 4 publications on environmentally exposed groups (Seveso residents and Yusho patients), 3 study on Vietnam veterans (Ranch Hands) and 13 case control studies

US EPA concludes that because of conflicting data or even contradictory evidence regarding the likelihood of exposure to 2,3,7,8-TCDD, a direct linkage could not be made that exposure specifically increases risks of STS. Therefore, the epidemiological findings regarding an association between exposure to 2,3,7,8-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. No further evaluation was undertaken with respect to STS specifically. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**WORLD HEALTH ORGANIZATION 2002**

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and STS.

**NATIONAL ACADEMY OF SCIENCES 2002**

NAS reviewed one additional study for the 2002 Update, investigating the general population living near a chemical plant in northern Italy. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts)

NAS concludes that findings from prior occupational, environmental and veteran studies show sufficient evidence to link herbicide exposure to STS. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **SUFFICIENT EVIDENCE** of an association between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and soft tissue sarcomas.

**Literature Updates**

No Literature Updates were identified that investigated the association between soft tissue sarcomas and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to STS, no animal studies have reported increased incidences of STS from exposure to dioxins or phenoxy herbicides to date (NAS, 2002).

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association exists between soft tissue sarcomas and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD, however, some of the studies reviewed provide inconsistent results. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigate this association. The putative causal link of non-specific cancer is biologically plausible, however, no animal studies support associations with STS specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a **PROBABLE CAUSAL LINK** between STS and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

**1.8 SKIN CANCER**

**Overview**

Skin cancers include neoplasms that develop from malignant melanoma and non-melanocytic skin cancers. Malignant melanomas are malignant tumours that develop from melanocytes of the skin and elsewhere in the body. They are common in Australia. A known causal agent for these tumours is ultra-violet radiation. However, it seems that pulse radiation, or radiation on skin not acclimatised to high levels of UV radiation, is more likely to have a causal role than accumulative radiation. Non-melanoma skin cancer comprises all forms of skin cancer other than melanoma. It is the commonest form of cancer in Australia, and comprises two common types – basal cell carcinoma and squamous cell carcinoma. Australian normative data on this type of cancer is provided in Appendix 1.

All studies of skin cancer have been unable to adequately control for the effects of ultraviolet radiation. As many of the studies have involved populations whose ultraviolet exposure may have differed from expectation, this is an important confounder. Skin cancer in general is more likely to occur in fair-skinned people. The risk for dark-skinned people is approximately 20 times lower compared to that of white-skinned people (NAS, 2002).
Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to melanoma or non-melanoma skin cancers. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins melanoma or non-melanoma skin cancers in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to melanoma or non-melanoma skin cancers. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and melanoma or non-melanoma skin cancers.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed melanoma and non-melanoma skin cancers separately. The same additional 3 studies were considered for the 2002 Update for both melanoma and non-melanoma, including a study on Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins), Dow Chemical workers involved in the production of 2,4-D and forestry workers in Sweden exposed to phenoxy herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Australian veterans and other veteran cohorts)

NAS concludes that these studies provide little information on the association between exposure to herbicides and the incidence of melanoma or non-melanoma skin cancer. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT evidence to determine if an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and melanoma or non-melanoma skin cancer.

Literature Updates
No Literature Updates were identified that investigated the association between melanoma or non-melanoma skin cancer and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

Biological Plausibility
The biological plausibility of the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to skin cancer, animal studies have indicated that continuous dermal exposure to 2,3,7,8-TCDD can induce skin tumours (fibrosarcomas, not squamous-cell carcinomas) in laboratory mice. In vitro and in vivo mechanistic studies support a role of 2,3,7,8-TCDD as a promoter in the carcinogenic process (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between skin cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupational and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigate this association. The putative causal link of non-specific cancer is biologically plausible, and animal studies provide some indication on associations with skin cancers specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE at this stage to evaluate whether and association exists between skin cancers and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.9 PROSTATE CANCER

Overview
Prostate cancer is a malignant disease affecting the prostate. It is the malignancy that is most affected by age while the condition is has not been reported in individuals below the age of twenty. More than 95% of these cancers are adenocarcinomas. The disease has considerable geographic variation being more common in Western countries. Prostate cancer is hormone dependant, however, relatively little is known about the causes of prostate cancer (WHO/IPCS, 2002). Australian normative data on this type of cancer is provided in Appendix 1.

There are multiple difficulties involved in conducting epidemiological studies of this type of cancer. In particular, prostate cancer is a predominant disease among elderly males and several cohorts that have been exposed to phenoxy herbicides or dioxins contain too few members that are at the age when prostate cancer can be expected to allow for meaningful observations. Further, prostate cancer was not initially considered to be of interest in epidemiological studies. Another difficulty that exists with this tumour relates to the development of certain screening strategies, such as prostatic specific antigen (PSA) testing. This has resulted in the detection of sub-clinical cases, resulting in an increase in incidence rate without evidence of a change in mortality. It s not clear what effect (if any) this phenomenon has on studies of cancer in populations exposed to phenoxy herbicides and 2,3,7,8-TCDD.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to prostate cancer. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

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Page 40
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins prostate cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to prostate cancer. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
Studies considered by WHO/IPCS were limited to specific site hormonally influenced cancers (breast cancer, endometriosis, testicular cancer, prostate cancer and thyroid cancer). For more detailed information on WHO/IPCS’s review on cancers, see section 1 “Total Cancer” and section 1.10 “Testicular Cancer”. With respect to prostate cancer, WHO/IPCS highlights that the limited epidemiological data on potential associations between this type of cancer and exposure to environmental EDCs (including dioxins and PCBs) are derived predominantly from occupational exposures (PCB workers, Seveso residents, 2,4,5-T workers of the NIOSH and other cohorts, herbicide sprayers), and all studies lack internal exposure assessments.

WHO/IPCS conclude that experimental data show that the development of prostate cancer can be affected perinatal/postnatal exposure to estrogens and phytoestrogens and possibly androgens and Ah receptors. Studies on PCB, 2,3,7,8-TCDD and DDT exposures show no association with increased prostate cancer. While exposure to herbicides or polyaromatic hydrocarbons has been linked to prostate cancer, the evidence is weak, the mechanism unknown and more research is required to provide a better understanding of the effects of other environmental factors.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 3 additional studies for the 2002 Update, including a study on Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins), Dow Chemical workers involved in the production of 2,4-D and forestry workers in Sweden exposed to phenoxy herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH, BASF and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans and other veteran cohorts). The main evidence on prostate cancer was drawn from occupational studies investigating exposure to a variety of pesticides and herbicides and from Vietnam veteran studies.

NAS concludes that the data provided by these studies are equivocal. It is highlighted that for common diseases such as prostate cancer, relative risks are not expected to be high for a particular causative factor, since the background rates are elevated. Although the data on prostate cancer reviewed are mixed, it is noted that the majority of Vietnam veterans have not yet reached the age of higher incidence of this type of cancer and that morbidity is likely to represent a more sensitive outcome than mortality in this case. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE evidence of an association between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and prostate cancer.

Literature Updates
No Literature Updates were identified that investigated the association between prostate cancer and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to prostate cancer, to date animal studies have not shown increases in prostate cancer after exposure to the phenoxy herbicides or 2,3,7,8-TCDD. However, since the prostate is responsive to hormones and 2,3,7,8-TCDD has been shown to disrupt the endocrine system, the prostate may represent a target organ. This is supported by several studies demonstrating direct responses with respect to enzyme induction of human prostate cells to 2,3,7,8-TCDD. Epidemiological data suggest that exposure to 2,3,7,8-TCDD, in particular resulting in concentrations above 20 ppt serum TCDD, are associated with alterations in male reproductive hormone concentrations (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides some evidence that an association exists between prostate cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD, however, most studies are limited by possible confounding factors that provide alternative explanations for the observed results. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered, however, the key evidence stems from occupationally exposed chemical workers. No Literature Updates were identified that investigate this association. The putative causal link of non-specific cancer is biologically plausible, however, animal as well as epidemiological data provides only weak support for associations with prostate cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK between prostate cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.10 TESTICULAR CANCER

Overview
Testicular cancer is a malignant disease that affects the testicles. A major risk factor for testicular cancer is cryptorchidism, or undescended testes. Family history of the disease also appears to play a role. Several other hereditary and environmental factors have been suggested, but results of research regarding them are inconsistent (NAS, 2002). Testicular cancer is more likely to occur in men younger than 40 compared to older males. Further, the risk for testicular
cancer is approximately 40 times higher for Caucasians compared to African Americans. Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to testicular cancer. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins testicular cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to testicular cancer. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
Studies considered by WHO/IPCS were limited to specific site hormonally influenced cancers (breast cancer, endometriosis, testicular cancer, prostate cancer and thyroid cancer). With respect to testicular cancer, WHO/IPCS notes that there are no published epidemiological studies of testicular cancer with internal environmental EDC concentration assessments.

WHO/IPCS conclude that limited data from animal studies show that exposure of male foetuses to high levels of oestrogen may increase the risk of testicular cancer, however, no analytical epidemiological studies examine a connection between exposure to estrogenic or antiandrogenic compounds and that type of cancer.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 1 additional study for the 2002 Update, investigating Dow Chemical workers involved in the production of 2,4-D. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents and fishermen) and Vietnam veterans (Australian veterans and other veteran cohorts). Only few significant associations were observed among these studies.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT evidence to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and testicular cancer.

Literature Updates
No Literature Updates were identified that investigated the association between testicular cancer and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to testicular cancer, no animal studies have reported increased incidences of this cancer from exposure to dioxins or phenoxy herbicides to date (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between testicular cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigate this association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with testicular cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE at this stage to evaluate whether and association exists between testicular cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.11 Urinary Bladder Cancer
Overview
Urinary bladder cancer is the most common of the genitourinary tract cancers. It is the fourth most common cancer in men and the ninth most common in women. It can occur at any age but is more common in patients over 50. 75% diagnosed are between 48-80 years. The bladder is located in the lower abdomen, storing urine (waste produced when the kidneys filter the blood). The bladder has a muscular wall that can expand and shrink according to amount of urine being stored. The wall of the bladder is lined with several layers of transitional cells. Approximately 90% of bladder cancers are transitional cell carcinomas that begin in the cells lining the bladder. Cancer that is confined to the lining of the bladder is known as superficial bladder cancer. In some cases, cancer that begins in the transitional cells spreads through the lining of the bladder and invades the muscular wall of the bladder. This is known as invasive bladder cancer. For those diagnosed early there is a 5-year survival rate of 90%. Australian normative data on this type of cancer is provided in Appendix 1.

Cancers, smoking and exposure to occupational exposure to aromatic amines, PAHs, and some other organic chemicals used in the rubber, leather, textile and paint products are well-established confounders of epidemiological studies investigating urinary bladder cancer. Development of cancers subsequent to exposure requires a long latency period of up to 30 years. Some studies often encompass only 10 years which limits their ability to detect these cancers.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to urinary bladder cancer. For information on IARC’s
conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**Agency for Toxic Substances and Disease Registry 1998**
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and urinary bladder cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**U.S. Environmental Protection Agency 2000**
No specific review or evaluation was undertaken by US EPA with respect to urinary bladder cancer. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**World Health Organization 2002**
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and urinary bladder cancer.

**National Academy of Sciences 2002**
NAS reviewed 2 additional studies for the 2002 Update, including a study on Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins) and Dow Chemical workers involved in the production of 2,4-D. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH, BASF and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents and farm residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts). Only few significant associations were observed among these studies.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **insufficient evidence** to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and urinary bladder cancer.

**Literature Updates**
A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including urinary bladder cancer in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results showed statistically significant increased morbidity in male residents from urinary bladder cancer (OR=3.6 (95% CI, 2.6-4.9)). A significantly lower urinary bladder cancer morbidity was observed in females. Mortality from cancer of the urinary tract was also significantly increased in males (OR = 2.6 (95% CI, 1.7-3.6), but not in females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and lifestyle habits cannot be ruled out. Overall, although a significant association was observed between urinary bladder cancer mortality in men and exposure to dioxins, the overall strength of the association is severely limited by the lack of controlling for chance, bias and confounding.

A pooled analysis of a cross-sectional, baseline and a follow-up morbidity study by (Sweeney et al., 2002) investigated cancer mortality, including urinary bladder cancer in chemical plant workers who were exposed to 2,4,5-T, 2,4-D and the co-contaminant 2,3,7,8-TCDD (and other pesticides) for a period of 2 to 35 years. Serum TCDD concentrations in 273 living cohort members were used as exposure surrogate (mean 220 ppt in workers and 7 ppt in referents). Subject exposure was correlated and classified according to their job history. A general, dose-related increase in mortality was observed from all cancers and did not appear to be related to excess in any specific type of cancer. The results also showed statistically significantly increased total cancer mortality in the two highest cumulative-exposure septime groups (SMR=1.68; 95% CI, 1.19-2.30). The highest rate of cancer was most evident in workers at the highest exposure categories. Significantly increased cancer mortality from bladder cancer was observed (SMR=1.99; 95% CI, 1.13-3.23), however, was attributed to exposure to 4-aminobiphenyl at one plant. The authors concluded that these results suggest that overall cancer mortality was influenced by high, long-term 2,3,7,8-TCDD exposure. Overall, the study uses well-designed (although only briefly described in the paper) previously published results from the NIOSH cohort and has the advantage of relatively large sample sizes. The main limitation of the study is the limited knowledge on the exposure of individuals and the categorisation of exposure based on serum TCDD from a living subgroup of workers and job details. Hence, the observation is limited by the potential for chance.

**Biological Plausibility**
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to urinary bladder cancer, no animal studies have reported increased incidences of this cancer type from exposure to 2,3,7,8-TCDD to date (NAS, 2002).

**Conclusions and Overall Evaluation**
The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between urinary bladder cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates did not provide strong evidence for such an association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with urinary bladder cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is **insufficient evidence** at this
1.12 RENAL CANCER

Overview

Renal cell cancer is also called renal adenocarcinoma or hypernephroma. Approximately 85% of renal cell cancers are adenocarcinomas of which most are proximal tubular origin. The remaining 15% are transitional cell carcinomas of the renal pelvis. The renal structures are exposed to filterable substances (e.g. phenoxy herbicides and PAHs) that appear in the urine. The majority of patients are diagnosed when the tumour is relatively localised and amenable to surgical removal. Approximately 40% of all patients with renal cancer survive 5 years. Renal cell cancer is twice as common in men as in women and more likely to occur in people over 50. Smoking is a well-established risk factor for renal cancer. Other risk factors include some diseases, diet, weight and occupational exposure to asbestos and cadmium. Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to renal cancer. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and renal cancer in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to renal cancer. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and renal cancer.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 2 additional studies for the 2002 Update, including a study on Chapaevsk residents in Russia exposed to a mixture of industry emissions (including dioxins) and Dow Chemical workers involved in the production of 2,4-D. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents and farm residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts). Only few significant associations were observed among these studies.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INSUFFICIENT evidence to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and renal cancer.

Literature Updates

A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including urinary bladder cancer in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results on morbidity in male residents from renal cancer 1.2 (95% CI, 0.7-2.0) were not significant. These results were also not significant for females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, no significant association was observed between renal cancer morbidity in men and exposure to dioxins, however, the overall strength of these findings is severely limited by the lack of controlling for chance, bias and confounding.

Biological Plausibility

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to renal cancer, no animal studies have reported increased incidences of this cancer type from exposure to 2,3,7,8-TCDD to date (NAS, 2002).

Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between renal cancer and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates did not provide strong evidence for such an association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with renal cancer specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE at this stage to evaluate whether and association exists between renal cancer and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.
1.13 BRAIN TUMOURS

Overview
Cancers of and affecting the brain fall into numerous histologic types and subtypes. Meningiomas, which are cancers of the tissue surrounding the brain and spinal cord, do not arise from nerve tissue and do not share a similar risk profile with cancers that do. Metastases from cancers elsewhere in the body may be found in the brain and may be difficult to distinguish from primary brain cancers (NAS, 2002). Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to brain tumours. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken with regards to an association between exposure to dioxins and brain tumours in particular. For more information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to brain tumours. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and brain tumours.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 2 additional studies for the 2002 Update, including a study on Dow Chemical workers involved in the production of 2,4-D and Swedish lumberjacks exposed to phenoxyacetic herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents, fishermen and farm residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts). Only few significant associations were observed among these studies.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE EVIDENCE OF NO ASSOCIATION between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and brain tumours

Literature Updates
No Literature Updates were identified that investigated the association between brain tumours and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

Biological Plausibility
The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to brain cancer, no new studies suggest that 2,3,7,8-TCDD induces cancers of the brain. The evidence that exposure to 2,4-D in animals causes brain tumours remains questionable. In a study in which Fischer 344 rats received 2,4-D at 45 mg/kg of body weight, six of 60 male rats developed brain tumours compared to one control rat. However, that study has been criticised for several reasons, and brain tumours have not occurred in other studies (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between brain tumours and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated this association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with brain tumours specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is EVIDENCE OF NO CAUSAL LINK between brain tumours and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.14 NON-HODGKIN’S LYMPHOMA

Overview
Non-Hodgkin’s Lymphoma (NHL) is a term which represents a heterogeneous group of malignant neoplastic diseases arising from the malignant, monoclonal transformation of lymphoid components of the immune system, the common feature of which is the absence of the Reed-Sternberg cells characteristic of Hodgkin’s disease. It is also known as reticulosarcoma or lymphosarcoma. As a disease group NHL encompasses a range of histological types, cell lines and tumour grades. About 85% derive from B cells, and the remainder from T cells. Australian normative data on this type of cancer is provided in Appendix 1.

NHL is now the fifth most common incident cancer and cause of cancer death in the US (AIHW, 1998). For unknown reasons, non-Hodgkin's lymphomas have increased in frequency in most Western populations. In the United States the increase in incidence has been at the rate of 3-4% per year since 1950. Overall, between 1973 and 1997, NHL incidence in the US grew by 81% (AIHW, 1998). There have been alterations in disease classification and in the recognition of the disease, however, despite these factors the underlying incidence also appears to be experiencing a real and continuing increase. The search for the cause or causes of this increase has precipitated considerable exploratory and analytical epidemiological research. However, no clear risk factors have emerged for NHL in the general population, apart from severe immunosuppression.
**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC reviewed studies with focus on evaluating the evidence of an association of all cancers combined, rather than each particular cancer site. Specific cancers reviewed in more detail are limited to STS, lung cancer, NHL, haematopoietic tumours, colon and nasopharyngeal/nasal cancers.

Non-Hodgkin’s lymphoma was investigated in 7 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, other chemical worker cohorts and herbicide sprayers), 3 publications on environmentally exposed groups (Seveso residents), 1 study on Vietnam veterans (Ranch Hands) and 5 case control studies.

In the 4 most highly exposed occupational cohort studies, the overall SMR for NHL was significantly elevated (SMR = 2.6; 95% CI, 1.3-4.7), but there was no increased risk in the large NIOSH cohort. A trend of increasing risks with increasing exposure in these cohorts was found, and although confidence limits are broad, the test for trend gave p values of 0.1 for non-Hodgkin’s lymphoma. It was highlighted that although it is plausible that other chemicals cause non-Hodgkin’s lymphoma, strong potential confounding factors are not known. IARC also noted that the lack of complete consistency among the studies and the weak effect detected in most of the positive ones, however, caution against a causal interpretation of the findings.

Overall, IARC concluded that epidemiological data from 5 occupationally exposed cohort studies provide strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. For more detailed information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR considered studies with focus on total cancer. Few studies on site specific cancers are mentioned in the review and, no evaluation was undertaken with regards to an association between exposure to dioxins and non-Hodgkin’s lymphoma in particular, although in its conclusion, ATSDR states that some epidemiology studies of highly exposed workers with long latency periods suggest a possible relationship between 2,3,7,8-TCDD exposure and non-Hodgkin’s lymphoma. For more detailed information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA reviewed studies with focus on evaluating the evidence of an association of all cancers, rather than each particular cancer site. Specific site cancers reviewed in more detail were limited to STS, NHL and lung cancer. NHL was investigated from 12 publications on occupationally exposed cohorts (including 2,4,5-T exposure of NIOSH, IARC, BASF, other chemical worker cohorts, pulp and paper mill workers, and herbicide applicators) and 11 case control studies.

US EPA highlights that recent evidence suggests an association between NHL and exposure to the herbicide 2,4-D, which may contain dioxins other than 2,3,7,8-TCDD. The evidence from large industrial cohorts of NIOSH and IARC and the Seveso cohort suggest little if any evidence of increased risk of NHL. The case-control studies reviewed also do not indicate a consistent and pronounced increase in risk. It was concluded that at the present time, existing studies do not present a consistent picture of increased risks of malignant lymphoma among persons probably exposed to 2,3,7,8-TCDD. No further evaluation was undertaken with respect to NHL specifically. For more detailed information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**WORLD HEALTH ORGANIZATION 2002**

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and NHL.

**NATIONAL ACADEMY OF SCIENCES 2002**

NAS reviewed 3 additional studies for the 2002 Update, including a study investigating Swedish lumberjacks exposed to phenoxyacetic herbicides, Dow Chemical workers involved in the production of 2,4-D and 2 case-control studies. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents, case-control studies and other population studies) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that these studies provide sufficient evidence to support a conclusion of an association between NHL and exposure to the chemicals of interest. Most of the evidence suggests that 2,4-D or 2,4,5-T, rather than 2,3,7,8-TCDD, is responsible for the associations observed in occupational cohorts since the main cohorts with 2,3,7,8-TCDD exposure do not show increased rates of NHL. The key evidence stems from occupational and other cohorts in which subjects were exposed to a variety of herbicides and herbicide components. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **SUFFICIENT EVIDENCE** to conclude that an association exists between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and non-Hodgkin’s lymphoma.

**Literature Updates**

A pooled analysis of two case-control studies investigating exposure to pesticides and NHL and hairy cell leukaemia (HCL) was undertaken by (Hardell et al., 2002). The male study subjects were sourced from the Swedish population (NHL and HCL patients from cancer registries and control group from population registry) who recalled their exposure to a range of herbicides including 2,4,5-T and 2,4-D. An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, however only a marginal increase in risk was reported for low exposure to 2,4-D + 2,4,5-T (Total OR = 1.48; 95% CI, 0.99-2.20; low exposure OR = 1.87; 95% CI, 1.08-3.20; high exposure OR = 1.20; 95% CI, 0.68-2.08). No dose-response
was observed for 2,4,5-T + 2,4-D. The highest OR was seen when first exposure occurred 10-20 years before diagnosis (10-20 years OR = 2.87 (95% CI, 0.81-11); 20-30 years OR = 1.87 (95% CI, 0.98-3.53); >30 years OR = 1.15 (95% CI, 0.67-1.93)). This trend was significant in phenoxyacetic acids as a group (2,4,5-T +2,4-D including MCPA). For 2,4,5-T + 2,4-D the risk was highest for exposure 1-10 years prior to diagnosis, whereas no increased risk was seen for those with last exposure >10 years from the time of diagnosis (1-10 years OR = 4.31 (95% CI, 1.12-21); 10-20 years OR = 1.85 (95% CI, 0.90-3.78)). Exposure to phenoxyacetic acids during different decades from the 1940s to 1980s showed increased risks during recent decades (1940s OR = 1.46 (95% CI, 0.37-5.23); 1950s OR = 1.44 (95% CI, 0.91-2.26); 1960s OR = 1.68 (95% CI, 1.10-2.55); 1970s OR = 2.37 (95% CI, 1.42-3.95); 1980s OR = 3.25 (95% CI, 1.53-7.07). A potential recall bias cannot be excluded in this study, although farmers as occupation did not increase the risk, indicating that the outcomes are not explained merely by misclassification of exposure. Observational bias was minimised by blinded data gathering and analysis. Adjustments were made for vital status and geographical area to minimise heterogeneity between study designs. However, confounding factors were not addressed and therefore remain as potential alternative explanations. The authors used years of recalled exposure as surrogate for dose and exposure, which is limiting and may have introduced errors in the classifications of exposure, duration and latency of exposure.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to NHL, animal studies have shown increased rates of lymphoma exposed to high concentrations of 2,3,7,8-TCDD. Other animal studies have not shown such an increase (NAS, 2002).

### Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association exists between NHL and exposure to the herbicides 2,4,5-T and 2,4-D and 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered, however, the key evidence stems from phenoxy herbicide exposed cohorts. The Literature Update supports an association between NHL and exposure to 2,4-D and 2,4,5-T, however, internal exposure was not assessed in this study. The putative causal link of non-specific cancer is biologically plausible, however, no animal studies support associations with NHL specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a **Probable Causal Link** between NHL and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

### 1.15 Hodgkin’s Disease

**Overview**

Hodgkin’s disease is a neoplastic disease characterised by painless, progressive enlargement of lymph nodes, spleen, and general lymphoid tissues. The disease is distinct from Non-Hodgkin’s Lymphoma in its cell of origin, demographics, and genetics (NAS, 2002). Australian normative data on this type of cancer is provided in Appendix 1.

Hodgkin’s disease is a relatively rare condition. Hence, typically low numbers of cases are present in cohorts so that interpretation of results becomes difficult. Inconsistencies among epidemiological studies may be due to variations in exposure assessment and in the predominant phenoxyacetic acid herbicide used in a geographic area. Most supportive data has been gleaned from Scandinavian case-control studies. Issues of confounding by other exposures and assessment of exposure as well as potential for study bias need particular consideration in studies investigating Hodgkin’s disease.

**Synthesis of Key Reviews**

**International Agency for Research on Cancer 1997**

No specific review or evaluation was undertaken with respect to Hodgkin’s disease. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**Agency for Toxic Substances and Disease Registry 1998**

No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and Hodgkin’s disease in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**U.S. Environmental Protection Agency 2000**

No specific review or evaluation was undertaken by US EPA with respect to Hodgkin’s disease. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**World Health Organization 2002**

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and Hodgkin’s disease.

**National Academy of Sciences 2002**

NAS reviewed 1 additional study for the 2002 Update, investigating Dow Chemical workers involved in the production of 2,4-D. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents, case-control studies and other population studies) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that the relatively low incidence of HD complicates the evaluation of epidemiological studies addressing this tumour. The data from the reviewed studies combined demonstrates a pattern of increased mortality and morbidity risk. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **Sufficient Evidence** to conclude that an association exists.
between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and Hodgkin’s disease.

**Literature Updates**

No Literature Updates were identified that investigated the association between Hodgkin’s disease and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to Hodgkin’s disease, no new studies have found in increased incidence of HD after exposure to 2,4,5-T, 2,4-D or 2,3,7,8-TCDD. However, although it has not been demonstrated as clearly as for NHL, a positive association between 2,3,7,8-TCDD and the development of HD is biologically plausible due to their common lymphoreticular origin and common risk factors (NAS, 2002).

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association exists between Hodgkin’s disease and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated this association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with HD specifically, although the common origin and risk factors compared to NHL argue for a biological plausibility. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a **possible causal link** between HD and exposure to a mixture of 2,4,5-T, 2,4-D and 2,3,7,8-TCDD.

### 1.16 Multiple Myeloma

**Overview**

Multiple myeloma is a malignant disease of the plasma cells caused by proliferation of bone marrow stem cells resulting in an excess of neoplastic plasma cells and the production of excess abnormal proteins, usually immunoglobulins. The aetiology of this condition is not known. The incidence of the tumour increases with increasing age. Individuals with workplace exposure to rubber, leather, paint and petroleum and high exposure to ionising radiation are at greater risk. Increased incidence has been observed in various occupational groups including farmers and agricultural workers and those with workplace exposure to the above compounds. Australian normative data on this type of cancer is provided in Appendix 1.

**Synthesis of Key Reviews**

**International Agency for Research on Cancer 1997**

No specific review or evaluation was undertaken with respect to multiple myeloma. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**Agency for Toxic Substances and Disease Registry 1998**

No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and multiple myeloma in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**U.S. Environmental Protection Agency 2000**

No specific review or evaluation was undertaken by US EPA with respect to multiple myeloma. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

**World Health Organization 2002**

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and multiple myeloma.

**National Academy of Sciences 2002**

NAS reviewed 2 additional studies for the 2002 Update, investigating Dow Chemical workers involved in the production of 2,4-D and Swedish forestry workers exposed to phenoxy herbicides. Previous NAS reviews considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH and other chemical worker cohorts and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that these studies provide some evidence for an association, in particular occupational and other studies in which subjects were exposed to a variety of herbicides and herbicide components. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **limited or suggestive evidence** of an association between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and multiple myeloma.

**Literature Updates**

No Literature Updates were identified that investigated the association between multiple myeloma and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to multiple myeloma, no animal studies have found an increased incidence of MM after exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD (NAS, 2002).

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association exists between multiple myeloma and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and
environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated this association. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with multiple myeloma specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK between multiple myeloma and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

1.17 LEUKAEMIA

Overview
Leukaemia is a neoplastic proliferation of white blood cell precursors. There are four primary types of leukaemia. These are acute and chronic lymphoid leukaemia (ALL and CLL) and acute and chronic myeloid leukaemia (AML and CML). ALL occurs predominantly in younger people and people over 70 years old. A known risk factor for ALL is exposure to high doses of ionising radiation. AML is the most common form of leukaemia in adults. Incidence of AML increases in people over 40. Risk factors of AML include high doses of ionising radiation and occupational exposure to benzene, as well as some medications used in cancer chemotherapy. CLL is the most common form of leukaemia in males. CLL incidence increases with age in people over 30 years old. Exposure to ionising radiation is a known risk factor for CLL. Australian normative data on this type of cancer is provided in Appendix 1.

Synthesis of Key Reviews
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
No specific review or evaluation was undertaken with respect to leukaemia. For information on IARC’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
No evaluation was undertaken by ATSDR with regards to an association between exposure to dioxins and leukaemia in particular. For information on ATSDR’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
No specific review or evaluation was undertaken by US EPA with respect to leukaemia. For information on US EPA’s conclusions regarding total cancer evidence, see section 1 “Total Cancer”.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDC and leukaemia.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed CLL separately from the other forms of leukaemia due to the fact that CLL shares immunohistochemical characteristics, B-cell origin, and progression to an acute aggressive form of NHL, with NHL. With respect to leukaemia other than CLL, 3 additional studies were considered for the 2002 Update, investigating Dow Chemical workers involved in the production of 2,4-D, residents of Chapaevsk, Russia exposed to dioxins from chemical industry and Swedish forestry workers exposed to phenoxy herbicides. With respect to CLL, 6 studies (previously reviewed under leukaemia combined) that investigated CLL specifically were reviewed including a rural farming community in Michigan, a population based case-control study in an agricultural area of Italy, Danish gardeners exposed to pesticides, farmers in Nebraska, an epidemiological study of Iowa males who died of leukaemia and a population based case-control interview of Iowa men with leukaemia and a 20-year follow-up of Seveso residents. Previous NAS reviews on leukaemia combined considered occupationally exposed cohorts (including 2,4,5-T exposure of IARC, NIOSH, BASF and other chemical worker cohorts, paper mill workers and herbicide applicators), environmentally exposed groups (Seveso residents and farm residents) and Vietnam veterans (Australian veterans, Ranch Hand and other veteran cohorts).

NAS concludes that the reanalysis of studies on CLL specifically indicates that farming occupation, especially if there was exposure to the herbicides 2,4,5-T and 2,4-D is associated with significant risk of CLL mortality. Most of the cases of CLL and NHL reflect malignant transformation of B-lymphocyte progenitor cells, so that both may share a common etiology. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and leukaemias other than CLL. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is SUFFICIENT EVIDENCE of an association exists between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and CLL. .

Literature Updates
A cohort study by (Revich et al., 2002) investigated the development of malignant tumours, including leukaemia in the population of Chapaevsk who were exposed to dioxins (and potentially various other chemicals) from industry emissions. The study uses populations as the unit of analysis rather than individuals and individual exposure is unknown (although residents from Chapaevsk have been shown to have elevated serum dioxin concentrations in a previous study), however, it uses a comparison group from the regional area. The results on mortality of male residents from leukaemia were not significant (1.5 (95% CI, 0.8-2.7)). These results were also not significant for females. There are a number of significant limitations to this study, including the use of residency as a surrogate for exposure without more detailed information or sub-characterisation of different exposure groups based on occupation or location relative to the chemical plant, the population-based approach and the lack of information on the method of obtaining mortality data. Hence, confounding by other factors, such as exposure to other contaminants and life style habits cannot be ruled out. Overall, no significant association was observed between renal cancer morbidity in men and exposure to dioxins, however, the overall strength of these findings is severely
limited by the lack of controlling for chance, bias and confounding.

**Biological Plausibility**

The biological plausibility on the carcinogenicity of 2,3,7,8-TCDD and the phenoxy herbicides 2,4,5-T and 2,4-D is summarised in section 1 “Total Cancer”. With respect to leukaemia, no animal studies have found an increased incidence of leukaemia (including CLL) after exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD (NAS, 2002).

### Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between leukaemia and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. In contrast, the reanalysis with respect to CLL undertaken by NAS shows some evidence that an association exists between CLL and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered, however the key evidence for an association with CLL stems from exposure to the herbicides 2,4,5-T and 2,4-D. The Literature Update provides no further evidence for such associations, however, the study is limited by chance, bias and confounding. The putative causal link of non-specific cancer is biologically plausible, however no data support associations with leukaemia specifically. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a **POSSIBLE CAUSAL LINK** between CLL and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD, and that there is **INSUFFICIENT EVIDENCE** at this stage to evaluate whether and association exists between other forms of leukaemia and exposure 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

## 2 Neurobehavioral Disorders

### Overview

The nervous system consists of the central nervous system (CNS – brain and spinal chord) and the peripheral nervous system (PNS – spinal rootlets, brachial and lumbar plexus, and peripheral nerves). CNS dysfunction can be divided into two general categories: neurobehavioral dysfunction and motor sensory dysfunction. Neurobehavioral difficulties involve cognitive decline, including memory loss and dementia; and neuropsychiatric disorders, including neurasthenia (a collection of such symptoms as difficulty in concentrating, headache, insomnia and fatigue), depression, posttraumatic stress disorder and suicide. Motor dysfunction is characterised by such problems as weakness, tremors, involuntary movements, incoordination and walking abnormalities; these are usually associated with subcortical or cerebellar disorders. PNS dysfunctions, involving either the somatic nerves or the autonomic system, are known as peripheral. Australian normative data on neurobehavioral disorders is provided in Appendix 1.

A major difficulty in ascertaining neurobehavioral effects from dioxins and/or phenoxy herbicides is that many symptoms (e.g. depression) can be attributable to the situation that the subject has experienced (e.g. Vietnam War) or the more pronounced physical effects that have resulted from exposure (e.g. chloracne). In addition, many types of neurologic alterations are biochemical and show no abnormalities on scanning tests. Some symptoms of neurologic importance appear acutely but are short-lived, whereas others appear slowly and are detectable for extended periods.

### Synthesis of Key Reviews

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

Only few studies investigating neurobehavioral disorders were summarised by IARC. These included investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure) and environmentally exposed groups (Seveso residents). No review or evaluation was undertaken with regards to an association between dioxins and neurobehavioral effects.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR summarised studies investigating neurobehavioral disorders, including investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure), acute exposure cases, Vietnam veterans (including Ranch Hand cohorts) and environmentally exposed groups (Seveso residents). In its summary, ATSDR highlights that the neurological effects may be transient and therefore difficult to diagnose in studies conducted years after exposure. From its review, ATSDR concludes that the overall evidence suggests that adverse neurological effects may occur in subjects exposed to relatively high levels of dioxins, or at least to levels that cause frank dermal effects. It is further noted that the nervous system in adults does not seem to be a particularly sensitive target for 2,3,7,8-TCDD toxicity, but 2,3,7,8-TCDD may represent a neurological hazard to the developing organism by, for example, altering hormone levels at critical times during the maturation of the central nervous system.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA reviewed 10 case reports of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure of the BASF and other chemical worker cohorts, scientists involved in the synthesis of 2,3,7,8-TCDD, and herbicide applicators), 4 cross-sectional studies among occupationally exposed groups (TCP production), 3 cross-sectional studies among environmentally exposed groups (including Seveso and other residents) and 2 cross-sectional studies among Vietnam veterans (Ranch Hand cohorts). Additionally, 5 studies on infants were also included in the review.

From its review, US EPA concludes that these case reports and epidemiological studies demonstrate that exposure to 2,3,7,8-TCDD-contaminated materials is associated with symptoms referable to the central and peripheral nervous systems shortly after following exposure, and, in some cases, lasting many years. Overall however, neurologic status of workers, community residents and Vietnam veterans exposed to 2,3,7,8-TCDD and evaluated from 5-7 years after last exposure appears to be normal. Although exposure to 2,3,7,8-TCDD may have been extensive, the effects may have
been transient and studies conducted years after the last exposure would not detect such changes. These results suggest that in adults, no long-term neurologic effects were caused by even high exposure to 2,3,7,8-TCDD.

Based on its review of epidemiological and animal data, US EPA concludes that neurobehavioral disorders are described in humans shortly after exposure to 2,3,7,8-TCDD but were not observed as chronic effects. Hence, neurologic disorders were classified as ACUTE EFFECTS.

**WORLD HEALTH ORGANIZATION 2002**
WHO/IPCS considers epidemiological studies that provide information to evaluate to which extent neurobehavioral changes following exposure to neurotoxic chemicals may be related to mechanisms of endocrine disruption. Developmental and adult neurobehavioral effects are considered separately. Also considered in this section are animal experimental studies that provide information on alterations of thyroid hormones due to their established role in neural development. With respect to adult humans and PCBs or dioxins, WHO/IPCS considers 4 studies investigating occupational exposed cohorts (predominantly PCB exposed workers, firemen) and 1 environmentally exposed group (patients from the Yu-Cheng episode).

From its review, WHO/IPCS concludes that a number of neurobehavioral alterations have been reported to be associated with pre/neonatal exposure to mainly PCBs although discrepancies exist in terms of the spectrum of effects. It is further highlighted that although consistent hypothyroid effects have been found in association with dioxins and PCBs in the pre-/neonatal period, a causal role in neurobehavioral dysfunction cannot be deduced from available human data. Biological plausibility is provided by animal experimental studies on some potential EDCs that indicate effects on sex-dependent and sexual behaviours, mediated via sex steroids. EDCs may alter hormonal actions in various processes related to neural plasticity, rendering the nervous system more susceptible to harmful events and potentially impairing the ability of adult organisms to adapt to environmental changes. No further specific evaluation was undertaken by WHO/IPCS with regards to an association between EDC and neurobehavioral disorders.

**NATIONAL ACADEMY OF SCIENCES 2002**
NAS reviewed 3 additional studies for the 2002 Update investigating cognitive and neuropsychiatric effects, including one study of occupational exposure to 2,4,5-T, one study on Alzheimer’s disease after environmental exposure to herbicides and insecticides and one update study of Vietnam veterans (Ranch Hand cohort). With respect to motor or coordination dysfunction, the review for Update 2002 considered 4 studies on occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure and pesticides) and 3 case-control studies. With respect to chronic persistent peripheral neuropathy, 1 additional study on Vietnam veterans (Ranch Hand cohort) was considered. With respect to acute and subacute transient peripheral neuropathy, no new studies were identified for the 2002 Update.

Previous evaluations concerning cognitive and neuropsychiatric effects were based mainly on Vietnam veterans of Operation Ranch Hand. Evaluations of previous NAS Updates regarding motor or coordination dysfunction were based on patients with Parkinson’s disease exposed to various chemicals used as herbicides and pesticides and patients with amyotrophic lateral sclerosis occupationally exposed to various chemicals. With respect to chronic persistent peripheral neuropathy, the main data of previous reviews was derived from Vietnam veteran studies.

Overall, NAS concludes that these studies provide little evidence for an association. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and disorders involving cognitive and neuropsychiatric dysfunction, motor or coordination deficits, or chronic persistent peripheral neuropathy.

**Literature Updates**
A cohort study by (Ingel and Prikhozhan, 2002) investigated the relationship between emotional stress in female residents of Chapaevsk and toxicological and genetic values. Females of Chapaevsk, Russia with different exposures to dioxins were combined into three groups: “Zavod” - 15 female factory workers where contact with dioxins was possible (average age was 32.9 +/- 3.9 years); “Titovka” - 16 females living in Titovka (average age was 30.8 +/-4.0 years) who never had occupational contact with dioxins but who lived near the factory; “Nagorny” – 14 females living in “Nagorny” (average age was 32.7 +/-3.7 years) who have never had any occupational contacts with dioxins and lived in the area with insignificant amount of polychlorinated biphenyl’s in environment. Investigations of the level of chromosome aberrations in cells of peripheral blood, estimation of the severity of stress and the determination of the dioxin concentrations in serum were undertaken. Some characteristics of lifestyle were taken into account. Psychological testing of Chapaevsk females found that the defined groups (see above) differed by the degree of stress. The highest severity of stress was observed in females occupationally exposed to dioxins. Serum dioxin concentration was significantly correlated with the severity of stress (level of psychological depression and severity of overfatigue (p < or = 0.001) and levels and spectra of chromosomal aberrations in peripheral blood cells (p < or = 0.05, p < or = 0.01 in different tests). The authors concluded that exposure to dioxins can cause stress and be one of the reasons of high level of genetic disorders of Chapaevsk females. It was also concluded that the severity of stress could be used as an indicator of the general toxic situation and also for the estimation of the personal sensitivity of human genome to genotoxic factors in the environment. Although this study determined internal serum 2,3,7,8-TCDD concentrations, only a few individuals were available for this assessment, limiting the finding of a positive correlation between exposure to dioxins and emotional stress. The study is further limited by the relatively small number of subjects in each cohort.

A cohort study by (Michalek et al., 2003a) investigated associations between serum dioxin and psychological functioning in U.S. Air Force Veterans of the Vietnam War.
compared to other U.S. Air Force veterans who served in Southeast Asia during the same period. Each veteran was assigned to one of four exposure categories according to current level and back extrapolated initial dioxin level: comparison (TCDD\textsubscript{current} \leq 10 ppt), background (current \leq 10 ppt), low (current > 10 ppt; initial \leq 94 ppt), high (current > 10 ppt; initial \geq 94 ppt). Ranch Hand veterans with higher dioxin levels showed some difficulties in anxiety, somatization, depression, and a denial of psychological factors. However, those with background levels also showed indications of emotional distress, primarily in emotional numbness and liability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or behaviours. The authors concluded that few consistent psychological abnormalities are associated with dioxin exposure and Vietnam veterans. The study is well designed and uses relatively large cohorts, although the relatively low sample size in the high category may have limited statistical power. Adjustments were made for all known confounders. The main limitation of the study rests with the uncertainties regarding the categorisation of exposure based on serum dioxin concentrations up to 26 years after the exposure has ceased and the back extrapolation using one compartment, steady state pharmacokinetic modelling, in particular with respect to the comparison and background groups. Overall, this study provides good evidence that compared to other veterans of war, cohorts of the operation Ranch Hand are not experiencing significantly higher psychological problems.

A cohort study by (Pelclova et al., 2002) investigated neuropsychological functioning in 12 men from the former Czechoslovakia that were occupationally exposed to 2,4,5-T (contaminated with 2,3,7,8-TCDD) during 1965-1968. Mean estimated TCDD serum at time of intoxication was back extrapolated to 5000 ppt (256 ppt in 1996, range 14-760 ppt). Workers were given internal, neuropsychological and ophthalmological examinations. Neuropsychological findings were assessed as normal only in three persons with lower 2,3,7,8-TCDD plasma levels. Significant correlations of some neuropsychological impairment with serum TCDD levels were observed only in the 1996 examination. Only 2 subjects (1\textsuperscript{st} and 3\textsuperscript{rd} most exposed) still presented signs of chloracne 35 years after exposure. The authors conclude that neuropsychological disturbances were frequent in this group of former 2,3,7,8-TCDD workers. The low number of subjects in this study and lack of a matched control group limits the study considerably.

A cohort study by (Thomke et al., 2002) investigated cranial nerve function in workers occupationally exposed to pesticides including 2,4,5-T. Presence and absence of chloracne was used as a surrogate for dose with serum TEQ concentrations in 28 workers with (median: 871 ppt, range: 160-14178 ppt) and 86 workers without (median: 230; range: 0-6606 ppt) chloracne. BAEP abnormalities were more frequent in workers with chloracne than those without chloracne, but this was not significantly significant (p<0.15). VEP abnormalities were seen in one worker with and two without chloracne. Clinically visual functions were normal except in one worker, who was amaurotic since birth. Blink reflex abnormalities without corresponding clinical findings were observed in two patients without chloracne. The authors concluded that severe exposure to PCDD/F is not followed by clinical signs of cranial nerve dysfunction but may create an increased risk to develop subclinical dysfunction of the hair cells in the organ of the cochlear nerve as indicated by a more than twofold increase in the frequency of abnormal BAEP findings in workers with chloracne. This study is limited by the use of absence or presence of chloracne as a surrogate for exposure. Although serum dioxin concentrations have been analysed in some workers, the data was not examined (probably due to the resulting low sample number) in that respect. The use of chloracne as a surrogate for exposure may introduce errors, in particular with respect to the comparison group of this study (who had relatively high TEQ and 2,3,7,8-TCDD levels); the relatively small sample size also limits the statistical power of the observations. Overall, this study indicates that exposure to dioxins is not followed by clinical signs of cranial nerve dysfunction, although subclinical dysfunction may result, however, due to the limitations of the study, these outcomes can only provide weak evidence for no association.

**Biological Plausibility**

In vivo experiments have demonstrated that 2,3,7,8-TCDD can affect biochemical processes, including effects on calcium uptake and neurotransmission (in particular serotonin metabolism). The mechanism by which 2,3,7,8-TCDD could exert neurotoxic effects is not established, however most studies are consistent with the hypothesis that the effects of 2,3,7,8-TCDD are mediated by the aryl hydrocarbon receptor (AhR), a protein in animal and human cells to which 2,3,7,8-TCDD can bind and together bind with DNA leading to changes in transcription. At the cellular level, 2,4-D inhibited neurite extension which is accompanied by a decrease in intracellular microtubules, inhibition of the polymerisation of tubulin, disorganisation of the Golgi apparatus, and inhibition of ganglioside synthesis. Studies in rats indicate an impairment of motor function, CNS depression, inhibition of myelination in the brain and behavioural alterations. Also 2,4,5-T may acutely affect neuronal and muscular function by altering cellular metabolism and cholinergic transmission.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides little evidence that an association exists between neurobehavioral disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates provide contradicting results, however, the lack of adequate exposure assessments or low number of subjects limits the findings of these studies. In addition, due to the complexity of neurobehavioral disorders that exist and the wide array of causative factors make this a particularly difficult impairment to assess. The putative causal link of neurobehaviral disorders with exposure to the compounds of interest is biologically plausible, however the mechanism by which these compounds could exert neurotoxic effects is not established. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is **INSUFFICIENT EVIDENCE** at this stage to determine whether an association exists between neurobehaviral dysfunction and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.
3 CHLORACNE

Overview

Chloracne is a persistent acneform rash characterised by comedones, keratin cysts and inflamed papules with hyperpigmentation that develops after exposure to chlorinated compounds (particularly 2,3,7,8-TCDD) by skin contact, ingestion or inhalation. However, individual host factors appear to play an important role in determining disease expression. Even at relatively high doses, not all exposed individuals develop chloracne, whereas others with similar or lower exposure manifest the condition. Although it is difficult to differentiate from acne, it is classically said to have a “butterfly” distribution over the face frequently involving the skin under the eyes and behind the ears. Chloracne occurs after recent exposure. With the reduction/removal of the phenoxy herbicides contaminated with 2,3,7,8-TCDD and better measures to control dioxin and furan emissions, there have been very few recent opportunities for this disease to occur. There is no normative data available for chloracne in Australia. The condition has not been reported in the literature as occurring in Australia. It is possible that there may have been cases but that these have been un-or misdiagnosed.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997

IARC summarises studies on chloracne including investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure, laboratory workers exposed to 2,3,7,8-TCDD) and environmentally exposed groups (Seveso residents and other residents of contaminated areas) and Vietnam veterans. Other dermatological alterations discussed include hypertrichosis, hyperpigmentation, increased prevalence of actinic or solar elastosis and Peyronie’s disease observed in chemical workers. No evaluation was undertaken with regards to an association between dioxins and chloracne or other effects on the skin.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998

ATSDR summarises results from studies investigating occupationally exposed cohorts (including laboratory workers, 2,4,5-T exposure of chemical workers) environmentally exposed groups (Seveso residents).

ATSDR concludes available data suggests that 2,3,7,8-TCDD is a dermal toxicant both in humans and animals. It is highlighted that although in humans chloracne indicates exposure to chlorinated or halogenated aromatics, lack of chloracne does not indicate that exposure has not occurred.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000

US EPA reviews studies on chloracne including investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure or the BASF and other chemical worker cohorts, laboratory workers exposed to 2,3,7,8-TCDD) and environmentally exposed groups (Seveso residents and other residents of contaminated areas) and Vietnam veterans (Ranch Hand and other veteran cohorts). Other dermatological alterations reviewed include red and irritated eyes, conjunctivitis, blepharitis, eyelid cysts, hyperpigmentation, hirsutism, actinic or solar elastosis and Peyronie’s disease, non-melanotic skin cancer in chemical workers, residents of contaminated areas and/or Vietnam veterans.

US EPA highlights that from an epidemiological perspective, chloracne is a common consequence of exposure to chemicals contaminated with 2,3,7,8-TCDD and some other polyhalogenated hydrocarbons. It is also noted that data available with internal dose assessments have not determined the threshold at which chloracne occurs. Other conditions, such as hyperpigmentation and hypertrichosis may be more acute effects of 2,3,7,8-TCDD exposure that resolve over time since they were not observed when examinations took place years after exposure. US EPA further note that actinic keratosis, Peyronie’s disease and basal cell carcinoma may not be due to 2,3,7,8-TCDD, because they have only been observed in a single cohort or study group.

From its review, US EPA concludes that chloracne has in general been observed in most incidences where substantial exposure has occurred, particularly among TCP production workers and Seveso residents. Based on its review on the available epidemiological and animal experimental data, US EPA concludes that there is good evidence that chloracne has a POSITIVE RELATIONSHIP with exposure to 2,3,7,8-TCDD. Hyperpigmentation, hypertrichosis and eyelid cysts may be acute effects of 2,3,7,8-TCDD exposure that resolve over time.

WORLD HEALTH ORGANIZATION 2002

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDC and chloracne.

NATIONAL ACADEMY OF SCIENCES 2002

NAS did not identify any additional studies for the 2002 Update that investigated an association between chloracne and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD. NAS note that chloracne has been extensively studied and used as a marker of exposure in studies of populations exposed to 2,3,7,8-TCDD and other organochlorine compounds. It is highlighted that chloracne is one of the few findings consistently associated with exposure to these compounds and is a well-validated indicator of high exposure to particularly 2,3,7,8-TCDD. However, if chloracne occurs, it typically appears shortly after exposure and usually regresses over time.

On the basis of its evaluation of the epidemiological evidence reviewed in previous NAS reports, the committee concluded that there is SUFFICIENT EVIDENCE that an association exists between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and chloracne.

Literature Updates

A cohort study by (Mo et al., 2002) investigated skin diseases in Korean Vietnam veterans. The prevalence of xerotic eczema (3.9%), seborrheic dermatitis (3.9%), psoriasis vulgaris (0.9%), photoallergic dermatitis (0.6%) and chronic urticaria (0.3%) was not significantly elevated compared to the general population. No appropriate comparison group was available for comparisons of dermatological diseases. Other limitations of this study include the lack of exposure data, a biased sampling of subjects (individuals that visited...
the hospital), the lack of a matched comparison group and the lack of reporting on the statistical evaluations undertaken.

A cohort study by (Pelcova et al., 2002) reported chloracne duration in 12 men from the former Czechoslovakia that were occupationally exposed to 2,4,5-T (contaminated with 2,3,7,8-TCDD) during 1965-1968. Mean estimated 2,3,7,8-TCDD serum at time of intoxication was back extrapolated to 5000 ppt (256 ppt in 1996, range 14-760 ppt). Subjects were follow-up examined for chloracne and duration of cases compared with 2,3,7,8-TCDD plasma levels in 1996. Only 2 subjects (1st and 3rd most exposed) still presented signs of chloracne 35 years after exposure. A statistically significant association between serum TCDD and patients with and without chloracne in 2001 was found (p=0.03), although the number of subjects limits this finding significantly.

**Biological Plausibility**

Animal studies have been effective in describing the relationship between 2,3,7,8-TCDD and chloracne (U.S. EPA, 2000c). The exact molecular mechanism that causes chloracne following exposure to chlorinated compounds is not understood. 2,3,7,8-TCDD has been shown to induce differentiation in human keratinocytes, which may be initiated by 2,3,7,8-TCDD binding to the AhR. This effect is antagonised by retinoids and may involve interactions between 2,3,7,8-TCDD and retinoids in the regulation of epithelial differentiation. 2,3,7,8-TCDD has been reported to decrease an acidic type I Keratin involved in epidermal development, leading to keratinocyte hyperproliferation and skin irritations such as chloracne.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides strong evidence that an association exists between chloracne and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates do not provide strong evidence for such an association, but are in agreement with the general findings of earlier studies. The putative causal link of chloracne with exposure to the compounds of interest is biologically plausible and has been observed in animals exposed to 2,3,7,8-TCDD. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is an ESTABLISHED CAUSAL LINK between chloracne and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

4 **PORPHYRIA CUTANEA TARDA**

**Overview**

The Porphyrias are a fairly uncommon group of diseases. Most are inherited but some are acquired. In all of the porphyrias the basic dilemma is that excessive amounts of porphyrins and their precursors accumulate in the body. Porphyria cutanea tarda (PCT) is one group of non-acute porphyrias which is found in both inherited and acquired forms and is the most common form of porphyria. People with PCT commonly develop skin problems. The skin is sensitive and patients complain that it is easily damaged and take a long time to heal. Certain parts of the body are affected by light, particularly hands, faces, legs and feet, on which blisters and open sores can develop. In time, the skin of the patients becomes thin, darkly pigmented, scarred and frequently found with excessive growth of hair. There are no data on the prevalence of PCT in Australians. In Europe there are substantial variations in the rate of sporadic PCT linked to societal variation in the use of alcohol. The inheritance of the familial form is thought to be between 1:10,000 and 1:20,000 of the population.

The numerous different forms of aetiological agents associated with induction of the acquired form of PCT leads to some difficulty in describing the precise aetiologic factor for induction of the condition. In addition to this, hereditary haemochromatosis is often found in conjunction with PCT. Known risk factors include high alcohol intake, estrogen intake (as oral contraceptives), liver disease, haemodialysis, HIV infection and diabetes

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC summarises studies on PCT including investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure of the NIOSH and other chemical worker cohorts) and environmentally exposed groups (Seveso residents). It is highlighted that some debate exists over whether an association exists between PCT and 2,3,7,8-TCDD exposure. No evaluation was undertaken with regards to an association between dioxins and PCT.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR notes that PCT has been reported in 2,3,7,8-TCDD exposed workers. No specific evaluation was undertaken by ATSDR with regards to an association between dioxins and PCT.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA summarises studies on PCT including investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure of the NIOSH and other chemical worker cohorts and laboratory workers exposed to 2,3,7,8-TCDD) and environmentally exposed groups (Seveso residents) and Vietnam veterans (Ranch Hand and other veteran cohorts).

US EPA highlights that the association between PCT and exposure to various chemical compounds is not clear, however, notes that 2,3,7,8-TCDD is a potent porphyrinogen in rats and mice and therefore, high acute exposure may have contributed to the observed changes in porphyrin levels in some populations. Hence, neurologic disorders were classified as ACUTE EFFECTS (it was noted that this may be an outcome of exposure to PCBs when there is a co-exposure to chlorophenols).

**Figure 1.**

**WORLD HEALTH ORGANIZATION 2002**

No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDC and porphyria cutanea tarda.
NAS did not identify any additional studies for the 2002 Update that investigated an association between porphyria cutanea tarda and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD. NAS note that PCT would be an early response to 2,3,7,8-TCDD and that recovery would occur after exposure ceased and would have been rare in any event. Although PCT has been observed after exposure to 2,3,7,8-TCDD in industrial settings, Ranch Hand veteran studies have not been found to have symptoms suggestive of this disorder.

On the basis of its evaluation of the epidemiological evidence reviewed in previous NAS reports, the committee concluded that there is LIMITED OR SUGGESTIVE EVIDENCE that an association exists between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and chloracne.

**Literature Updates**

No Literature Updates were identified that investigated the association between porphyria cutanea tarda and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

The close association between inhibition of uroporphyrinogen decarboxylase and onset of sporadic PCT means that any compound known to inhibit this enzyme must be considered as a probable candidate for causation of this disease. This conclusion is supported by the animal evidence of experimental forms of the disease that have been developed following exposure to 2,3,7,8-TCDD. The lack of sound epidemiological support for these studies in humans can be ascribed to the mixed exposures generally found in these conditions and to the levels of exposure to 2,3,7,8-TCDD in both industrial and domestic environments.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association may exist between porphyria cutanea tarda and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD, although the findings are contradicting between studies. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated such an association. The putative causal link of PCT with exposure to the compounds of interest is biologically plausible. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK between porphyria cutanea tarda and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

**5 Respiratory Disorders**

**Overview**

Respiratory disorders refer to acute and chronic lung diseases other than cancer. Acute responses to lung injury include airway reactivity, pulmonary oedema, pneumonia and other lung infections that could be induced when normal defence mechanisms of the lower respiratory tract are compromised. Chronic responses of the lung to injury include fibrosis, emphysema, asthma which can be induced by exposure to wide range of environmental pollutants in the forms of aerosol, gas/vapour or particulates. Examples of common industrial toxicants that produce lung diseases are asbestos, silica, coal dust, ammonia, iron oxide, nickel, sulphur dioxide and ozone. Some severe chronic lung disorders, such as fibrosis, are hereditary. US Vietnam veterans underwent health screening, no severe hereditary chronic lung disorders are expected in this population (NAS, 2002). Australian normative data for respiratory disorders are provided in Appendix 1.

One of the common and non-evasive tests for pulmonary function is the measurement of Forced Expiratory Volume (FEV₁) during the first second of an active exhalation. The test is often used in epidemiological studies. A reduction in FEV₁ is usually indicative of impaired ventilation such as that found in restrictive (increased lung stiffness) or obstructive (obstructed airflow) lung disease. Diagnosis of respiratory disorders is relatively easy. However, epidemiological study of these diseases in relation to herbicide/dioxin are not simple because the difficulties in isolating confounders such tobacco smoke, allergens and other environmental pollutants as mentioned above. For example, US Vietnam veterans are reported to smoke more heavily than non-Vietnam veterans (NAS, 2002). Accurate measurements of acute responses are not possible because in the majority of cases, the exposure took place many years ago. Assessment of chronic responses is complicated by often unreliable dose (exposure) data.

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC summarises studies on respiratory disorders including 2 investigations of occupationally exposed cohorts (including 2,4,5-T and 2,4-D exposure of the NIOSH and other chemical worker cohorts) and one study on Vietnam veterans (Ranch Hand cohort). No evaluation was undertaken with regards to an association between dioxins and respiratory disorders.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR summarizes two studies investigating respiratory disorders in Vietnam veterans (Ranch Hand and other veteran cohorts) and two studies in highly exposed chemical plant workers.

From its review, ATSDR concludes that intense acute exposure to 2,3,7,8-TCDD can produce respiratory irritation, but the findings from controlled epidemiologic studies do not support an association between 2,3,7,8-TCDD exposure and chronic respiratory disease. It was noted, however, that chronic bronchitis and related effects were observed in many Yusho and Yu-Cheng patients, who were exposed to PCDFs, which are structurally related to 2,3,7,8-TCDD.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA summarises studies on respiratory disorders including 2 case reports among occupationally exposed cohorts (including exposure to herbicides and fungicides), 3 controlled epidemiological studies (including 2,4,5-T exposure) and 2 studies on Vietnam veterans (Ranch Hand cohort)

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US EPA concludes that the case reports indicate that intense acute exposure to 2,3,7,8-TCDD can produce respiratory irritation, however, that the findings from controlled epidemiological studies do not support an association between 2,3,7,8-TCDD exposure and chronic non-cancer effects on the respiratory system. Hence, neurologic disorders were classified as ACUTE EFFECTS.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was undertaken by WHO/IPCS with regards to an association between EDCs and respiratory disorders.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed one additional study for the 2002 Update that investigated mortality from non-malignant respiratory disorders in male Dow Chemical Company workers involved in the production of 2,4-D. NAS notes that observations from most studies are tentative and the information insufficient to determine whether an association exists.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and non-malignant acute or chronic respiratory disorders.

Literature Updates
A large cohort study by (Hoppin et al., 2002) investigated wheeze among farmer pesticide applicators exposed to a variety of compounds including 2,4-D. Self-reported annual pesticide use and frequency of application was used as a surrogate for dose. Eleven pesticides were significantly associated with wheeze when evaluated for ever use, of these, all 10 for which dose-response models were constructed had significant tests for trend (p<0.05). 2,4-D application was not significantly associated with wheeze (OR = 0.99; 95% CI, 0.99-1.11; p = 0.46) and no dose-response was observed. This study uses a large study population, but the potential for recall and selection bias were not minimised. The use of self-reported frequency of pesticide use as surrogate for dose and exposure frequency is extremely limiting (no information on active ingredient concentration, solvents or other ingredients) and may have introduced chance with respect to the exposure classifications. No comparison group was included. The exclusion of farmers that have applied pesticides prior to the year before the study limits the detection of potential latency effects.

A relatively small cohort study by (Van Den Heuvel et al., 2002) investigated respiratory complaints in Flemish adolescents associated with environmental exposure to various chemicals including PCBs and dioxins. PCB markers and CALUX measurements were used as surrogate for exposure to these compounds. After adjustment for sex and family history of hay fever, serum TEQ were negatively associated with the odds of having a positive RAST for house dust mites (OR=0.68; p=0.01), cat dander (OR=0.63; p=0.03) and grass pollen (OR=0.70; p=0.02). A history of upper airway allergy was negatively associated with serum TEQ (OR=0.66; p=0.02). A negative association was observed between the odds of bronchial wheezing and serum TEQ (OR=0.25; p=0.03), however this was not the case after adjustment for family history of hay fever and/or asthma. A negative association was found between medical treatment for asthma and serum TEQ (OR=0.58; p=0.005) and a positive association existed between ever having asthma and serum PCB concentration (OR=2.12; p=0.05). The odds of suffering hay fever increased with higher serum PCB concentrations (OR=1.63; p=0.04), however, this was not the case after correction for sex. The biomarkers used in this study for exposure include all Ah-receptor mediating compounds, which provides a better understanding of effects from exposure to such chemicals as a whole, however, it is therefore not possible to determine which of the observed effects may be associated with exposure to 2,3,7,8-TCDD. Potential confounders were assessed and controlled, but the study may be limited by the relatively low sample size.

Biological Plausibility
Lung tissue has been found to have high concentration of the aryl hydrocarbon receptor (AhR), which mediates the effects of 2,3,7,8-TCDD, and both CYP 1A1 and CYP1A2 are expressed in lung biopsy specimens from human subjects. It is biologically plausible that exposure to 2,3,7,8-TCDD may result in acute and chronic lung diseases. It is also noted that major confounder for these disorders is cigarette smoking. The cytochrome P450 enzymes are responsible, at least in part, for the activation of many chemicals found in tobacco smoke (which also contains AhR ligands) to more-toxic intermediates, so it is also biologically plausible that exposure to 2,3,7,8-TCDD may increase the toxic effects of a variety of other chemicals to which human lung tissue is exposed (NAS, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides little evidence that an association may exist between respiratory disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates could not provide strong evidence for such an association. The putative causal link of respiratory disorders with exposure to the compounds of interest is biologically plausible. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE to determine whether an association exists between respiratory disorders and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

6 IMMUNE SYSTEM DISORDERS

Overview
The immune system has a critical role in maintaining health. Suppressed immunological function can result in increased susceptibility to infection by microorganisms and development of some forms of cancers. Conversely, uncontrolled enhanced immune development can result in allergic and autoimmune diseases. 2,3,7,8-TCDD is a known
immunosuppressant in laboratory animals and one of the most potent immunotoxicants known to exist in the environment (NAS, 2002). Australian normative data for immune system disorders are provided in Appendix 1.

Studies of human immune responses to dioxins and phenoxy herbicide compounds provide inconsistent results. The broad range of “normal” responses in humans due to the large variability inherent in a heterogeneous population, the limited number and sensitivity of tests performed, and the poor exposure characterization of the cohorts in studies compromise any conclusions about the ability of a given study to detect immune alterations.

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC assessed studies on immune system disorders including 3 investigations of occupationally exposed cohorts (including 2,4,5-T exposure or the BASF and other chemical worker cohorts), 3 environmentally exposed groups (Seveso residents and other residents of contaminated areas), 3 studies on Vietnam veterans (Ranch Hand and other veteran cohorts) and one case report. IARC notes that with the exception of one study (TCP production workers), no clear relationship was found between exposure and impaired immunological status. No evaluation was undertaken with regards to an association between dioxins and immune system disorders.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR summarizes 7 studies of occupational cohorts (including exposure to 2,4,5-T of the BASF and other chemical worker cohorts), 5 studies of environmentally exposed groups (Seveso residents and residents of other contaminated areas, fishermen) and 1 study of Vietnam veterans (Ranch Hand cohort). It was noted that of the limited number of studies that have examined the immunotoxicity of 2,3,7,8-TCDD in humans most of have found potential alterations in lymphocyte populations, cell surface markers or lymphoproliferative responses, however, the interpretation of these studies is limited by the lack of data correlating changes in immune function and changes in host resistance to disease challenges.

ATSDR concludes that although human exposure studies to date found no conclusive evidence of immunotoxicity, the animal data show that the immune system is a target for 2,3,7,8-TCDD toxicity in many species. ATSDR notes that a defined 2,3,7,8-TCDD-induced immune deficiency syndrome has not emerged largely because the immune response observed in animals depends on the species studied, the dose of 2,3,7,8-TCDD, and the antigen and exposure protocol studied.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA summarizes 7 studies of occupational cohorts (including exposure to 2,4,5-T of the BASF, NIOSH and other chemical worker cohorts), 5 studies of environmentally exposed groups (Seveso residents and residents of other contaminated areas, fishermen) and 2 studies of Vietnam veterans (Ranch Hand cohort).

US EPA highlights that animal toxicological studies have demonstrated numerous immunologic effects after exposure to 2,3,7,8-TCDD. In humans, the information with which to assess the immunologic consequences of exposure is sparse and the findings contradictory between cohorts. Studies using more advanced functional analysis suggest a decreased ability of T-cells to respond in individuals more heavily exposed to dioxins.

US EPA concludes that there is too little information to suggest definitely that 2,3,7,8-TCDD, at the levels observed, causes long-term adverse effects in adult humans. Hence, immunologic effects were classified as an endpoint for which the animal data have demonstrated exposure-related effects, but the human data are INCONCLUSIVE and required further study.

**WORLD HEALTH ORGANIZATION 2002**

WHO/IPCS reviewed studies investigating occupational exposure to PCBs and dioxins, studies on environmental exposure (including Seveso residents, Yusho patients and general populations) and studies on Vietnam veterans (Ranch Hand veterans)

WHO/IPCS concludes that PCBs and dioxins are one of the few compounds with immunotoxic properties that have been shown to cause immunotoxicity that is mediated through an endocrine disrupting mechanism. The reported alterations of human immune parameters following accidental, occupational and general population exposure to PCBs and dioxins are in line with studies in experimental animals, however, the mechanism of action is unknown. No specific evaluation was undertaken with regards to an association between dioxins and immune system disorders.

**NATIONAL ACADEMY OF SCIENCES 2002**

NAS did not identify any additional studies for the 2002 Update. NAS conclude that 2,3,7,8-TCDD is one of the most potent immunotoxicant known to exist in the environment and is immunosuppressant in laboratory animals. It is noted however, that to date, the immune effects described in humans exposed to 2,3,7,8-TCDD have been marginal and highly inconsistent. Furthermore, no pattern of increased infectious disease has developed in people exposed to high concentrations of 2,3,7,8-TCDD or herbicides used in Vietnam. The consistent immunosuppressive effects observed in laboratory animals that have been exposed to 2,3,7,8-TCDD have not been confirmed in humans.

On the basis of its evaluation of the epidemiological evidence reviewed in previous NAS reports, the committee concluded that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and immune suppression or autoimmunity.

**Literature Updates**

The most significant contribution to the literature since 2002 was by (Baccarelli et al., 2002) investigating current immune systems in residents exposed to 2,3,7,8-TCDD in Seveso in 1976. The authors examined plasma immunologic parameters in a random sample of the population of the area
and found significant negative correlation in immunoglobulin antibody IgG concentrations (the most common of the immunoglobulin antibodies) and lipid-adjusted 2,3,7,8-TCDD levels. This finding was slightly more pronounced in females than males. Confounding factors such as smoking (formerly and currently) and consumption of livestock at the time of the accident were adjusted for using multivariable regression, as these factors were determined to be significantly negatively correlated to lower IgG concentrations independently of each other, compared to non-smokers and subjects that did not eat livestock at the time, respectively. Although circulating IgG antibodies are well documented to protect against infections and allergic diseases, no IgG levels found in this study approached levels of those typically observed in patients with antibody immunodeficiency disorders (less than or equal to 350 mg/dL). The serum TCDD assessment, matched control group and detailed assessment of personal medical history and laboratory test validations of the investigated conditions provide some strength to the findings. However, the study was based on a relatively small random sample of acutely exposed resident populations. Nevertheless, this study provides some evidence of an association between decreased IgG levels and exposure to 2,3,7,8-TCDD.

A cohort study by (Van Den Heuvel et al., 2002) investigated changes in humoral or cellular immunity in relation to serum marker PCBs and CALUX biomarkers of exposure to Ah receptor meditated compounds (including PCBs and dioxins) in Flemish adolescents. The eosinophil count was negatively and independently correlated with serum dioxin-like chemical concentration (p=0.009). Monocytes tended to decrease with increasing serum TEQ (p=0.055). A negative, borderline significant correlation was observed between the number of NK cells and serum TEQ (p=0.05). No significant association was observed between other lymphocyte phenotypes and serum TEQ. Dioxin-like activity was negatively correlated with serum IgE (p=0.02) but positively correlated with IgA (p=0.05). A negative correlation was found between IgG levels and the concentration of the combined marker PCBs (p=0.009). The authors concluded that biomarkers of internal exposure to dioxin-like compounds were related to biomarkers of the immune status. The effects of exposure to dioxin-like compounds in adolescents were associated with a lower prevalence of allergic diseases. The biomarkers assessed for this study does not allow the evaluation of which compounds were responsible for the observed findings. The study may also be limited by the relatively low sample size.

A population based cohort study by (Watanabe et al., 2002) investigated immunologic biomarkers, including T lymphocytes (CD3, CD4, CD8), NK activity and natural killer cell activity in Japanese residents from 17 areas. The results were compared to serum dioxin concentrations. An inverse correlation with dioxin and PCB body burden was reported for NK cell marker and NK activity. However, this study does not report the statistical outcomes. Further, it was not reported whether the potential for confounding was addressed. Hence, this study does not provide the necessary detailed data to assess the potential for bias and confounding and can therefore not add any supportive information.

**Biological Plausibility**

2,3,7,8-TCDD is a known immunosuppressive in laboratory animals and can alter the number and function of immune cells in some animals. The effect of 2,3,7,8-TCDD on immune response in the mouse after injection with the influenza virus demonstrate the humoral and cell-mediated response is suppressed suggesting that multiple cellular targets within the immune system are altered by 2,3,7,8-TCDD. Evidence also suggests that the immune system in animals is indirectly targeted by TCDD-induced changes in non-lymphoid tissues.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides contradicting evidence on whether an association exists between immune system disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates are consistent in their findings suggesting an association of alterations of the immune system, however, limitations to the studies due to small sample size or confounding and bias weaken the strength of the reported findings. The putative causal link of immune system disorders with exposure to the compounds of interest is biologically plausible and animal studies are consistent in their findings of immunosuppression due to 2,3,7,8-TCDD exposure. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK between immune system disorders and exposure to 2,4,5-T; 2,4-D and/or 2,3,7,8-TCDD.

7 MALE REPRODUCTIVE DISORDERS

**Overview**

Male reproduction is a complex system under the control of several components such as hormones whose proper coordination is important for normal development and function. Traditionally, semen quality is considered as the most significant marker of male reproductive function. However, several other characteristics are used for monitoring the function of male reproductive organs such as determining circulating hormone levels, incidence of testicular cancer (see testicular cancer review), fecundity, congenital malformations of genital organs (dependent on time of exposure) and altered sex ratio in offspring. Any adverse reproductive/developmental outcome in an exposed male is dependant on timing and level of exposure i.e. in utero (via maternal exposure), pre-pubertal, pubertal or exposure as an adult male. Australian normative data for male reproductive disorders are provided in Appendix 1.

The epidemiological literature dealing with dioxins and reproductive effects vary greatly in the nature (environmental and occupational), route of exposure (inhalation, ingestion, adsorption), in the reproductive or developmental outcomes examined (sperm counts, circulating hormones, pregnancy outcome), assessment of exposure (maternal, paternal or both) and timing of exposure. For the purposes of this
review, the main focus will be on effects of chemicals (dioxin, 2,4-D or 2,4,5-T) exposure on adult males. Effects specific to females and children are summarised in a separate section below.

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC assessed studies on endocrine and gonadal effects including 1 investigation of occupationally exposed cohorts (including 2,4,5-T exposure of chemical worker cohorts) and 3 studies on Vietnam veterans (Ranch Hand and other veteran cohorts). Effects on pregnancy outcomes were investigated separately from studies on Vietnam veterans, environmentally exposed cohorts (including Seveso residents and other residents of contaminated areas) and occupationally exposed cohorts (including 2,4,5-T exposed workers and herbicide sprayers). With respect to male reproductive system effects, only animal experimental studies have been reviewed.

IARC concludes that most studies on human reproductive effects of dioxins concern paternal exposure, usually long after a high exposure occurred and that most studies have limited power to detect elevations in specific birth defects. It is further concluded that 2,3,7,8-TCDD is both a developmental and reproductive toxicant in experimental animals. No specific evaluation was undertaken with regards to an association between dioxins and reproductive disorders.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR summarizes 4 studies of occupational cohorts (including exposure to 2,4,5-T of chemical worker and herbicide sprayer cohorts), 1 study of environmentally exposed groups (Seveso residents) and 5 studies of Vietnam veterans (Ranch Hand cohort) and studies on paternal exposure outcomes.

ATSDR conclude that the human reproductive toxicity studies investigating the possible association between 2,3,7,8-TCDD exposure and reproductive toxicity in humans is inconsistent. A common limitation of the studies, particularly those conducted prior to 1984 (i.e. prior to development of assays to quantify serum and adipose levels of 2,3,7,8-TCDD) is the lack of exposure data. However, ATSDR notes that a number of reproductive effects have been observed in animals, including decreased fertility, altered hormone levels, and gonad damage in males and females. Overall, it was concluded that the similarity between some of the effects observed in humans and animals suggest that reproductive effects may also occur in humans exposed to 2,3,7,8-TCDD.

**U.S. ENVIRONMENTAL PROTECTION AGENCY 2000**

US EPA reviews 4 studies of occupational cohorts (including exposure to 2,4,5-T of chemical workers) and 3 studies on Vietnam veterans (Ranch Hand and other veteran cohorts). It was concluded that the human data offer some evidence of alterations in male reproductive hormone levels associated with substantial occupational exposure to 2,3,7,8-TCDD. These results support the data obtained from animal studies, in which dioxins related effects have been observed on the hypothalamic-pituitary-Leydig-cell and on testosterone synthesis.

US EPA concludes that the results from occupationally exposed NIOSH cohorts and Ranch Hand veterans are limited by the cross-sectional nature of the data and the type of clinical assessments conducted. However, the available data provide evidence that alterations in human male reproductive hormone levels are associated with serum TCDD. In its assessment, US EPA considers alterations of human reproductive hormones as an effect having a **POSITIVE RELATIONSHIP** with exposure to 2,3,7,8-TCDD. With respect to semen changes, US EPA concludes that the human data are **INCONCLUSIVE** and require further study.

**WORLD HEALTH ORGANIZATION 2002**

WHO/IPCS provided an extensive review on studies investigating reproductive outcomes and exposure to EDCs in humans and animals. With respect to male reproductive disorders, the review addresses sperm quality and testis function investigations, fecundity and fertility and male reproductive tract abnormalities.

WHO/IPCS concludes that with respect to sperm quality and testis function, most studies have been retrospective and many biases could influence the observed results. With respect to fecundity and fertility, it was concluded that the studies demonstrating an association between delayed conception and exposure to high levels of environmental contaminants remain speculative due to the complex array of issues that may alter normal human reproduction. With respect to male reproductive tract abnormalities, it was concluded that although considerable experimental evidence exists that hormones and other endocrine-active chemicals can affect prostate development, data on trends in men are lacking. Most of the human data investigating male reproductive tract abnormalities have focused on pesticides and included small numbers of occupationally exposed subjects, with no appropriate exposure data. No conclusions could be drawn on whether there is a causal association with pesticide exposure or whether there is endocrine involvement, although animal data clearly demonstrate that hormonal mechanisms can be involved in the etiology of male reproductive tract abnormalities.

With respect to reproductive outcomes overall, WHO/IPCS concludes that the major limiting factor in drawing any conclusion on putative links to EDCs is the absence of exposure data. Another major problem common to many of the human studies are small sample sizes which do not permit detection of a potentially present effect. Thus, it is concluded that the available human data are inadequate to support a conclusion that human reproductive health has been adversely affected by exposure to EDCs. However, the biologically plausibility of possible damage to human reproduction from exposure to EDCs is strong.

**NATIONAL ACADEMY OF SCIENCES 2002**

NAS provided an extensive review on studies investigating reproductive outcomes from epidemiological studies. Studies investigating male reproductive disorders were limited to investigations on fertility. NAS reviewed one additional study for the 2002 Update on fertility, investigating highly exposed residents near chemical industry. Previous NAS reviews considered occupationally exposed cohorts (pesticide applicators and sawmill workers) and Vietnam veterans (Ranch Hand cohorts).

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It was concluded that the observation of delayed sexual maturation and lower testicular volume observed in adolescents supports a potential effect on male reproductive capacity, but that the implications on adults is unclear. On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is **INADEQUATE OR INSUFFICIENT EVIDENCE** to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, picloram or cacodylic acid) and altered hormone concentrations, decreased sperm counts or quality, subfertility, or infertility.

**Literature Updates**

No Literature Updates were identified that investigated the association between male reproductive disorders and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

There is evidence from animal studies that suggests human reproduction and development may be highly sensitive to dioxin. In animals, dioxin exposure is known to initiate biological amplification of Ah-receptor-mediated responses via a cascade of growth factors and hormones (Birnbaum, 1995). Hence, exogenous chemicals such as 2,3,7,8-TCDD are thought to mimic, inhibit or modulate endogenous hormones potentially disrupt normal reproduction/development. These chemicals are often referred to an “endocrine-disruptors”. In male animals, sperm counts and production and seminal vesicle weight have been affected by 2,3,7,8-TCDD. Effects are also seen on female reproductive organs. The mechanism(s) of these effects is not known, but one hypothesis is they are mediated through effects on hormones. These effects are not always associated with reduced fertility or adverse outcomes in offspring. The supporting animal data suggests a connection between 2,3,7,8-TCDD exposure and adverse effects on human reproduction is biologically plausible. However, differences in susceptibility of individual animal species and the exposure kinetics (route, dose, timing of treatment) makes extrapolating results to humans extremely complex. A mechanism by which 2,3,7,8-TCDD could exert effects on male reproduction is not known.

In terms of reproductive toxicity, the number of studies are too limited to draw conclusions regarding the effect of 2,4-D and 2,4,5-T on male or female reproductive toxicity. However, in animals both 2,4-D and 2,4,5-T do appear to cause developmental effects in exposed females but only at high does. There is no evidence developmental effects occur in the offspring of exposed males. This indicates that these chemicals do not have reproductive effects and have developmental effects only at high does. Overall, a mechanism by which 2,4-D or 2,4,5-T could exert effects on male reproduction is not known.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides limited evidence on whether an association exists between male reproductive disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated the association. The putative causal link of male reproductive disorders with exposure to the 2,3,7,8-TCDD is biologically plausible and animal studies have shown adverse reproductive health outcomes. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is **INSUFFICIENT EVIDENCE** to determine whether an association exists between male reproductive disorders and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

**8 DIABETES**

**Overview**

Primary diabetes is a hetrogenous metabolic disorder characterised by hyperglycaemia and quantitative and/or qualitative deficiency of insulin action. The two main types of diabetes are classified as:

- **Type I diabetes** (insulin-dependent diabetes IDDM) results from β-cell dysfunction, caused by a genetically based autoimmune destruction. It comprises approximately 10% of all diabetes cases. Typically, it onset is abrupt in youth, although it may appear at later stages of life. A number of environmental triggers in genetically susceptible subjects have been proposed.
- **Type II diabetes** (non-insulin-dependant diabetes NIDDM) accounts for the majority of diabetes cases. It is rare before age 30, but increases steadily with age thereafter. Main factors for increased risk of Type II diabetes include age, obesity, central fat deposition, a history of gestational diabetes, physical inactivity, ethnicity and family history of the disease.

Australian normative data for diabetes are provided in Appendix 1. The epidemiological study of diabetes is considered extremely difficult due to a) a wide variety of pathogenetic mechanisms leading to diabetes (e.g. genetic susceptibility, environmental and health behaviour factors) and b) a diagnostic uncertainty as the result of lack of formal standardised testing to detect undiagnosed cases (US Institute of Medicine, 2002). In addition, a variety of endpoints have been used across studies investigating associations between diabetes and herbicide/dioxin exposure (e.g. mortality, prevalence, fasting glucose, severity, time to onset, 2-h postprandial glucose levels), resulting in difficulties to compare the outcomes (reviewed in (Greene et al., 2003)).

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC summarised 3 studies from occupationally exposed cohorts (2,4,5-T and TCP production workers) and 2 Vietnam veteran investigations (Ranch Hands and other Vietnam veterans). No conclusion or evaluation was provided with regards to an association between dioxins and diabetes.
From its review, ATSDR summarised results obtained from 2 Vietnam veteran (Ranch Hand) studies, 2 occupationally exposed cohorts (2,4,5-T and TCP production workers) and one environmentally exposed cohort (Seveso residents).

From its review, US EPA concludes that the current epidemiological studies suggest that exposure to high concentrations of 2,3,7,8-TCDD may induce long-term alterations in glucose metabolism. It was noted that administration of 2,3,7,8-TCDD to animals results in a wide range of endocrine responses, which are not only species-dependent, but also exhibit variability within species. Overall, ATSDR stated that the available information suggests that 2,3,7,8-TCDD may cause adverse endocrine effects in humans.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
US EPA considered 5 epidemiological studies on Vietnam Veterans (Ranch Hands and other Vietnam veterans), 5 occupationally exposed cohorts (BASF, NIOSH and IARC cohorts as well as other TCP and 2,4,5-T production workers) and two environmentally exposed populations (Seveso cohort and background exposure groups).

From their review, US EPA concludes that the current epidemiological and toxicological data to date do not support a strong relationship between exposure to 2,3,7,8-TCDD and diabetes or alterations in glucose metabolism. However, US EPA notes that some evidence exists to suggest that, particularly at high doses, 2,3,7,8-TCDD may perturb glucose metabolism in some species, a fact which was identified for further exploration. Based on their review, diabetes and fasting glucose levels are evaluated as possible effects of exposure to 2,3,7,8-TCDD or mixtures of dioxins, furans and PCBs.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was provided by WHO/IPCS with regards to an association between dioxins and diabetes.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 3 studies for the 2002 Update including one study on workers exposed to high concentrations of dioxins, one combined analysis of Ranch Hand veteran and NIOSH study outcomes and one population based survey. Previous NAS reviews included numerous studies on occupationally exposed cohorts (municipal waste incinerators, paper and pulp workers, NIOSH and BASF cohorts and other 2,4,5-T and TCP production workers with a range of serum TCDD concentrations), environmentally exposed populations (Seveso and Vertac/Hercules Superfund site residents) and Vietnam veterans (Ranch Hands, other US Vietnam veterans and Australian Veterans).

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is limited or suggestive evidence of an association between exposure to at least one of the chemicals of interest (2,4,5-T, 2,4-D, TCDD, picloram or cacodylic acid) and diabetes.

Literature Updates
(Remillard and Bunce, 2002b; Remillard and Bunce, 2002c) investigated the influence of background exposure to dioxins on the risk for diabetes, by applying the Harber’s Rule on previously reported data on reference groups from occupationally exposed cohorts. The referent group serum TCDD levels were 7 pg/g lipid (TEQ = 35 pg/g; n=259). The authors conclude that present background levels of dioxins are unlikely to constitute an important risk factor for type II diabetes in the general population (5×10^{-4} estimated increase in risk of diabetes). A number of assumptions were made in this study, most importantly the assumption that Harber’s Rule (stating that the product of concentration and time of exposure is constant; the constant appropriately a particular level of response) applies to a link between dioxin exposure and diabetes.

(Watanabe et al., 2002) reported a significant, marginal correlation of past history of diabetes mellitus and serum TEQ (PCDD/F and PCB) in 585 participants from the general population of Japan in a conference paper. The table presented in the paper indicates a higher TEQ body burden in males with diabetes (5.3 ng/kg) compared to males without diabetes (4.4 ng/kg). The opposite trend was reported for females. A body burden of 5 ng/kg bw was suggested by the authors to represent a possible risk level. This study was reported in a preliminary conference paper. Although reference is made in the text to a marginal significant correlation, no information on the statistical methodology and odds ratios are given, nor do the authors discuss if and how they controlled for confounding factors. In its preliminary form, this study can therefore not provide evidence for a causal relationship between background exposure and diabetes.

Biological Plausibility
Evidence regarding the potential of 2,3,7,8-TCDD to induce clinical diabetes is inconclusive to date. The effects of dioxins on serum glucose and other compounds and enzymes associated with diabetes is heterogeneous and inconsistent across species and strain (Greene et al., 2003). The well-established effect of 2,3,7,8-TCDD on glucose transport in a variety of cells including human granulosa cells dependent protein kinase and mice and rats provides some basis for biological plausibility (US Institute of Medicine, 1998). Effects of 2,3,7,8-TCDD on triglycerides and high-density lipoproteins, glucose transport, protein kinase C, and other lipoproteins in animals suggest that dioxins may stimulate development of diabetes. 2,3,7,8-TCDD treatments have shown to decrease glucose transport and alter lipoprotein degradation in adipose-tissue cell lines, which may constitute a physiological mechanism for linking 2,3,7,8-TCDD exposure to diabetes (US Institute of Medicine, 2002).

Conclusions and Overall Evaluation
The epidemiological evidence summarised in the Key Reviews provides some evidence on whether an association exists between diabetes and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. However, chance, bias or confounding factors have not been fully controlled in most studies. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. Literature
Updates investigating the association do not provide any conclusive evidence on whether a causal relationship exists between exposure to the chemicals of interest and diabetes. The putative causal link is biologically plausible, however evidence from animal studies is inconclusive to date. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a possible causal link between diabetes and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

9 LIPID AND LIPOPROTEIN DISORDERS

Overview

Lipoprotein disorders are typically the result from overproduction and/or decreased clearance of lipoproteins. The major types of lipids include cholesterol and triglycerides. They are carried in the blood stream attached to proteins to form lipoproteins. Lipoproteins can be classified according to their density:

- Very-low-density lipoproteins (VLDL) are the major triglyceride component produced in the liver
- Intermediate-density lipoproteins (IDL) are the product of the catabolism of VLDL via lipoprotein lipase, an insulin-mediated enzyme
- Low-density lipoproteins (LDL) are products of VLDL catabolisation. They represent the major “bad” cholesterol components and are cleared by LDL receptors in the liver and other tissues. LDL is thought to be involved in the delivery of cholesterol to the tissues.
- High-density lipoproteins (HDL) are products of VLDL catabolism and are also produced in the small intestine and liver. They represent the “good” cholesterol components. HDL facilitates the return of cholesterol to the liver for biliary excretion.

Lipoprotein disorders include elevation of cholesterol (hypercholesterolemia), triglycerides (hypertriglyceridemia) and both cholesterol and triglycerides (mixed hyperlipidemias). Australian normative data for lipid and lipoprotein disorders are provided in Appendix 1.

The majority of blood lipid concentrations are genetically determined. In addition, diet (in particular saturated fat content and high carbohydrate diet), obesity, activity, and factors such as drugs, age, gender, hormones or concurrent illness are known influencing parameters. Diabetes is associated with increased triglycerides and decreased HDL cholesterol, whereas for example thyroid and renal disorders often result in hypercholesterolemia (NAS, 2002). Hence a multitude of biological and environmental factors can influence lipid and lipoprotein concentrations.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997

IARC summarised lipid and lipoprotein investigations in occupationally exposed cohorts (BASF cohort and other TCP and 2,4,5-T production workers, laboratory workers), Vietnam veterans (Ranch Hands and other US Vietnam veterans) and environmentally exposed cohorts (Seveso, Missouri residents). No conclusion or evaluation was provided with regards to an association between dioxins and lipid or lipoprotein disorders.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1999

No specific review or evaluation was provided by ATSDR with regards to an association between dioxins and lipid or lipoprotein disorders.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000

US EPA considered epidemiological studies on Vietnam veterans (Ranch Hands and other US Vietnam veterans), occupationally exposed cohorts (BASF cohort and other TCP and 2,4,5-T production workers, laboratory workers), and environmentally exposed populations (Seveso and Missouri residents).

From their review, US EPA concludes that high exposure to 2,3,7,8-TCDD contaminated substances are not related to significantly increased lipid concentrations, specifically total cholesterol and triglycerides. They note that, nevertheless, slight but chronic elevations in serum lipids may put an individual at increased risk for disorders such as atherosclerosis and other conditions affecting the vascular system. Based on its review, changes in lipid concentration were evaluated by US EPA as possible effect of exposure to 2,3,7,8-TCDD or mixtures of dioxins, furans, and PCBs.

WORLD HEALTH ORGANIZATION 2002

No review or evaluation was provided by WHO/IPCS with regards to an association between dioxins and lipid or lipoprotein disorders.

NATIONAL ACADEMY OF SCIENCES 2002

NAS reviewed 1 new study for the 2002 Update which investigated an occupational cohort exposed to dioxins at a municipal waste incinerator. Previous NAS reviews included numerous studies on occupationally exposed cohorts (municipal waste incinerators, 2,4,5-T and TCP production workers), environmentally exposed populations (Seveso residents) and Vietnam veterans (Ranch Hands, other US Vietnam veterans and Australian Veterans).

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee concluded that there is inadequate or insufficient evidence to determine whether an association exists between exposure to the chemicals of interest (2,4,5-T, 2,4-D, 2,3,7,8-TCDD, pchloror or cacodylic acid) and lipid and lipoprotein disorders.

Literature Updates

(Watanabe et al., 2002) reported a significantly increased odds ratio of self-reported history of hyperlipidaemia and serum TEQ (PCDD/F and PCB) concentrations in the general population of Japan. Both males and females with a history of hyperlipidaemia showed a higher median TEQ body burden (5.1 and 6.3 ng/kg, respectively) compared to individuals without self-reported hyperlipidaemia (4.3 and 4.9 ng/kg, respectively). A body burden of 5 ng/kg bw was suggested by the authors to represent a possible risk level. The study was reported in a preliminary conference paper. Although reference is made in the text to a significantly
increased odds ration, no information on the statistical methodology and odds ratios are provided, nor do the authors discuss if and how they controlled for confounding factors. In its preliminary form, this study can therefore not provide evidence for a causal relationship between background exposure and lipid or lipoprotein disorders. 

(Pelclova et al., 2002) reported data from a 35-year follow-up of former Czechoslovakia workers, exposed to relatively high concentrations of 2,4,5-T and 2,3,7,8-TCDD during an uncontrolled decomposition reaction in 1965-1968. The health status of 12 former workers was investigated for multiple endpoints, including blood cholesterol and triglycerides, which were measured and compared to the serum TCDD concentrations obtained in a 1996 follow-up. Nine of the 12 individuals showed elevated plasma lipids, and hyperlipidaemia was statistically more frequent in patients with higher 2,3,7,8-TCDD levels (p=0.03). The level of 2,3,7,8-TCDD correlated with the highest level of triglycerides (p=0.02) and cholesterol (p=0.01) determined during the various follow-up studies (Table 7.3). The authors conclude that hyperlipidaemia was frequent in this roup of former 2,3,7,8-TCDD workers and may have played an important role in the prevalence of a number of other disorders observed. The levels of triglycerides and cholesterol in workers with high serum TCDD are considerably higher compared to background levels and are amongst the highest reported compared to other exposed cohorts. However, the relatively low number of subjects in this study and lack of a matched control group reduces its strength. Cholesterol and triglyceride correlations to serum TCDD indicate a dose-response relationship. However, no information on potential other influencing factors, such as obesity, alcohol consumption patterns or diet is presented.

**Biological Plausibility**

The relatively weak and inconsistent epidemiological evidence on associations of lipid and lipoprotein disorders are in contrast with extensive data that provide a biologically plausible mechanism for such an association. However, the relevance of animal data to humans, and the fact that considerable variations in responses are observed between and within animal species highlights that human data such as lipoprotein kinetic studies are still required to determine whether and how 2,3,7,8-TCDD-exposed subjects have altered lipoprotein metabolism.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides weak evidence that an association exists between lipid and lipoprotein disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. However, chance, bias or confounding factors have not been fully controlled in most studies and only show marginal positive responses are found in the majority of studies which show an association.Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. Literature Updates investigating the association do not provide any conclusive evidence on whether a causal relationship exists between exposure to the chemicals of interest and lipid or lipoprotein disorders. The putative causal link is biologically plausible, although considerable variations are observed between and within animal species.

Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is a POSSIBLE CAUSAL LINK between lipid and lipoprotein disorders and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

## 10 THYROID HOMEOSTASIS

**Overview**

Thyroid hormones influence a range of body functions including basal metabolic rate, heart rate, lipolysis, carbohydrate metabolism, insulin sensitivity, food intake and are essential for growth and development, including the nervous and reproductive systems. The hormones thyroxine (T4), triiodothyronine (T3) and calcitonin are secreted by the thyroid gland to stimulate metabolic rate and control the calcium concentration in the blood and storage in bones, respectively. Thyroid-stimulating hormone (TSH), secreted by the anterior pituitary gland, controls the release of T4 and T3. Thyrotropin-releasing hormone (TRH), released by the hypothalamus, stimulates the pituitary to produce TSH. Iodine plays a central role in thyroid physiology, providing a constituent of thyroid hormones and regulating the glandular function. The hormone homeostasis is regulated mainly by a negative feedback that includes the thyroid, the pituitary and the hypothalamus. Alteration of thyroid hormone levels can be stimulatory (hyperthyroidism, symptoms include: flushed and moist skin, weak and tremulous muscles, tachycardia and increased appetite) or suppressive (hypothyroidism, symptoms include: drowsiness, sluggishness, hypothermia, mental and growth retardation) (NAS, 2002). Effects of 2,3,7,8-TCDD on the thyroid homeostasis appear to be species-dependent and may reflect both the dose and the duration of exposure (NAS, 2002). Australian normative data for thyroid homeostasis are provided in Appendix 1.

**Synthesis of Key Reviews**

**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997**

IARC summarised thyroid homeostasis investigations in occupationally exposed cohorts (TCP and 2,4,5-T production workers) and Vietnam veterans (Ranch Hands and other US Vietnam veterans). No conclusion or evaluation was provided with regards to an association between exposure to dioxins and thyroid homeostasis.

**AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998**

ATSDR considered 2 epidemiological studies occupationally exposed cohorts (2,4,5-T production workers of the BASF and other cohorts), 1 study on Vietnam veterans (Ranch Hand chort).

From their review, ATSDR concluded that the evidence available from epidemiological studies suggests that exposure to high concentrations of 2,3,7,8-TCDD may induce subtle alterations (of unknown clinical relevance) in thyroid function. Overall, ATSDR stated that the available information suggests that 2,3,7,8-TCDD may cause adverse endocrine effects in humans.
U.S. ENVIRONMENTAL PROTECTION AGENCY 2000

US EPA considered 3 epidemiological studies on TCP and 2,4,5-T production workers (including BASF and NIOSH cohorts) and two studies on Vietnam veterans (Ranch Hands and Army Veterans).

From their review, US EPA point out that Ranch Hand and NIOSH study outcomes suggest few long-term effects on adult thyroid function, however, note that more information is required on longitudinal data to assess the potential for long-term effects associated with thyroid function changes observed in some studies. Based on the review, a shift in thyroid hormone distribution was evaluated as possible effect of exposure to 2,3,7,8-TCDD or mixtures of dioxins, furans, and PCBs.

WORLD HEALTH ORGANIZATION 2002

No review or evaluation was provided by WHO/IPCS with regards to an association between exposure to dioxins and thyroid homeostasis.

NATIONAL ACADEMY OF SCIENCES 2002

NAS Update was the first NAS series to review the literature investigating thyroid homeostasis. The reviewed studies included 3 environmental exposure groups (background exposure), one occupationally exposed cohort (2,4,5-T production) and one study on Vietnam veterans (Ranch Hands).

NAS concludes that increases in TSH in three human studies without evidence of increases in T4 indicate that the infants and the Ranch Hand personnel studied were able to adapt to the changes that may have been induced by the higher TCDD and TEQ body burdens. On the basis of its evaluation of the epidemiological evidence reviewed in 2002, the NAS committee found that there is inadequate or insufficient evidence to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and thyroid homeostasis.

Literature Updates

No Literature Updates were identified that investigated the association between thyroid homeostasis and the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

Biological Plausibility

While 2,3,7,8-TCDD is known to affect thyroid hormone concentrations, animal studies are inconsistent with respect to providing evidence on whether the effects are stimulatory or suppressive (Greene et al., 2003; NAS, 2002; U.S. EPA, 2000c). However, long-term exposure to 2,3,7,8-TCDD typically results in suppression of T4 and T3 hormones and stimulation of TSH in animals. The exact mechanism of action in humans is unknown to date. From animal studies, a plausible mechanism is that dioxins increase mainly T4 metabolism and excretion, stimulating the pituitary gland to secrete more TSH and thereby enhancing thyroid hormone production. Overcompensation for the loss of T4 can result in small excesses of circulating T4 to the increased TSH, however, animals exposed to higher doses are unable to maintain homeostasis, resulting in elevated TSH and decreased T4 levels.

Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides only weak evidence that an association may exist between thyroid homeostasis and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Although some of the epidemiological studies summarised in the Key Reviews suggest some alteration in thyroid homeostasis in relation to 2,3,7,8-TCDD and dioxin-like compounds, the results are predominantly observed after perinatal exposure and are equivocal among the different cohorts investigated. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. No Literature Updates were identified that investigated the association. The putative causal link is biologically plausible, although animal data provide inconsistent results with respect to whether effects are stimulatory or suppressive. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is insufficient evidence to determine whether an association exists between thyroid homeostasis and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

11 CIRCULATORY DISORDERS

Overview

Circulatory disorders cover a variety of conditions including hypertension, heart failure, arteriosclerotic heart disease, peripheral vascular disease and cerebrovascular disease. Known risk factors for circulatory disorders include exposure to inorganic arsenic and cacodylic acid. Australian normative data for circulatory disorders are provided in Appendix 1.

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997

IARC summarised 8 studies investigating occupationally exposed cohorts (TCP and 2,4,5-T exposure of chemical production workers and herbicide applicators), 2 studies on environmentally exposed groups (Seveso residents) and 3 Vietnam veteran studies (Australian veterans, Ranch Hands and other US Vietnam veterans). No conclusion or evaluation was provided with regards to an association between exposure to dioxins and circulatory disorders.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998

ATSDR summarised 3 studies investigating occupationally exposed cohorts (including 2,4,5-T exposure of chemical workers), 3 environmentally exposed groups (including residents of Seveso and other contaminated areas) and 2 Vietnam veteran studies (Ranch Hand cohort). It was concluded that most available data indicate that exposure to dioxins does not induce cardiovascular effects.

From its review, ATSDR concluded that while some studies have found an association between CDD exposure and cardiovascular disease, most studies have not found a clear association between exposure to 2,3,7,8-TCDD and diseases of the heart and circulatory system. It was highlighted that the human studies have suffered from a number of limitations such as examination of the cohorts after exposure has ended.
thus allowing for tissue repair to occur; lack of good exposure data; and inability to examine the relationship between serum 2,3,7,8-TCDD levels and cardiovascular disease in most studies. Overall, ATSDR concludes that there is no conclusive evidence that the cardiovascular system is a target for 2,3,7,8-TCDD toxicity.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
US EPA considered 18 epidemiological studies on TCP and 2,4,5-T production workers (including 2,4,5-T exposure of BASF, NIOSH, IARC and other chemical worker cohorts, herbicide sprayers), 2 environmental exposure studies (including residents of Seveso and other contaminated areas), 3 studies on Vietnam veterans (Australian veterans, Ranch Hands and Army Veterans) and 6 case reports.

From their review, US EPA conclude in general, results from TCP production workers were remarkably similar and mostly show SMRs close to 100. Only one study estimated exposure, and found a positive response between total TEQ and cardiovascular disease. Among most Ranch Hands and other Vietnam veterans, circulatory diseases were non-significantly elevated or close to 100. Among the studies that examined mortality from circulatory system diseases, none directly adjusted SMRs for known risk factors. Therefore, it is not possible to rule out physical and personal risk factors in the etiology of this disease. In summary, it was concluded that animal studies suggest that 2,3,7,8-TCDD causes pathologic changes that may lead to later circulatory system disease. Few epidemiological studies were designed to control for the numerous risk factors known to cause circulatory system and heart disease, but a consistent absence of the “healthy worker effect” (workers are typically healthier compared to the general population, hence SMRs in workers tend to be less than 100) in numerous mortality studies and the positive relationship observed in one study between total TEQ and circulatory disease suggest the need for additional research in this area. Hence, US EPA classifies diseases of the circulatory system as an endpoint for which human data are INSUFFICIENT and animal data have demonstrated exposure related effects.

WORLD HEALTH ORGANIZATION 2002
No review or evaluation was provided by WHO/IPCS with regards to an association between exposure to dioxins and circulatory disorders.

NATIONAL ACADEMY OF SCIENCES 2002
NAS reviewed 3 studies for the 2002 Update including one study on 2,4-D production workers, one study on municipal waste incinerator workers and one study on residents of Chapaevsk in Russia, exposed to dioxins from a chemical plant in the area. NAS notes that important sources of uncertainty among all studies in this and previous reviews include the quality of measurements of health outcomes, incomplete assessment of confounding, and inconsistency of the findings among magnitudes of exposure.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the NAS committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and circulatory disorders.

Literature Updates
A cohort study by (Dwyer et al., 2002) investigated hypertension in Air Force veterans of Operation Ranch Hand compared to veterans who served in South East Asia. Serum TCDD were measured in 1987, 1992 or 1997 and classified into quintile exposure ranges. Physical examinations were carried out in 1982, 1985, 1987, 1992 and 1997 and personal interviews recorded history of medical diagnosed hypertension which was verified by medical records. No difference was observed with respect to the risk of hypertension between the Ranch Hand and comparison cohorts (RR = 1.02, 95% CI, 0.90-1.16; p=0.76). Body mass index was significantly associated with hypertension. The relative risk of hypertension by quintile serum TCDD were significantly increased in the 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} and 5\textsuperscript{th} quintiles in the Ranch Hand and comparison group after adjustment for confounding factors. However, relative risk estimates are not provided. Serum TCDD was significantly and adversely related to the risk of hypertension within each of the two cohorts. This relation was not explained by confounding factors, although all of these contributed significantly to the model. The authors conclude that although no significant difference was found between cohorts, serum TCDD was significantly associated to the risk of hypertension within each of the two cohorts. A possible explanation was suggested as metabolic factors that are causal in the development of hypertension and for which serum TCDD is indicative. This study was reported in conference proceedings, however, provided enough detailed information for inclusion in this review. The study controlled for confounding factors and used a relatively large study population. Even though the comparison group was not spraying herbicides, serum TCDD results demonstrate that some have been exposed to dioxins above that of the general background. Although the internal dose was determined by serum TCDD analysis, analysis are up to 10 years apart and may therefore introduce errors in the quintile exposure grouping. All quintiles above the 5.35 ppt showed significant associations between serum TCDD and hypertension, with increasing relative risk with increasing serum TCDD quintile. This study provides some evidence that exposure to 2,3,7,8-TCDD is associated with risk of hypertension.

History of hypertension was reported by (Watanabe et al., 2002) in male and female residents from 17 areas in Japan (general population). Dioxins and PCB serum concentrations were obtained. Although the authors report that past history of hypertension was significantly correlated with dioxin and PCB body burden, and mention increased odds ratios, no statistical evaluation has been reported. The study was reported in conference proceedings as a short paper and only presents preliminary results. The questionnaire administered to volunteers includes a range of questions regarding potential confounding factors, however, the authors do not discuss if and how they controlled for these. Overall, in its preliminary form, this study does not provide detailed information to assess the potential for bias and confounding and can therefore only provide minimal information for an association between hypertension and exposure to dioxins and PCBs.
Biological Plausibility

Developmental effects in the cardiovascular system have been observed in 2,3,7,8-TCDD treated birds and fish. A dose-dependent increase in myocardial fibrosis has been found in marmosets subjected to acute exposure to relatively low 2,3,7,8-TCDD concentrations. Subchronic 2,3,7,8-TCDD treatment of hyperlipidemic ApoE-deficient mice, which have a lipoprotein profile similar to that of humans, resulted in a trend for earlier onset and greater severity of atherosclerotic lesions. Therefore, these results suggest that some biologic plausibility exists for an association between 2,3,7,8-TCDD exposure and increased risk of cardiovascular disease.

Conclusions and Overall Evaluation

The epidemiological evidence summarised in the Key Reviews provides only weak evidence that an association may exist between circulatory disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Although some of the epidemiological studies summarised in the Key Reviews show significant circulatory disorders with exposure to the compounds, the results are mostly close to unity and confounding could not be ruled out as a cause for the findings. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered. The Literature Updates provide some evidence for an association between serum 2,3,7,8-TCDD and hypertension, however does not provide the statistical details for hypertension. The putative causal link is biologically plausible, and animal studies suggest that 2,3,7,8-TCDD causes pathologic changes that may lead to later circulatory system changes. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is insufficient evidence to determine whether an association exists between cardiovascular disease and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

12 Gastrointestinal Disorders

Overview

Included in this are diseases of the oesophagus, stomach, intestines, rectum, liver and pancreas. The symptoms and signs of gastrointestinal disease and liver toxicity are highly varied and often vague. The gastrointestinal tract absorbs nutrients and eliminates waste products. This involves numerous chemical and molecular interactions on the mucosal surface, as well as complex local and distant neural and endocrine factors. The most convenient way of categorising diseases that affect the gastrointestinal system is by the affected anatomic segment. Peptic ulcer disease and liver toxicity are commonly investigated among epidemiological studies on gastrointestinal disorders (NAS, 2002). Australian normative data for gastrointestinal disorders are provided in Appendix 1.

Peptic ulcer disease is an ulcerative disorder of the gastrointestinal tract, caused by the action of acid and pepsin on the stomach duodenal mucosa. About 10% of the population has clinical evidence of duodenal ulcer during their lifetimes. Risk factors for peptic ulcer disease include genetic predisposition, cigarette smoking, psychologic factors and some blood groups are associated with increased risk. Liver disease is mainly diagnosed using blood tests reflecting liver function. Increase in serum bilirubin and the serum activity of hepatic enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and γ-glutamyltransferase (GGT) are common in liver disorders, however, the relative sensitivity and specificity of these diagnoses vary. Increase in GGT is a regularly recorded abnormality associated with 2,3,7,8-TCDD, however, is indicative of numerous conditions such as alcohol and drug hepatotoxicity, infiltrative lesions of the liver, parenchymal liver disease and biliary tract obstruction. Cirrhosis of the liver is also commonly reported in association with herbicide or 2,3,7,8-TCDD exposure, however, it is generally not possible to distinguish the various causes of cirrhosis by the clinical signs and symptoms or pathologic characteristics. causes include excessive alcohol consumption and viral infection (NAS, 2002).

Synthesis of Key Reviews

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER 1997
IARC summarised GGT, AST, ALT and D-glutaric acid (DGA) effects reported in studies investigating occupationally exposed cohorts (TCP and 2,4,5-T exposure of chemical production workers and herbicide applicators), environmentally exposed groups (Seveso residents) and Vietnam veterans (Australian veterans, Ranch Hands and other US Vietnam veterans). IARC concludes that none of the studies reporting elevations in ALT, AST or DGA identified clinical evidence of liver disease. Therefore it is possible that the observed findings of increased levels are related to high-level, acute exposure to 2,3,7,8-TCDD contaminated chemicals and that, barring additional exposure, the levels decrease with time. No evaluation was provided with regards to an association between exposure to dioxins and gastrointestinal disorders.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY 1998
ATSDR summarised effects reported in 3 studies investigating occupationally exposed cohorts (including 2,4,5-T exposure of chemical workers), and 1 Vietnam veteran study.

It was highlighted that limited human data is available regarding gastrointestinal effects of 2,3,7,8-TCDD in humans and that only few studies have observed effects in animals. Overall, ATSDR concluded that the available information suggests that the gastrointestinal tract is not a target for 2,3,7,8-TCDD toxicity in humans.

U.S. ENVIRONMENTAL PROTECTION AGENCY 2000
US EPA considered liver size, enzyme levels, GGT, AST and ALT, D-Glutaric acid and other gastrointestinal disorders. These were reviewed separately from studies on TCP and 2,4,5-T production workers, environmental exposure studies (including residents of Seveso and other contaminated areas), studies on Vietnam veterans (Australian veterans, Ranch Hands and Army Veterans) and case reports.

From its review, US EPA note that there seems to be a consistent pattern of increased GGT levels among individuals
exposed to 2,3,7,8-TCDD. All epidemiological investigations with increased GGT level outcomes investigated groups with a high likelihood of substantial exposure to 2,3,7,8-TCDD, although some do not report elevation of GGT. Dose-response relationships indicate that effects occur only at the highest level of exposure. However, increased GGT levels at borderline significance were also observed close to background exposure in Army veterans who experienced close to background exposure.

Overall, US EPA conclude that GGT is the only hepatic enzyme that was found in a number of studies to be chronically elevated in adults exposed to high levels of 2,3,7,8-TCDD. The consistency of the findings in a number of studies suggests that the finding may reflect a true effect of exposure but for which the clinical significance is unclear. Hence, US EPA classifies changes in GGT levels as an endpoint with good evidence that the effect has a POSITIVE relationship with exposure to 2,3,7,8-TCDD. Liver enzymes other than GGT and hepatomegaly are classified as endpoints for which human data are INCONCLUSIVE and animal data have demonstrated exposure related effects.

**WORLD HEALTH ORGANIZATION 2002**

No review or evaluation was provided by WHO/IPCS with regards to an association between exposure to dioxins and gastrointestinal disorders.

**NATIONAL ACADEMY OF SCIENCES 2002**

NAS reviewed 2 studies for the 2002 Update including a case report of heavy 2,3,7,8-TCDD intoxication and an investigation on Vietnam veterans of Operation Ranch Hand. NAS notes that the evaluation of the effect of herbicide and 2,3,7,8-TCDD exposure on gastrointestinal disorders is difficult and that clinical experience suggests that the strong interdependence between characteristics of a given person and body burden of 2,3,7,8-TCDD complicate the already difficult task of assessing associations.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the NAS committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and gastrointestinal and digestive diseases.

**Literature Updates**

No Literature Updates were identified that investigated the association between gastrointestinal disorders and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

**Biological Plausibility**

The liver is the primary target organ of 2,3,7,8-TCDD in animals, hence it would be expected that 2,3,7,8-TCDD exposure induces liver toxicity in humans at appropriate doses. Direct effects of 2,3,7,8-TCDD and herbicides on other gastrointestinal and digestive diseases have not been found.

**Conclusions and Overall Evaluation**

The epidemiological evidence summarised in the Key Reviews provides some evidence that an association may exists between in particular elevated GGT levels and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Occupationally and environmentally exposed groups as well as Vietnam veterans were considered and both relatively high and low exposed groups show effects. However, results are not consistent among all studies and confounding factors remain as alternative explanations. Only weak evidence is provided for other markers of gastrointestinal diseases. No Literature Updates were identified that investigated an association between the compounds of interest and gastrointestinal disorders. The putative causal link is biologically plausible, however, direct effects have not been observed. Hence, on the basis of the total available epidemiological and toxicological evidence, and the evaluation criteria defined for this review, we conclude that there is INSUFFICIENT EVIDENCE to determine whether an association exists between gastrointestinal disorders and exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD.

13 **Health Effects Specific to Females and Children**

The following summarises the evaluation outcomes of NAS (NAS, 2002) with respect to health effects specific to females and children associated with the exposure to the phenoxy herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD.

13.1 **Breast Cancer**

Breast cancer incidence generally increases with age. Risk factors other than age include personal or family history of breast cancer and some characteristics of reproductive history—specifically, early menarche, late onset of menopause, and either no pregnancies or first full-term pregnancy after the age of 30 years.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and breast cancer.

13.2 **Cancer of the Female Reproductive System**

This category includes cancer of the cervix, endometrium (also referred to as the corpus uteri), ovaries and other cancers of the female reproductive system. Incidence patterns and risk factors for these diseases vary. Cervical
cancer occurs more often in black women than in whites, whereas whites are more likely to develop endometrial and ovarian cancers. The incidence of endometrial and ovarian cancer also depends on age, with older women at greater risk. Human papilloma virus infection is the most important risk factor for cervical cancer. Diet, a family history of the disease, and breast cancer are among the risk factors for endometrial and ovarian cancer.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and uterine, ovarian, or cervical cancer.

### 13.3 Birth Defects

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is still LIMITED OR SUGGESTIVE evidence of an association between exposure to the chemicals of interest and spina bifida, and that INADEQUATE OR INSUFFICIENT EVIDENCE remained to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and all other birth defects.

### 13.4 Spontaneous Abortion

The committee found that for 2,3,7,8-TCDD the data are inadequate to determine whether an association with risk of spontaneous abortion and maternal exposure exists. The following conclusions do not mention whether the findings are based on maternal or paternal exposure. For herbicides – namely 2,4-D and 2,4,5-T- the committee found that there was inadequate or insufficient evidence to determine whether an association exists.

Overall, on the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and spontaneous abortion in pregnancies that begin after exposure.

### 13.5 Stillbirth, Neonatal Death, and Infant Death

On the basis of its evaluation of the epidemiological evidence reviewed previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and stillbirth, neonatal death, and infant death.

### 13.6 Low Birthweight and Preterm Delivery

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and low birth weight or preterm delivery.

### 13.7 Childhood Cancer

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and child cancers.

### 13.8 Endometriosis

Endometrium is the tissue that lines the inside of the uterus and is built up and shed each month during menstruation. In endometriosis, endometrium is found outside the uterus-usually in other parts of the reproductive system, the abdomen, or the tissues near the reproductive organs. That misplaced tissue develops into growths or lesions that continue to respond to hormonal changes in the body and break down and bleed each month in concert with a woman’s menstrual cycle. Unlike blood released from endometrium in the uterus, blood released from the tissue in endometriosis has no way to leave the body, and this results in inflammation, internal bleeding, and degeneration of blood and tissue from the growth and can cause scarring, pain, infertility, adhesions and intestinal problems.

On the basis of its evaluation of the epidemiological evidence reviewed in the 2002 Update and previous NAS reports, the committee found that there is INADEQUATE OR INSUFFICIENT EVIDENCE to determine whether an association exists between exposure to the chemicals of interest (2,4-D, 2,4,5-T or its contaminant 2,3,7,8-TCDD, picloram, or cacodylic acid) and endometriosis.
Forty-seven studies describing the patterns of self-reported signs and symptoms, diagnosed diseases and/or death matched the inclusion criteria for this review. The majority of studies (n = 30) were case reports describing the patterns of signs, symptoms or diagnosed disease (and death) from individual cases. Seventeen case series or medical surveys were identified reporting the patterns of conditions observed in a defined exposure cohort.

These studies investigated a total of 12157 individuals and have been classified according to exposure type. Three classifications were defined:

1. Long-term exposure (23 studies): includes studies where exposure was known or presumed to have lasted several months to several years.
2. Short term exposure (9 studies): includes studies where exposure was known or presumed to have lasted for only days to several weeks.
3. Acute exposure or poisoning (15 studies): includes studies where exposure was known or presumed to have occurred via direct contact of the raw compound on one occasion (2 studies) or via accidental or deliberate poisoning (13 studies).

Among each of the exposure categories studies have been summarised separately according to the compound investigated, including exposure to 2,3,7,8-TCDD, exposure to 2,4,5-T (and the co contaminant 2,3,7,8-TCDD), exposure to 2,4-D and exposure to mixtures thereof. Since the vast majority of studies did not assess exposure or analysed internal concentrations, a sub-comparison of patterns of conditions observed in high versus low exposure groups in the long- or short-term exposure category was not feasible. However, a short summary of conditions found in each study, including information on the exposure duration and dose where available, was provided.

In summarising the health findings of case reports and case series, it has to be highlighted that the majority of studies have no statistical power and investigated individuals or cohorts at a wide range of point-in-times relative to time of exposure, ranging from reports of health findings immediately after the first symptoms occurred to several years post-exposure. In addition, lack of consistency among signs and symptoms reported amongst studies may be the result of differences in medical assessment, evaluation of the disease/condition and/or the focus on certain disease groups. Overall, evaluations on the strength of association between a sign/symptom/disease and exposure observed in such studies are not feasible and this summary is restricted to observations of general patterns in disease groups from exposure to the compounds of interest.

1. Long-term exposures (several months to years)

1.1 Long-term exposure to 2,3,7,8-TCDD

(Hoffman et al., 1986) reported health effects of 75 male and 79 female (average age 26.5 years) Missouri residents of a 2,3,7,8-TCDD contaminated site after the introduction of contaminated sludge in 1971. The Exposure duration is unknown, however the mean period of residency in the contaminated area was 2.8±1.9 years. Exposure dose is unknown, however the levels of TCDD in soil samples ranged from 39-2200 ppb, measured in 1983. Medical examination and professional interviews were carried out and findings were compared to 155 unexposed persons living in the same area. There was no significant difference between the two groups except for ‘other skin problems’ and ‘other miscellaneous diseases’. Signs and symptoms included Numbness or pins and needles in the hands or feet (p<0.05), persistent severe headaches (p<0.05), tremors (p=0.07), chronic memory loss (p=0.06), tension/anxiety (p<0.01), anger/hostility (p<0.05), depression/dejection (not significant), fatigue/inertia (not significant), Non-specific dermatitis (p<0.01), Anergy (22 persons), relative anergy (50 persons), Increased serum cholesterol, Elevated urinary uroporphyrins, Decreased serum bilirubin, elevated white blood cell count. The authors conclude that long-term exposure to TCDD may have adverse consequences, and was associated with depressed DTH responses and in vitro immune abnormalities.

(McConnell and Anderson, 1987) reported 316 male cases of exposure to 2,3,7,8-TCDD at the truck terminals in St. Louis, Missouri. Contamination of several sites occurred via contaminated oil used for dust control. Exposure dose and durations are unknown, however dioxin concentration of 18.7 ppb was found in rafter dust in 1983 and 75 participants worked for 3 or more months on site between January 1971 and December 1974. No detectable levels were found at two other sites. Fat TCDD concentrations of two high exposure participants were 78 and 13.8 ppt (whole-weight basis) in 1983. Symptoms in the high exposure group were compared to the low exposure group. Symptoms were self-reported via a medical survey and formal medical diagnoses were carried out. The following signs and symptoms were reported (numbers in brackets give the number of participants with that have reported the condition, or the significance of the findings). Pelvic angiosarcoma (1), soft tissue sarcoma (1), Pins and needles in hands and feet (p<0.01), trouble falling or staying asleep (p<0.01), weakness in arms or legs (p<0.05), dizziness (p<0.05), numbness in hands and feet (p<0.05), feeling sad or blue (p<0.05), Suspected chloracne (2), skin lesions (30), porphyria cutanea tarda (1). Diseases or conditions for which medical attention was first sought in high or low exposed participants between January 1971 and December 1982 included Hepatitis (low: 2, high: 2), cirrhosis (low: 5, high: 0), Yellow jaundice (low: 2, high: 2), Other liver disease (low: 2, high: 0), Nephritis (low: 18, high: 9), Bloody urine (low: 13, high: 9), Protein in urine (low: 5, high: 3), other kidney disease (low: 6, high:0), Cystitis or...
bladder infection (low: 8, high: 4), Neurologic disease (low: 5, high: 2), Heart disease (low: 25, high: 8), Psoriasis (low: 9, high: 4), Dermatitis (low: 28, high: 10), Acne (low: 8, high: 2), Eczema (low: 2, high: 0), Eye infection or red eye (low: 15, high: 3), Seizures, fits or epilepsy (low: 3, high: 0), Mental illness (low: 3, high: 0), Depression (low: 13, high: 4), Diabetes (low: 13, high: 3), High blood pressure (low: 51, high: 15), Chronic itching to burning skin irritation (low: 46, high: 11), Other serious skin problem (low: 25, high: 3), Chronic itching or burning eyes (low: 13, high: 6), Weakness in legs or arms (low: 23, high: 14), Tremors (low: 10, high: 6), Dizziness (low: 18, high: 13), Numbness in hands or feet (low: 27, high: 15), Pins and needles in hands or feet (low: 21, high: 15), Severe headaches (low: 16, high: 7), Joint or bone pain (low: 40, high: 12), Muscle aches or pains (low: 24, high: 13), Trouble falling or staying asleep (low: 10, high: 9), Excessive nervousness or irritability (low: 23, high: 7), Trouble remembering things (low: 7, high: 2), Loss or lack of appetite (low: 10, high: 1), Feeling blue or sad (low: 5, high: 5), Feeling worried or anxious (low: 8, high: 5), Loss of 10 lb or more in 1 month while not on a diet (low: 8, high: 5), Impotence (low: 25, high: 11), Loss of sex drive (low: 21, high: 12), Cancer (low: 24, high: 4).

(McConnell et al., 1993) investigated angiosarcoma, porphyria cutanea tarda, and probable chloracne in a male truck driver exposed to waste oil contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Exposure occurred during work (unhooking trailers) at a TCDD contaminated site in Missouri, U.S.A during the period of early 1970s to 1980. It was reported that exposure was considered minimal for many years, but high exposure occurred for 2-3 months per year during the early 1970s. Internal dose is unknown, however, the soil samples at the terminal showed TCDD concentrations in 1983 as high as 17 ppb. Signs and symptoms were self-reported and formal medical diagnoses were carried out. These included Angiosarcoma in groin, Right groin pain and weakness in right leg. Blistering on dorsa of hands, probable chloracne, Porphyria cutanea tarda, Increased hair growth over dorsa of hands, unexplained weight loss.

(Rodriguez-Pichardo et al., 1991) studied chloracne caused by ingestion of olive oil accidentally contaminated with PCDDs and PCDFs in a Spanish family (2 adults, 6 children). The olive oil was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. Exposure occurred during work by ingestion of olive oil accidentally contaminated with PCDDs and PCDFs in a Spanish family (2 adults, 6 children). The olive oil was contaminated with 2,3,7,8-TCDD toxic equivalents (NATO) of 79.7 ng/g oil and quaternary ammonium compounds. Ingestion of contaminated olive oil lasted from December 1981 to October 1982 on a daily basis, however, the amount of oil ingested by each family member was unknown. Adipose tissue analysis revealed 1720 ppb of TEQ (NATO) 5 years after cessation of exposure. Medical assessments were carried out during the period of exposure (July 1982) with subsequent medical examinations until 1990. Signs and symptoms reported included chloracne, hyperpigmentation of the facial skin, dyspnoea at the slightest effort, dizziness when breathing, cough, mucous expectoration, Vomiting, transitory renal failure, proteinuria, Oedema of the eyelids, facial hypertrichosis (hirsutism). Symptoms specific to children were reported (e.g. growth retardation).

(Stehr et al., 1986) reported health findings from 68 residents of Missouri (age and gender unknown) exposed to 2,3,7,8-TCDD following the spraying of contaminated waste oil in 1971. Participants were individuals who lived or worked at least 6 months in an area with 2,3,7,8-TCDD levels exceeding 100 ppb, or for 2 years at 20-100 ppb, or participated more than once a week in activities involving direct contact with the soil for at least 6 months where TCDD levels exceeded 100ppb, or for 2 year at 20-100 ppb. The health findings (using physical, neurological and dermatological examination, and laboratory tests) were compared to a group of 36 low exposed or not exposed individuals. Few significantly higher incidences of symptoms in the high risk group were reported, but several trends were noted. These included Chloracne-like skin disorders (10.3%), Elevated serum cholesterol (23.1%), Urinary tract abnormalities (trend – not significant), Diminished peripheral pulses (weak trend – no data), Elevated mean platelet count (p<0.05, but within normal range), elevated serum triglycerides (17.9%).

**Conclusions and summary**

The majority of studies (n=4) reporting on long-term exposure to 2,3,7,8-TCDD were derived from Missouri residents or workers exposed to contaminated waste oil sprayed for dust control. One case of long-term ingestion of contaminated olive oil was also reported. A total of 547 individuals were reported within these groups. A wide range of signs and symptoms has been observed in these groups (see Table 5). All studies reported some skin and metabolic disorders or problems with chloracne, dermatitis, itching or burning and skin lesions listing amongst the most frequent observations. Gastrointestinal, motor-sensory, neuropsychiatric and cognitive disorders or complaints also were among the most frequently reported, in particular elevated uroporphyrins, numbness or pins and needle sensations, persistent or severe headaches, memory loss and dizziness.

**Table 5. Summary of signs, symptoms and diagnosed disease reported in 5 studies investigating long-term exposure to 2,3,7,8-TCDD**

<table>
<thead>
<tr>
<th>Total number of studies, number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies, n = 317</td>
<td>Cancer (7)</td>
<td>Angiosarcoma (2), Cancer (4), soft tissue sarcoma (1)</td>
</tr>
<tr>
<td>1 study, n = 316</td>
<td>Circulatory (2)</td>
<td>High blood pressure (1), heart disease (1)</td>
</tr>
<tr>
<td>1 study, n = 8</td>
<td>Respiratory (3)</td>
<td>Cough (1), dyspnoea (1), mucous expectoration (1)</td>
</tr>
<tr>
<td>1 study, n = 316</td>
<td>Hepatic (4)</td>
<td>Hepatitis (2), yellow jaundice (2)</td>
</tr>
<tr>
<td>2 studies, n=546</td>
<td>Renal (&gt;53)</td>
<td>Nephritis (9), renal failure (1), Blood in urine (9), cystitis or bladder infection (4), urinary tract abnormalities (nd), elevated urinary uroporphyrins (25*), proteinuria (5)</td>
</tr>
</tbody>
</table>
1 study, n = 8  Gastrointestinal (1) vomiting (1)
4 studies, n = 539  Metabolic (38) Diabetes (3), porphyria cutanea tarda (2), increased cholesterol (21*), elevated triglycerides (12)
2 studies, n = 222  Hematologic (>9) Elevated mean platelet count (nd*), decreased serum bilirubin (1*), elevated white blood cell count (8*)
1 study, n = 154  Immunologic (>84) Anergy (26), relative anergy (58)
3 studies, n = 478  Cognitive (>31) Dizziness (>14*), memory loss (15*)
1 study, n = 154  Hematologic (>9) Elevated mean platelet count (nd*), decreased serum bilirubin
4 studies, n = 539  Motor-sensory (111) Eye infection or red eye (3), muscle aches or pains (13), Numbness or pins and needles in hand and feet (74*), tremor (20*), groin pain (1)
3 studies, n = 471  Neuropsychiatric (>132) Anger/hostility (18*), loss of appetite (1), depression (4), feeling sad or blue (nd*), anxiety/tension (26*), persistent or severe headaches (47*), loss of libido (12), difficulty sleeping (9*), weakness (15*)
5 studies, n = 547  Skin (102) Acne (2), suspected and confirmed chloracne (18), dermatitis (26*), hyperpigmentation (1), itching/burning (17), oedema (1), psoriasis (4), skin lesions (30), other serious skin problems (3)
3 studies, n = 325  Other (31) Hirsutism (2), Joint or bone pain (12), weight loss (6), impotence (11)

Total number of studies = 5; total number of individuals = 547
Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - significant results have been reported in any study
nd – no data

1.2 Long-Term Exposure to 2,4,5-T or TCP (and 2,3,7,8-TCDD)

(Basharova et al., 1997) reported neuropathologic symptoms in 73 Russian shop workers exposed to 2,4,5-T and dioxins during the production of 2,4,5-T. Exposure dose was unknown but the levels were high enough to induce chloracne in 83% of workers. Exposure lasted for 2 years during 1965-1967. Symptoms were self-reported and clinical examinations were carried out post-exposure. A health review was undertaken in 1991-1994 by means of clinicofunctional and laboratory methods. Signs and symptoms included Headache, sleepiness, restless intermittent sleep or insomnia, increased irritability, fatigue, weakness, reduced memory, reduced potency, depression, increase in tendon reflexes, eyelid tremor, neurosis, radiculitis, lumbago, vertebral osteochondrosis, dizziness, rapid change of mood, pain in limbs, sensation of numbness in hands especially at night, gnawing pain in joints and backbone, reduced sensitivity to pain in extremities, decreased capacity for work, rapid exhaustion, joint, muscle and radicular pain, encephalopathy with hypothyramus, crisis, Slight coordination disturbance, Steady red dermographism, chloracne, acrocyanosis, Nausea, Pain near the heart, tachycardia, arterial tension fluctuations, hypertension, Weight loss, hypertonia, hypoxia, slight asymmetry of nasolabial folds, Neurological status showed chloracne took place on the background of vegetative-dysfunctions of predominantly symptomatic-adrenal character. Many years post-exposure, symptoms transformed into vascular diseases of the brain.

(Neuberger et al., 1999) reported persistent health effects of 50 chemical workers (49 male, 1 female, aged 57.8 ± 6.8 years, including laboratory research and clean-up workers) exposed to 2,4,5-T and 2,3,7,8-TCDD during herbicide production in Austria. Exposure occurred between 1969 and 1975. Duration of exposure is unknown, however the production of herbicide was developed in 1969 to 1971 and production took place from 1971 to 1973. Clean up after closure of the chemical plant continued until 1975. The 2,4,5-T produced contained around 50 ppm TCDD and blood serum TCDD analysed from 9 workers ranged from 98-659 ppt, measured in 1990. The worker cohort was compared to 2 different control groups of non-chemical workers and asbestos cement workers. Laboratory analyses of blood and urine samples were performed in 1996 and health interviews by trained occupational physicians were undertaken following a standardised questionnaire. Significantly higher prevalence of sleep disturbance, dyspnoea on exertion, loss of appetite, stomach trouble, chronic inflammation and chronic liver disease were found in the exposed group compared to the control groups. Control groups were not tested for neurological symptoms. Signs and symptoms included Sleep disturbance, headache, dizziness, neuralgia, loss of appetite, impaired potency, depression, Chloracne, Dyspnoea on exertion, Stomach troubles, chronic liver disease (including cirrhosis), Chronic inflammation.

(Pazderova-Vejlupkova et al., 1981) reported the development and prognosis of chronic intoxication by 2,4,5-T and 2,3,7,8-TCDD in a Czechoslovakian chemical production worker cohort of 55 males (average age 36.3 years). Exposure occurred for a minimum of 3 years during 1965-1968, and possibly for a period prior to that, during production of 2,4,5-T. Internal dose was not assessed. Self reported symptoms and result from formal medical diagnoses were reported including fatigue, weakness in lower extremities, pain under right coastal arch, pathological changes, polyneuropathy, encephalopathy, severe neurotic
Conclusions and summary

Studies reporting on long-term exposure to 2,4,5-T (and its co-contaminant 2,3,7,8-TCDD) investigated a total of 714 chemical production or clean-up workers (n=4 studies) and Seveso residents (n=1 studies). Wide ranges of signs and symptoms have been observed in these groups (see Table 6). Skin and neuropsychiatric complaints or disorders were reported in all studies and included most frequently chloracne, actinic elastosis, headache, insomnia or sleep disturbance, sleepiness and loss of appetite. Other frequently reported signs and symptoms pertained to respiratory, hepatic, gastrointestinal, cognitive and motor-sensory problems. Among these the most frequently reported conditions included pulmonary function abnormalities, liver enlargement and/or jaundice, gastrointestinal ulcers and numbness. Other frequent complaints included loss of libido.

Table 6. Summary of signs, symptoms and diagnosed disease reported in 5 studies investigating long-term exposure to 2,4,5-T and/or TCP (and the co contaminant 2,3,7,8-TCDD)

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies, n = 128</td>
<td>Circulatory (&gt;34)</td>
<td>Arterial tension fluctuations (many), arteriosclerosis (8), insufficient cerebral circulation (nd), hypertension (11), heart pain (15), tachycardia (nd)</td>
</tr>
<tr>
<td>3 studies, n = 586</td>
<td>Respiratory (58)</td>
<td>Dyspnoea (11*), pulmonary function abnormalities (32*), respiratory tract problems (15)</td>
</tr>
<tr>
<td>3 studies, n = 437</td>
<td>Hepatic (&gt;33)</td>
<td>Hepatic lesions (11), liver disease (nd*), liver enlargement and/or scleral jaundice (22)</td>
</tr>
<tr>
<td>2 studies, n=387</td>
<td>Renal (23)</td>
<td>urinary tract infections (11), uroporphyrinuria (12)</td>
</tr>
<tr>
<td>4 studies, n = 659</td>
<td>Gastrointestinal (&gt;145)</td>
<td>Gastritis (23), upper gastrointestinal ulcer (42*), nausea (&gt;23), abdominal pain (23), stomach troubles (11*), vomiting (23)</td>
</tr>
<tr>
<td>1 studies, n = 55</td>
<td>Metabolic (116)</td>
<td>Diabetes mellitus (4), low glucose tolerance (10), hyperlipidemia (37), hyperphospholipaemia (23), hypercholesterolemia (31), porphyria cutanea tarda (11),</td>
</tr>
<tr>
<td>2 studies, n = 128</td>
<td>Hematologic (&gt;54)</td>
<td>Increased blood plasma (20-24), increased blood proteins (7), hypoxia (9), decreased plasma albumen (18)</td>
</tr>
<tr>
<td>3 studies, n = 178</td>
<td>Cognitive (&gt;90)</td>
<td>Dizziness (&gt;15), Encephalopathy (&gt;4), Hypothalamus crisis (nd), reduced memory (15), neuralgia (15), neurasthenia syndromes (6), neurosis (&gt;35), osteochondrosis (nd), decreased work capacity (nd, many)</td>
</tr>
<tr>
<td>3 studies, n = 460</td>
<td>Motor-sensory (&gt;213)</td>
<td>Coordination disturbance (nd, often), eye irritation (13), hypertonia (almost 36), numbness (most of 73), pain in joints, back, muscles, ribs, limbs (nd, many), reduced sensitivity to pain (nd, often), polyneuropathy (13), pseudoneurasthenia syndromes (8), radiculitis (51), increased tendon reflexes (nd, many), tremor nd, (many), impaired vision (19)</td>
</tr>
<tr>
<td>5 studies, n = 714</td>
<td>Neuropsychiatric (&gt;253)</td>
<td>Loss of appetite (29*), depression (&gt;8), rapid exhaustion (nd, many), fatigue (&gt;21), headache (10), insomnia/sleep disturbance (31*), increased irritability (26), mood changes (most), headache (63), reduced/impaired</td>
</tr>
</tbody>
</table>
1.3 Long-Term Exposure to 2,4-D

(Johnston et al., 1998) reported a case of possible exposure to 2,4-D (unconfirmed) by an amateur golfer from licking golf balls during games in Britain. Exposure lasted for several years prior to 1997. Formal diagnosis by a medical practitioner and results of laboratory tests were reported. Signs and symptoms included fatigue, Abdominal pain, diarrhoea, vomiting, dark urine, pale faeces, chronic hepatitis progressing to cirrhosis, Itching, enlarged spleen.

Conclusions and summary

Only one study was identified that reported a case of long-term exposure to 2,4-D. A summary of signs and symptoms reported is provided in Table 7.

Table 7. Summary of signs, symptoms and diagnosed disease reported in 1 study investigating long-term exposure to 2,4-D

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study, n = 1</td>
<td>Hepatic (2)</td>
<td>Cirrhosis (1), hepatitis (1)</td>
</tr>
<tr>
<td>1 study, n = 1</td>
<td>Renal (1)</td>
<td>dark urine (1)</td>
</tr>
<tr>
<td>1 study, n = 1</td>
<td>Gastrointestinal (4)</td>
<td>Diarrhoea (1), pale faeces (1), pain (1), vomiting (1)</td>
</tr>
<tr>
<td>1 study, n = 1</td>
<td>Neuropsychiatric (2)</td>
<td>Fatigue (1)</td>
</tr>
<tr>
<td>1 study, n = 1</td>
<td>Other (2)</td>
<td>Itching (1), enlarged spleen (1)</td>
</tr>
</tbody>
</table>

Total number of studies = 1; total number of individuals = 1

Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.

* - significant results have been reported in any study

1.4 Long-Term Exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD

(Bleiberg et al., 1964) reported 29 cases production workers who were exposed to 2,4-D and 2,4,5-T. The signs and symptoms of three individuals were described in more detail (c/s). Formal medical diagnoses were carried out. Signs and symptoms included right upper quadrant pain (nd), Chloracne (21), hyperpigmentation (17), fragility of the skin (8), vesiculobullous eruptions on exposed skin (2 c/s), Porphyria cutanea tarda (11), darkening/reddening of urine (3 c/s), increased urinary uroporphyrins (11), hepatic dysfunction (2 c/s), Hirsutism (14). A Follow up of these and other workers from the same factory was reported in Poland et al (1971).

(Bogen, 1979) reported cases of 78 Vietnam veterans (average age 31.7 years) exposed to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) during spraying of the herbicide in the Vietnam War. Exposure duration or doses are unknown. A ten-month study was undertaken using medical assessments and laboratory analysis. Non-specific cancers were reported. Signs and symptoms included Joint pain, stiffness, hypersonnolence, extreme fatigue, tingling, numbness, dizziness, headache, autonomic dyscontrol, depression, suicidal attempts, violent rages, reduced concentration, reduced memory, loss of libido. Persistent rash aggravated by sunlight. Dyspnoea, Gynecomastia, Gastrointestinal ulcerations, anorexia, nausea, vomiting, hematemesis, diarrhoea, constipation, abdominal pain, hepatitis, jaundice, brown urine, hematuria, Sinus bradycardia, premature ventricular contractions, Swelling, blurred vision, galactorrhea, infections, allergies.

(CDC, 1988a) reported the physical health status of 2490 Vietnam veterans. Potential exposure (dermal, ingestion, inhalation) to Agent Orange (2,4,5-T, 2,4-D and 2,3,7,8-TCDD) occurred during service in the Vietnam war. Formal medical examination was carried out and included standard neuropsychological tests and laboratory tests. Outcomes were compared to non-Vietnam veteran (n=1972). The health outcomes that Vietnam veterans reported significantly more often (% and odds ratios shown, * indicates confidence interval included 1.0) than veterans who served elsewhere...
include Cancer (1.9%, OR1.4*), Fair or poor general health (20.3%, OR1.9), limitation in activity (26.9%, OR1.1*), somatic symptoms (nervousness, fatigue, gastrointestinal tract ailments, dizziness, headaches) (10.2%, OR1.7), peripheral neuropathy symptoms only (numbness, tingling, burning sensation, or weakness of arms or legs) (3.0%, OR1.5*), peripheral neuropathy signs only (nerve conduction velocity) (8.2%, OR1.2*), peripheral neuropathy symptoms and signs (1.0%, OR1.2*), Chloracne (1.9%, OR7.3), other skin conditions (33%, OR1.7), hyperpigmentation (4.0%, OR1.2*), Chest roentgenogram findings (22.4%, OR1.1*), Gastrointestinal tract ulcers (12.6%, OR1.1*), hepatitis (4.8%, OR1.3*), cirrhosis (0.7%, OR1.1*), other liver conditions (3.6%, OR1.7), urinary tract problems (16.8%, OR1.1*), Hypertension (25%, OR1.2), benign growth hormone (1.0%, p<0.05), increased glucose (5.3%, p<0.05), increased thyroid-stimulating hormone finding (4.7%, OR1.2*), any electrocardiographic finding (14.3%, OR1.1*), altered peripheral arterial hemodynamic finding (4.7%, OR1.2*), Increased serum hemoglobin (5.3%, p<0.05), increased thyroid-stimulating hormone (1.0%, p<0.05), increased γ-glutamyl transferase (5.5%, p<0.05), Hypertension (25%, OR1.2), benign growth (20.1%, OR1.1*), diabetes (1.7%, OR1.1*), high frequency hearing loss (42.2%, OR1.4). The authors concluded that Vietnam veterans more frequently reported current somatic symptoms and physician-diagnosed diseases than did non-Vietnam veterans, but most of these symptoms were not detectable by the comprehensive physical and laboratory screening examinations used in the study. One physical difference that is still detectable is that Vietnam veterans have greater hearing loss.

(Decoufle et al., 1992) reported the self-reported health status of 7924 Vietnam veterans in relation to perceived exposure to herbicides and combat. Exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) occurred during service in the Vietnam war between 1965 and 1971 via dermal exposure, ingestion and inhalation. Interviews were carried out by trained specialists herbicide exposures was self-reported. Results were compared to non-Vietnam veterans (n=7364). Vietnam veterans reported 20 of the 21 health outcomes more often than did veterans who served elsewhere. These included (odds ratios – all significant - are given in brackets) Fair or poor general health (1.9), limitation in activity (1.3), experienced at least 6 of 15 listed psychological symptoms (3.1), symptoms consistent with posttraumatic stress disorder (3.9), headaches (1.7), dizziness (1.8), ringing in ears (1.6), neuromuscular (1.6), Chloracne (3.9), other skin conditions (1.9), Gastrointestinal ulcer (1.2), urinary tract condition (1.2), other liver condition (1.4), Benign tumour, growth or cyst (1.1), hypertension (1.3), diabetes (1.3– confidence interval included 1.0). For all the above conditions the odds ratio was higher for Vietnam veterans exposed to moderate or high levels of herbicide compared to those with no or low exposure. It was concluded that the strong, positive associations found between health outcomes and self-reported herbicide exposure in this group of Vietnam veterans are probably not accounted for by exposure to chemical herbicides in Vietnam. Rather, these relations more likely resulted from a combination of psychological stress reactions and conditioning by intense and prolonged media portrayal of herbicides as a health threat that produced hypochondriasis, somatization and increased medical care utilization in some Vietnam veterans. (Dolan, 1988) reported a case of exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) in one Vietnam veteran (aged 34) during military service in areas subjected to spraying of Agent Orange. Exposure duration and dose is unknown. Results from medical diagnoses were reported and included Cancer of the larynx with metastases to the throat, leading to a tracheostomy, Xerostomia, extreme odour from trachea and lungs.

(Fleck, 1985) reported a case of dermal and oral exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) from contaminated food and water in Vietnam veteran. Exposure occurred for 2 years during 1966-1967. Exposure dose is unknown. Self-reported symptoms and findings from medical diagnoses, including electrophysiological studies were reported. Signs and symptoms included Nummness, paresthesia, weakness, fasciculations, coldness in extremities, pain in neck, shoulders, arms, legs, hands and feet, headache, disorientation, insomnia, tremors, lack of concentration, impaired potency, excessive sweating in lower extremities, Chloracne, blisters on chest, Ablacescency, foot, ear and nose infections, subdural hematomas.

(Kayser et al., 1986) reported a case of exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) from contaminated food and water in one Vietnam veteran (age 40). Exposure occurred for 2 years during 1969-1970. Self-reported symptoms and findings from formal medical diagnoses were reported. Signs and symptoms included Chest pain, dyspnoea, exudative postnasal dripping, maxillary sinusitis, allergic asthmoid bronchitis with pronounced obstruction, acute aseptic pleuritis, cough, severe tissue damage of lungs, Pyrexia, Feeling of sickness.

(Levy, 1988) reported cases of exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) in six Vietnam veterans with chloracne symptoms. Exposure duration (between 1964 and 1970) and doses are unknown; chloracne was used as a medical indicator to determine exposure to Agent Orange. Exposure occurred during active service in areas subjected to spraying of Agent Orange. A comparison of 25 matched control veterans with no current or history of chloracne was used. Medical assessments were performed to diagnose chloracne. Organic psychological deficits were determined by administering neuropsychological battery and by conducting interviews. The exposed group showed significantly greater deficits on brain function, and significantly more incidents of posttraumatic stress disorder (PTSD). Signs and symptoms reported included PTSD, depression, anxiety, uncontrollable pressures, verbal violence, violence against objects, assaults, suicide thoughts, brain dysfunction in areas of vocabulary, word fluency, digit/written and oral, Rey-List B variables. The authors concluded that among the veterans meeting criteria of PTSD, there are those whose condition cannot be explained by combat stress alone. It is acknowledged that chloracne symptoms 16-22 years after exposure may underestimate the number of veterans exposed to Agent Orange.

(Meyer, 2002a) reported cases of 7 male Vietnam veterans with Cutaneous T-cell lymphoma (CTCL). Findings from medical diagnoses and self-reported symptoms included Cutaneous T-cell lymphoma, Hodgkin’s disease, Posttraumatic stress syndrome, joint pain, peripheral...
neuropathy, Rash, patch/plaque erythroderma, Gastrointestinal problems, Pruritus.

(Poland et al., 1971) reported outcomes of a health survey of chemical workers (male, average age 39.3 years, 55 Caucasian, 18 African-American, n = 73) exposed to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD. The period of employment was prior to February 1969 and average employment duration was 8.3 years in the factory. Medical history was reviewed, formal medical examination; laboratory tests and psychological tests were carried out. Signs and symptoms included Lower extremity fatigue or difficulty in climbing stairs (2), headaches (8), decreased sense of proprioception (1), absence of Achilles tendon reflexes (2), tremors of the hands (3), hypomanic-hysterical (4), hypomanic-psychopathic (6), Minimal active acne (35), moderate to severe active acne (13), hyperpigmentation (30), hirsutism (16), Increased serum cholesterol (7). Nausea, vomiting, diarrhoea, abdominal pains, or blood in the stool (22), uroporphyrinuria (1), palpable liver (6). Itching of the eyes (7), frequent tearing (14), bloodshot eyes (5), sties (7), conjunctivitis (3), hyperaemia of the nasal mucosa (23), inflammation of the buccal mucosa (8), ulcers (6), decreased auditory acuity (10).

(Robinowitz et al., 1989) reported cases of exposure to Agent Orange (2,4-D, 2,4,5-T and 2,3,7,8-TCDD) in 153 Vietnam veterans (average age 33.67 years) who were admitted to alcohol or drug dependence treatment units. Exposure occurred during the Vietnam conflict through handling of Agent Orange. Self-reported exposure was moderate to high for 58 veterans and minimal to low for 95 veterans. Internal dose was not assessed. The psychological characteristics of high versus low exposure groups were compared. Significantly higher scales of personality measures as well as other psychological characteristics (see symptoms below) were found for the high exposure group. Psychological characteristics were established using standardised psychological battery and included Infrequency, hypochondriasis, depression, paranoia, psychasthenia, schizophrenia, hypomania, social intrusion, poor morale, psychoticism, organic symptoms, family problems, hostility, phobias.

(Tong et al., 1989) reported a case of exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD by spraying the Herbicide Esteron Brush Killer. Approximately 1.6 Litres per day of raw herbicide were sprayed; one analysed sample contained 7.7 ng/g TCDD. Adipose tissue concentrations in the farmer were 77 pg/g (lipid) 5 years post-exposure. Exposure lasted for 14 years during 1969-1983. Spraying with the herbicide was done frequently during spring and summer, and occasionally during winter. Protective clothing was not worn. The exposure history is self-reported and symptoms were recorded in a diary. Formal diagnoses were carried out by a medical practitioner. Signs and symptoms included three incidences of cancer: adenocarcinoma (treated), tumour of adrenal gland (treated). Extreme fatigue, leg cramps, weakness, tingling extremities, insomnia, loss of appetite, Allergic blepharitis and dermatitis, oedema of eyelids, Elevated cholesterol, Diarrhoea, urinary tract infection, distal colonic obstruction (cause: adenocarcinoma metastatic from lung), Nocturnal leg cramps and systolic heart murmur, aortic stenosis, Occasional nose bleeds, weight loss, fever.

Conclusions and summary

Long-term exposure to mixtures of 2,4,5-T, 2,4-D and 2,3,7,8-T included investigations on groups or individuals exposed during chemical production (2 studies), herbicide sprayers (1 study) and Vietnam veterans (9 studies). A total of 10764 individuals were investigated in these groups. Wide ranges of signs and symptoms have been observed in these groups (see Table 8). The most frequent signs and symptoms observed pertained to cancer, gastrointestinal, cognitive, motor-sensory, neuropsychiatric and skin disorders or complaints. Specific symptoms among these groups which were most frequently reported included general cancer, general gastrointestinal problems, dizziness, hearing loss, neuromuscular problems, headache, activity limitations, general psychological problems, posttraumatic stress disorder, chloracne and other skin conditions, benign growth and generally fair or poor health. Other frequent conditions included hypertension and general liver conditions.

Table 8. Summary of signs, symptoms and diagnosed disease reported in 12 studies investigating long-term exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 studies, n = 10574</td>
<td>Cancer (&gt;74)</td>
<td>Adenocarcinoma (1), adrenal gland tumour (1), cancer (58*), cutaneous T-cell lymphoma (7), Hodgkin’s disease (nd), laryngeal cancer (1), ulcers (6)</td>
</tr>
<tr>
<td>5 studies, n = 10494</td>
<td>Circulatory (&gt;3223)</td>
<td>Aortic stenosis (1), peripheral arterial hemodynamic finding (117*), bradycardia (not infrequent), any electrocardiographic finding (356*), subdural haematoma (1), hypertension (2707*), hypertrophy of the left ventricular (40*), systolic murmur (1), premature ventricular contractions (not infrequent)</td>
</tr>
<tr>
<td>2 studies, n = 79</td>
<td>Respiratory (11)</td>
<td>Dyspnoea (6), bronchitis (1), cough (1), dyspnoea (1), lung-tissue damage (1), Pleuritis (1)</td>
</tr>
<tr>
<td>5 studies, n = 10568</td>
<td>Hepatic (1073)</td>
<td>Hepatic dysfunction (2), hepatitis (128*), jaundice (4), cirrhosis (17*), elevated gamma glutamyl transferase (137*), other liver conditions (779), palpable liver (6)</td>
</tr>
<tr>
<td>3 studies, n = 40</td>
<td>Renal (40)</td>
<td>Increased uroporphyrins (11), darkening/reddening of urine (21), hematuria</td>
</tr>
</tbody>
</table>
7 studies, n = 10574
Gastrointestinal (> 1921)
Constipation (24), diarrhea (63), hematemesis (6), nausea (68), abdominal pain (41), gastrointestinal ulceration (>1408), vomiting (32), gastrointestinal problems/condition (>254), sickness (1), blood in stool (22), colonic obstruction (1), urinary tract infection (1)

5 studies, n = 2671
Metabolic (268)
Porphyria cutanea tarda (11), gynecomastia (3), diabetes (42*), increased serum glucose (132*), increased thyroid stimulating hormone (25*), increased serum cholesterol (8), Ischemia (47*)

2 studies, n = 79
Immunologic (>1)
Allergies (nd), infections (>1)

6 studies, n = 10500
Cognitive (> 1639)
Brain dysfunction (nd*), reduced concentration (14), digit/written and oral difficulties (nd), disorientation (1), dizziness (1623), reduced memory (16)

8 studies, n = 10575
Motor-sensory (> 7798)
Autonomic dyscontrol (14), numbness (47), joint pain (55), stiffness (46), blurred vision (42), high frequency hearing loss (1050), peripheral neuropathy signs (>309), neuromuscular (4057), ringing in ears (2131), fasciculations (1), neck, shoulder, arms, legs, chest, hands, feet pain (2), paresthesia (1), tremor (4), decreased auditory acuity (10), conjunctivitis (3), bloodshot eyes (5), fatigue (2), itching of eyes (7), absence of Achilles tendon reflexes (2), decreased sense of proprioception (1), sties (7), leg cramps (2)

9 studies, n = 10733
Neuropsychiatric (>7660)
Anorexia (32), depression (>57*), fatigue (317), hypersomnolence (34), headache (1962), suicide attempts (6), suicide thoughts (nd), violence/rages (>35), limitation in activity (2777*), nervousness (254), at least 6 of 15 psychological symptoms (1331), posttraumatic stress disorder (>840*), insomnia (1), weakness (2), anxiety (nd), reduced memory (16), decreased auditory acuity (10), psychosomatic (nd*), phobias (nd*), decreased sense of proprioception (1), sties (7), leg cramps (2)

9 studies, n = 10606
Skin (3767)
Abscesses (1), minimal active acne (35) active acne - moderate to severe (13), blepharitis (1), blisters (1), chloracne (180), dermatitis (1), fragility of the skin (8), hyperpigmentation (147*), oedema (1), patch/plaque erythoderma (1), pruritus (2), rash (>66), other skin conditions (3294), frequent tearing (14), vesiculobullous eruptions on exposed skin (2)

11 studies, n = 10758
Other (>4894)
benign growth (2109*), loss of libido (37), impaired potency (1), hirsutism (30), galactorrhea (4), swelling (35), tingling (44), xerostomia (1), Coldness in extremities (1), Sweating (1), Maxillary sinusitis (1), exudative postnasal dripping (1), pyrexia (2), joint pain (nd), inflammation of the buccal mucosa (8), infrequency (nd*), nose bleeds (1), weight loss (1)

Total number of studies = 12; total number of individuals = 10764
Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group. * - significant results have been reported in any study
nd – no data

2 Short-Term Exposure (Days-Several Weeks)

2.1 Short-Term Exposure to 2,3,7,8-TCDD
(Beale et al., 1977) investigated long-term effects of exposure to 2,3,7,8-TCDD in 1 adult female and 2 children exposed for several days after spraying of a farm (Missouri, U.S.A) with contaminated waste oil for dust control. Exposure occurred in 1971 for several days. Signs and symptoms (formal diagnosis by medical practitioners and self-reported) included headache, Diarrhoea, blood in urine, painful micturition, abdominal pain, oedematous bladder, calyceal diverticulum in right kidney, proteinuria, numerous punctuate haemorrhagic areas in the bladder, Systolic murmur, Nosebleeds.

(Oliver, 1975) reported Toxic effects after exposure to 2,3,7,8-tetrachlorodibenzo-1,4-dioxin in 3 scientists from the UK during synthesis of dioxins and/or laboratory work with dioxins. The duration of exposure is unknown but probably lasted for weeks to months in 1970 and was reported as transient minimal exposure. Internal dose is unknown. Previous general medical histories of the exposed subjects were available. Symptoms were self reported and a medical examination was carried out in the year of exposure and 3 years post-exposure (blood cholesterol, liver function). Signs and symptoms reported were Fatigue, headache, unusual loss
of vigour and drive, easily irritable, diminished concentration, blurring of vision, loss of appetite, diminution in sense of taste, flickering of vision, occasional palpitations, difficulty focusing eyes, difficulties in sleeping, superficial neuralgic pains, Difficulties with muscular and mental coordination, Oiliness of skin, Chloracne, follicular rash, High blood cholesterol, Type 2A and mild hyperlipoproteinemia, Abdominal pains, indigestion, marked flatulence, intermittent diarrhoea, Unexplained weight loss, body hirsutism. The authors conclude that no conclusive evidence could be provided, however it seems likely that the observed effects were due to dioxin exposure.

(Schecter and Ryan, 1992) reported some signs and symptoms experienced by a scientist exposed to 2,3,7,8-TCDD (and 2,3,7,8-TBrDD (tetrabrominated dibenzodioxin)). Exposure occurred in 1956 during the synthesis of TCDD in the U.S.A. No protective clothing was worn. Serum TCDD concentrations were 18 ppt in 1991 (35 years after exposure).

Signs and symptoms were self-reported and formal medical diagnosis was carried out. Signs and symptoms included headache, backache, leg pain on exertion, chloracne, the feeling of being quite sick.

Table 9. Summary of signs, symptoms and diagnosed disease reported in 3 studies investigating short-term exposure to 2,3,7,8-TCDD

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies, n = 6</td>
<td>Circulatory (2)</td>
<td>Systolic murmur (1), palpitations (1)</td>
</tr>
<tr>
<td>1 study, n = 3</td>
<td>Renal (4)</td>
<td>Calyceal diverticulum (1), painful micturition (1), blood in urine (1), Proteinuria (1)</td>
</tr>
<tr>
<td>3 studies, n = 7</td>
<td>Gastrointestinal (13)</td>
<td>Diarrhoea (3), oedema (1), abdominal pain (4), diarrhoea (1), flatulence (2), indigestion (1), feeling sick (1), high cholesterol (3), hyperlipoproteinemia (1)</td>
</tr>
<tr>
<td>1 studies, n = 3</td>
<td>Metabolic (4)</td>
<td>Diminished concentration (1), mental coordination (1), superficial neuralgic pain (1)</td>
</tr>
<tr>
<td>1 studies, n = 3</td>
<td>Cognitive (3)</td>
<td>Blurring – vision (1), eye focusing difficulties (1), flickering of vision (1), muscle coordination (1), diminished taste (1), back or extremity pain (1)</td>
</tr>
<tr>
<td>2 studies, n = 4</td>
<td>Motor-sensory (6)</td>
<td>Chloracne (3), follicular rash (1), oiliness of skin (2)</td>
</tr>
<tr>
<td>3 studies, n = 7</td>
<td>Neuropsychiatric (12)</td>
<td>Headache (5), loss of appetite (1), fatigue (2), irritable (1), difficulties sleeping (1), loss of vigour/drive (2)</td>
</tr>
<tr>
<td>2 studies, n = 4</td>
<td>Skin (6)</td>
<td>Haemorrhage (1), nosebleeds (1), hirsutism (2), weight loss (1)</td>
</tr>
<tr>
<td>2 studies, n = 6</td>
<td>Other (5)</td>
<td></td>
</tr>
</tbody>
</table>

Total number of studies = 3; total number of individuals = 7
Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - significant results have been reported in any study

Conclusions and summary
Three studies reported on relatively short-term exposure in Missouri residents (1 study) and laboratory workers exposed during synthesis of and/or working with TCDD. A total of only 7 individuals were investigated in these groups. All three groups showed gastrointestinal disorders or problems, including most frequently diarrhoea and abdominal pain, and neuropsychiatric disorders or complaints including most frequently headache. Other observations reported from more than one individual among this group were flatulence, chloracne and fatigue. A summary of all signs and symptoms is provided in Table 9.

2.2 SHORT-TERM EXPOSURE TO 2,4,5-T OR TCP (AND TCDD)

(May, 1973) reported cases of 14 production workers exposed to 2,4,5-T and 2,3,7,8-TCDD during a reactor explosion in April 1968. Exposure was presumed via dermal and inhalation routes. Formal medical diagnosis and laboratory tests were carried out. Signs and symptoms included Tiredness (2), tightness of the chest (3), Chloracne (14), Abnormal liver function test(s) (11), Mild conjunctivitis (nd).

(Reggiani, 1980) reported 17 cases (4 adults and 13 children, 11 female, 6 male) of 2,3,7,8-TCDD exposure of residents in Seveso, Italy. Exposure occurred in 1976 after a reactor accident of a TCP production plant. Soil samples showed 2,3,7,8-TCDD concentrations up to 5000 µg/m². Dermal exposure occurred in 17, and ingestion in 16 of the participants. Formal medical diagnosis and laboratory tests were carried out under court supervision. Signs and symptoms (by number of individual with the condition) included Itching, redness and swelling of the skin, acute dermatitis (16), chloracne (12), Short-lived gastrointestinal tract disturbances (no data), slightly enlarged liver (5), Lacrimation, sensation of grit in the eyes, burning of the eyes.

Conclusions and summary
Only two studies were identified that reported on short-term exposure to 2,4,5-T (and its co-contaminant TCDD), including production workers and residents of Seveso. The
total number of individuals investigated in these groups was 31. Both groups showed hepatic, a range of motor-sensory and skin disorders or problems, including most frequently abnormal liver function tests, chloracne and acute dermatitis. A summary of all signs and symptoms is provided in Table 10.

Table 10. Summary of signs, symptoms and diagnosed disease reported in 2 studies investigating short-term exposure to 2,4,5-T or TCP (and 2,3,7,8-TCDD)

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies, n = 31</td>
<td>Hepatic (16)</td>
<td>Abnormal liver function test(s) (11)</td>
</tr>
<tr>
<td>1 study, n = 17</td>
<td>Gastrointestinal (nd)</td>
<td>Slightly enlarged liver (5)</td>
</tr>
<tr>
<td>2 studies, n = 31</td>
<td>Motor-sensory (nd)</td>
<td>Short-lived gastrointestinal tract disturbances (nd)</td>
</tr>
<tr>
<td>1 study, n = 14</td>
<td>Neuropsychiatric (2)</td>
<td>Burning of the eyes (nd), mild conjunctivitis (nd), lacrimation (nd), sensation of grit in the eyes (nd)</td>
</tr>
<tr>
<td>2 studies, n = 31</td>
<td>Skin (&gt;42)</td>
<td>Tiredness (2)</td>
</tr>
<tr>
<td>1 study, n = 14</td>
<td>Other (3)</td>
<td>Chloracne (26), acute dermatitis (16), itching and redness and swelling of the skin (nd)</td>
</tr>
</tbody>
</table>

Total number of studies = 2; total number of individuals = 31
Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - significant results have been reported in any study
nd – no data

2.3 Short-Term Exposure to 2,4-D

(Leonard et al., 1997) reported a case of a male amateur golfer (aged 65 years) from Dublin, Ireland who was exposed to herbicides including 2,4-D via licking golf balls during games. Exposure duration and doses are unknown, however, daily exposure was presumed during golf games following the spraying of the course with 2,4-D. Formal diagnoses were carried out by medical practitioner and included laboratory tests. Signs and symptoms included Lethargy, Upper abdominal discomfort, dark urine, and acute hepatitis. The authors concluded that there seems little doubt that the patient’s hepatitis was due to ingestion of 2,4-D from his golf balls. The symptoms ceased once the habit of golf ball licking was discontinued and re-appeared within a month of the patient resuming the habit after a second spraying of the course.

(Radionov et al., 1967) reported cases of 25 agricultural workers (gender and age unknown) from Russia, who were exposed to 2,4-D in June 1964 during spraying of fields. 2kg of 2,4-D per 25l solution was sprayed per hectare. Signs and symptoms were self-reported (number in brackets gives frequency of observation) and included Headache (23), vertigo (23), weakness (23), unconsciousness (2), Burning sensation on skin of face (no data), Nausea (23), heartburn (23), Irritation of eyes (no data), saline taste in the mouth (no data), sore throat (no data), irritation of the nasopharyngeal mucosa (no data), substernum pain (no data).

(Todd, 1962) reported one case of 2,4-D dermal exposure from two occurrences of herbicide field spraying in 1962. The patient was a male farmer aged 52 years in Burlington, U.S.A. Self-reported symptoms and findings from formal diagnosis, carried out by medical practitioners, were reported. Signs and symptoms included Felt weak, unable to walk, weakness of arms, hands and forearms, absence of deep muscle pain sensation in legs and arms, absence of pinpoint sensation in big toes, absence of vibratory sensation in arms and feet, paralysis of thigh and leg muscles, absence of deep tendon reflexes, Nausea, vomiting, diarrhoea, Loss of weight, low grade fever, hypoplastic bone marrow.

Conclusions and summary
Three studies, investigated relatively short-term exposure to 2,4-D, including oral exposure and herbicide spraying of a total of 27 individuals. Gastrointestinal and neuropsychiatric conditions were observed in all groups and included most frequently nausea, headache and weakness. Another frequently reported condition was heartburn. A summary of the signs and symptoms reported are shown in Table 11.

Table 11. Summary of signs, symptoms and diagnosed disease reported in 3 studies investigating short-term exposure to 2,4-D

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study, n = 1</td>
<td>Hepatic (1)</td>
<td>Acute hepatitis (1)</td>
</tr>
<tr>
<td>1 studies, n = 1</td>
<td>Renal (1)</td>
<td>dark urine (1)</td>
</tr>
<tr>
<td>4 studies, n = 52</td>
<td>Gastrointestinal (50)</td>
<td>Abdominal discomfort (1), nausea (24), diarrhoea (1), vomiting (1), Heartburn (23)</td>
</tr>
</tbody>
</table>
1 study, n = 1
Hematologic (1)
Hypoplastic bone marrow (1)

1 study, n = 25
Cognitive (25)
Unconsciousness (2), Vertigo (23)

2 studies, n = 26
Motor-sensory (>6)
Irritation of the eyes (nd), irritation of the nasopharyngeal mucosa (nd), saline taste in the mouth (nd), paralysis of thigh and leg muscles (1), Absence of deep tendon reflexes (1), absence deep muscle pain sensation in legs and arms (1), absence of pinpoint sensation in big toes (1), Absence of vibratory sensation in arms and feet (1), unable to walk (1)

3 studies, n = 27
Neuropsychiatric (49)
Lethargy (1), headache (23), weakness (25)

1 study, n = 25
Skin (nd)
Burning sensation on skin of face (nd)

2 studies, n = 26
Other (2)
Substernum pain (nd), sore throat (nd), low grade fever (1), loss of weight (1)

Total number of studies = 3; total number of individuals = 27
Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - significant results have been reported in any study
nd – no data

2.4 **SHORT-TERM EXPOSURE TO 2,4,5-T, 2,4-D AND 2,3,7,8-TCDD**

(Klawans, 1987) reported cases of 45 railroad workers exposed to 2,3,7,8-TCDD and 2,4-D during clean-up work of a chemical spill in Missouri, U.S.A. Workers did not wear protective clothing. Chemical clean-up work took 10 weeks and analysis of the spilled material showed TCDD levels between 45-46 ppb. Periodic medical examinations were carried out after exposure, and detailed neurological examination was performed 6 years post-exposure. Symptoms were self-reported and previous general medical histories were available. Signs and symptoms included Severe fatigue, irritability, nervousness, memory loss, stiffness and soreness, dizziness, light headedness, numbness and tingling in both arms, changes in reflexes, spasms and cramping of the fingers, Peripheral neuropathy, postural and terminal intention tremor, dystonia of the hands, Irritation of nose, throat and eyes, yellow spots in vision.

**Conclusions and summary**

Only one study reported on patterns of signs and symptoms after relatively short-term exposure to a mixture of 2,4,5-T, 2,4-D and 2,3,7,8-TCDD in chemical clean-up workers. Most frequent observations included peripheral neuropathy and tremor. A summary of all symptoms reported is provided in Table 12.

**Table 12. Summary of signs, symptoms and diagnosed disease reported in 1 study investigating short-term exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD**

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study, n = 45</td>
<td>Cognitive (3)</td>
<td>Dizziness (1), light headedness (1), Memory loss (1)</td>
</tr>
<tr>
<td>1 study, n = 45</td>
<td>Motor-sensory (99)</td>
<td>Cramps (1), dystonia (24), numbness (1), peripheral neuropathy (43), changed reflexes (1), soreness (1), spasms (1), stiffness (1), tremor (35), yellow spots in vision (1)</td>
</tr>
<tr>
<td>1 study, n = 45</td>
<td>Neuropsychiatric (4)</td>
<td>Fatigue (1), irritability (1), irritation (1), nervousness (1)</td>
</tr>
<tr>
<td>1 study, n = 45</td>
<td>Other (1)</td>
<td>Tingling (1)</td>
</tr>
</tbody>
</table>

Total number of studies = 1; total number of individuals = 45

Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - significant results have been reported in any study

3 **ACUTE EXPOSURE AND POISONINGS**

3.1 **ACUTE EXPOSURE TO 2,3,7,8-TCDD**

(Geusau et al., 2001) reported clinical and laboratory effects from 2,3,7,8-TCDD intoxication (accidental poisoning) in two female secretaries in Austria, Vienna. Dose and origin of TCDD contamination are unknown, however, body burden of TCDD was 6-25 µg/kg body weight 6-9 months after exposure. Exposure occurred in 1997, most likely via ingestion, and duration is unknown. Formal medical diagnosis was carried out on first occurrence of symptoms and 2 years post-exposure. Signs and symptoms included Loss of appetite, Chloracne, palmar plantar keratoderma,
Decreased percentage of NK cells, Nausea, vomiting, epigastric pain, acute helicobacter-negative gastritis, Normocytic, normochromic anaemia, leukocytosis, thrombopenia, Normocellular bone marrow with prominent myelopoiesis. The authors concluded that Chloracne and gastrointestinal symptoms were associated with TCDD intoxication, but this was not indicated by the routine laboratory investigation.

Table 13. Summary of signs, symptoms and diagnosed disease reported in 1 studies investigating acute exposure to 2,3,7,8-TCDD

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study, n = 2</td>
<td>Gastrointestinal (5)</td>
<td>Acute helicobacter-negative Gastritis (1), nausea (1), Epigastric pain (2), Vomiting (1)</td>
</tr>
<tr>
<td>1 study, n = 2</td>
<td>Hematologic (3)</td>
<td>Anaemia (1), leukocytosis (1), thrombopenia (1)</td>
</tr>
<tr>
<td>1 study, n = 2</td>
<td>Immunologic (1)</td>
<td>Natural Killer cells - decreased % (1)</td>
</tr>
<tr>
<td>1 study, n = 2</td>
<td>Neuropsychiatric (1)</td>
<td>Loss of appetite (1)</td>
</tr>
<tr>
<td>1 study, n = 2</td>
<td>Skin (3)</td>
<td>Chloracne (2), palmpoplantar keratoderma (1)</td>
</tr>
</tbody>
</table>

Note: frequency of reported disease groups are the sum of individual conditions reported; any individual may have reported more than one sign/symptom in a particular disease group.
* - Significant results have been reported in any study

3.2 ACUTE EXPOSURE TO 2,4-D

(McMillin and Samples, 1985) reported a case of dermal exposure with 2,4-D containing Herbicide Weedone LV-4. An unknown quantity of the herbicide was exposed to the right eye. Formal medial diagnoses were made. Signs and symptoms included Headache, generalised weakness, Reduced visual acuity, ocular irritation, photophobia, loss of accommodation in right eye, conjunctival injection, and toxic iritis.

(Davies and Jung, 1976) reported signs and symptoms following the deliberate oral ingestion of 40 ml of the Herbicide Verdone (including 2,4-D) by one adult female in the U.K. Medical assessment was carried out following admission to hospital 1 hour after exposure, until discharge 4 days later. Signs and symptoms included Drowsiness, tremors, loss of bladder sensation, Haemoptysis, dyspnoea, crepitations in both lung bases, reduced forced vital lung capacity, Repeated hematemesis, hematuria. The authors conclude that Lung involvement may occur with Verdone, but is reversible.

(Dudley and Thapar, 1972) reported a fatal human ingestion of 2,4-D. Exposure dose was unknown, but it was estimated that approximately 1 pint of 2,4-D in a kerosene-like solvent was ingested. Medical assessment was carried out following admission to hospital 20 hours after exposure; death occurred 6 days later. Signs and symptoms reported included Comativeness, followed by deep coma, hyperactive deep tenden reflexes, myotonia, Hyperventilating, enyalipsemia, pulmonary oedema, Vomiting, gastroenteritis, Mild fever.

(Durakovic et al., 1992) reported cases of four agricultural workers and miners in Croatia who were exposed to 2,4-D (deliberate and accidental poisoning). 100-400ml of 40% 2,4-D (40mg-200mg) was ingested, equating to 250-2000 mg/kg body weight. Serum concentrations were measured 3-10 hours after exposure, and ranged from 370 to 1770 ppm, falling to 158-773 ppm after 3-5 hours of haemodialysis. Medical assessment was carried out following admittance to hospital 3-10 hours after exposure, until discharge up to one month later. Coma (degree III) occurred in 2 patients. Signs and symptoms reported included drowsiness, pupils constricted with a slow reaction to light, cold extremities, Immobile, absent reflexes, no reaction to painful stimulus, Weak respiratory murmur/bronchial murmurs, Bloato stomach, Sinus tachycardia, prolonged corrected QT interval, arterial hypotension, Metabolic acidosis, mild hypoxia, Febriile. The authors conclude that as a result of treatment by haemodialysis all patients survived with no long-term effects; however, it is noted that most cases of poisoning at these concentrations are fatal.

(Fraser et al., 1984) reported a fatal overdose of 2,4-D, mecoprop, and dicamba by ingestion of the herbicide Killex. An unknown quantity of herbicide containing 100g of 2,4-D/L was ingested. Blood concentration of 2,4-D was 520 mg/L, measured 1 hour after exposure. Medical assessment was carried out following admission to hospital 1 hour after exposure; death occurred 4.5 hours later. Prior to coma and cardiac arrest, the signs and symptoms included distressed behaviour, heavy breathing, Vomiting, Marked hypotension, elevated white blood cell count, distension of abdomen.

(Friesen et al., 1990) reported acute exposure to 2,4-D by deliberate ingestion of the herbicide C.I.L. Dandelion Killer by one adult female. 50g of 2,4-D (150-200 ml of herbicide containing 250g 2,4-D/L) were ingested. Blood concentration of 2,4-D was 392 mg/L, measured 2 hours after admission to hospital. Medical assessment was carried out following admission to hospital an unknown time after exposure; death occurred 6 days later. Signs and symptoms included Pinpoint pupils, no deep tendon reflexes, coma (grade 3), Bradypnea, respiratory muscle paralysis, Vomiting,
elevated liver enzymes, haemoglobin and red blood cells in urine, Hypotensive. The authors note that marked nervous system depression was the prominent feature in the overdose patient.

(Jorens et al., 1995) reported a 2,4-dichlorophenoxyacetic acid induced fatality in a Belgium farmer through ingestion of 0.5L Animex, containing 3g of 2,4-D/kg. Blood levels were 192 mg 2,4-D/L 2 hours post-exposure. Medical assessment was carried out following admission to hospital 2 hours after exposure. Death occurred 3 hours later. The patient was in coma, and findings reported included Respiratory failure, pulmonary oedema, Profuse upper gastrointestinal bleeding, hematemesis, gastritis, Tachycardia, hypotension, cardiac shock, interstitial oedema of left ventricle, Elevated white blood cell count, thrombocytopenia, hypocalcaemia, hypophosphatemia, hypoxemia, metabolic acidosis, Lysis of myocytes. The Authors conclude that profuse upper gastrointestinal bleeding can be added to the symptoms associated with acute oral overdose of pure 2,4-D.

(Kancir et al., 1988) reported a fatal poisoning with the herbicide Herbatox (including 9.1% 2,4-D) in Denmark. Medical assessment was carried out following admission to hospital shortly after exposure, until death at day 15. Reported signs and symptoms include Confusion, aggression, followed by coma, Areflexia, Deterioration of spontaneous respiration, Vomiting, intestinal bleeding, acute renal failure, liguria, Low blood pressure, hyperphosphatemia, hypocalcaemia, ecchymosis, petechiae, Hypertonic then hypotonic.

(Keller et al., 1994) reported a fatal overdose of 2,4-D by deliberate ingestion of an unknown quantity of the herbicide U 46 D-Fluid (containing 500g 2,4-D/L). An estimated 25-35 g 2,4-D was ingested. Blood concentrations of 2,4-D were 389 mg/L, measured 24 hours after admission to the hospital. Medical assessment was carried out following admission to hospital an unknown time after exposure, death occurred 48 hours later. Signs and symptoms included Complete disorientation, Deterioration of spontaneous respiration, damage to oesophagus, Vomiting, diarrhoea with blood, pain in whole abdominal area, massive haemorrhage leading to accumulation of blood in stomach, mild necrosis, acute kidney failure, Unstable circulation, tachycardia, Hypophosphatemia.

(Osterloh et al., 1983) reported a fatal overdose by poisoning with 2,4-D, MCPP, and chlorpyrifos. A solution of 10.8% 2,4-D in 360mL of Ortho Weed-B-Gone M was ingested. Blood levels were 389.5 µg 2,4-D/mL, measured 46 hours after exposure. Medical assessment was carried out following admission to hospital immediately after exposure; death occurred 30 hours later. Signs and symptoms included Agitation, hostility, pin-point pupils, followed by coma, myoclonus, Congested, oedematous lungs, Profuse diarrhoea, denuded duodenal mucosa with haemorrhaging, mild necrosis of liver, Sinus and supraventricular tachycardia, hypertension, then bradycardia and cardiac arrest, Metabolic acidosis.

(Prescott et al., 1979) reported a case of poisoning with 6.8g of 2,4-D using a herbicide containing 10% 2,4-D in Scotland. Plasma concentration was 400µg/ml 2 hours post-exposure. Medical assessment was carried out following admission to hospital 2 hours after exposure, until discharge 11 days later. Reported signs and symptoms included Confusion, aggression, followed by deep coma, unresponsive to painful stimuli, lack of tendon reflexes replaced by myotonia, proximal muscle weakness leading to mild myopathy, Hypermimilation, cyanosis, Vomiting, Tachycardia, vasodilatation, resulting in suspected cardiomypathy, Mild metabolic acidosis, hypoxemia, high concentrations of plasma urea, Pyrexia.

(Wells et al., 1981) reported clinical features of two males after poisoning with the Herbicide Verdone (including 2,4-D). 2,4-D concentration in serum was 79.6 mg/L, 11 hours after exposure; and 118 mg/L, 3 hours after exposure, respectively. Medical assessment was carried out following admission to hospital 3-10 hours after exposure, until discharge 2-8 days later. Findings included Deep coma (Grade 4), dilated pupils, Minor liver damage and renal dysfunction, bowel sounds diminished, Metabolic acidosis, raised blood urea and creatinine concentrations, Hypoxia, Symptoms are attributed to Verdone poisoning.

(Torrington, 1983) report 2 cases of inhalation and dermal exposure (lasting for 2 days) through direct contact with the herbicide Karmex (including 2,4-D). Exposure occurred via raw herbicide escaping from tank cars which was continuously blown directly onto the exposed skin of the two railway workers. Medical examinations were carried out and self-reported symptoms were recorded. Signs and symptoms included Mild headache, muscle twitching, throat soreness, weakness, Small ulcerations of skin, Chest discomfort, cough producing mucoid sputum, dyspnoea, itching and burning of oral and nasal mucosa and conjunctiva.

Conclusions and summary
Thirteen studies reported acute exposure to 2,4-D in a total of 18 individuals. These include mostly deliberate or accidental poisonings, however, 2 studies of dermal exposure were included in this group. The majority of signs and symptoms pertain to circulatory, respiratory, hematologic symptoms, cognitive, motor-sensory and neuropsychological problems. These included most frequently hypotension, tachycardia, dyspnoea, and coma. A summary of all reported observations is given in Table 14.

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
</table>

Table 14. Summary of signs, symptoms and diagnosed disease reported in 13 studies investigating acute exposure to 2,4-D
7 studies, n = 10  Circulatory (29)  Hypotension (6), hypertension (1), prolonged corrected QT interval (2), sinus and/or supraventricular tachycardia (6), cardiac arrest (2), cardiac shock (1), oedema (1), low blood pressure (1), ecchymosis (1), hyperphosphatemia (1), hypertonic (1), hypotonic (1), petechiae (1), bradycardia (1), cardiomyopathy (1), tachycardia (1), vasodilation (1)

11 studies, n = 16  Respiratory (26)  Bradypnoea (1), Breathing heavy (1), Bronchial murmur (1), Cough producing mucoid sputum (2), Crepitations in both lung bases (1), Dyspnoea (3), Emphysema (1), Haemoptysis (1), Hyperventilation (2), reduced forced vital lung capacity (1), Pulmonary oedema (2), congested, oedematous (1), Oesophagus damage (1), Discomfort (2), Paralysis of respiratory muscles (1), Deterioration of spontaneous respiration (2), Respiratory failure (1), Respiratory murmur weak (1), Tachypnoea (1)

3 studies, n = 4  Hepatic (3)  Liver enzymes elevated (1), Liver necrosis (1), Liver damage (1)

6 studies, n = 10  Renal (7)  Renal failure (3), Renal dysfunction (1), hematuria (1), oliguria (1), haemoglobin and red blood cells in urine (1)

11 studies, n = 15  Gastrointestinal (18)  Upper gastrointestinal bleeding (1), diminished bowel sounds (1), diarrhoea (2), distension of abdomen (1), Acute helicobacter-negative gastritis (1), gastroenteritis (1), hematemesis (2), intestinal bleeding (1), abdominal pain (1), bloated stomach (1), vomiting (6)

5 studies, n = 9  Metabolic (7)  Metabolic acidosis (5), Acidosis (1), raised creatinine (1)

7 studies, n = 11  Hematologic (12)  Raised blood urea (2), hypocalcaemia (2), hypophosphatemia (2), Hypoxemia (2), Hypoxia (2), Thrombopenia (1), White blood cell elevated (1)

10 studies, n = 14  Cognitive (19)  Coma (12), Confusion (2), disorientation (1), pupils - pin-point (2), constricted pupils (1), pupils dilated (1)

10 studies, n = 14  Motor-sensory (27)  Areflexia (2), loss of bladder sensation (1), conjunctival injection (1), loss of eye focusing (1), immobile (1), ocular irritation (1), itching, burning (4), lysis of myocytes (1), muscle twitching (2), myoclonus (1), Myopathy (1), myotonia (2), unresponsive to painful stimuli (1), absent reaction (1), subicteric sclera (1), hyperactive tendon reflexes (1), lack of tendon reflexes (1), no deep tendon reflexes (1), toxic irritis (1), tremor (1), visual acuity reduced (1)

9 studies, n = 13  Neuropsychiatric (14)  Aggression (2), Agitation (1), Combative (1), Distressed (1), Drowsy (2), Hostility (1), headache (2), Photophobia (1), Proximal muscle weakness (1), general weakness (2),

1 studies, n = 2  Skin (2)  Small ulceration (2)

6 studies, n = 10  Other (10)  Fever (1), Extremities cold (1), Febrile (1), Subfebrile (1), haemorrhage (2), Necrosis (1), Pyrexia (1), Throat pain (2)

<table>
<thead>
<tr>
<th>Total number of studies, total number of individuals investigated</th>
<th>Sign, symptom, disease group (frequency)</th>
<th>Sign/symptom (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study, n = 1</td>
<td>Circulatory (3)</td>
<td>Respiratory alkalosis (1), hypocapnia (1), hypoxemia (1)</td>
</tr>
<tr>
<td>1 study, n = 1</td>
<td>Respiratory (1)</td>
<td>Hyperventilation (1)</td>
</tr>
</tbody>
</table>

3.3 Acute Exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD

(O'Reilly, 1984) reported a case of deliberate ingestion of a herbicide containing 24g of 2,4-D and 7.5g of 2,4,5-T in one adult male. Medical assessment was carried out following admission to hospital 1 hour after exposure, until discharge 7 days later. **Signs and symptoms** included Deep coma, hyperreflexia of lower limbs, peripheral neuropathy, gross delay in lateral peroneal nerve conduction, Hyperventilation, hypocapnia, respiratory alkalosis, Hypoxemia, Pyrexia.

**Conclusions and summary**

Only one study was identified that reported acute exposure to 2,4,5-T, 2,4-D and 2,3,7,8-TCDD. A summary of the signs and symptoms is provided in Table 15.
Overall conclusions and summary

A wide range of signs, symptoms and diagnosed diseases were reported from case reports, case series and in health surveys investigating individuals or groups exposed to the compounds of interest. These studies are often limited by the small number of exposed individuals investigated, the lack of statistical evaluation, lack of validation possibilities of the symptom or disease (i.e. self-reported) and by the numerous confounders for most of the conditions reported. Furthermore, in the majority of cases, exposure duration or dose was not assessed. In addition, comparisons between studies are complicated by different medical diagnoses or time of recall of signs and symptoms in relation to time of exposure. Hence, bias, confounding and chance cannot be ruled out and an evaluation of the strength of association is not feasible.

Patterns observed in the exposed individuals and groups showed a wide range of possible health effects that may be association with the exposure to the compounds investigated.

The most frequently observed signs and symptoms in individuals exposed to 2,3,7,8-TCDD on a long-term basis included skin and metabolic, gastrointestinal, motor-sensory, neuropsychiatric and cognitive disorders or complaints. Long-term exposure to 2,4,5-T (and its co-contaminant 2,3,7,8-TCDD) showed most frequently disorders or complaints pertaining to skin, neuropsychiatric, respiratory, hepatic, gastrointestinal, cognitive and motor-sensory problems. Frequent observations from long-term exposure to mixtures of 2,4,5-T, 2,4-D and 2,3,7,8-TCDD included most frequently cancer, gastrointestinal, cognitive, motor-sensory, neuropsychiatric and skin disorders or complaints.

Among short-term exposure to 2,3,7,8-TCDD, gastrointestinal disorders or problems and neuropsychiatric disorders or complaints were most frequent. Short-term exposure to 2,4,5-T (and its co-contaminant TCDD showed hepatic, motor-sensory and skin disorders as the most frequent observations. Short-term exposure to 2,4-D showed gastrointestinal and neuropsychiatric conditions most frequently. Among short-term exposure groups to a mixture of 2,4,5-T, 2,4-D and 2,3,7,8-TCDD peripheral neuropathy was observed most frequently.

The majority of signs and symptoms observed from acute exposure to 2,4-D pertain to circulatory, respiratory, hematologic symptoms, cognitive, motor-sensory and neuropsychological problems.

Overall, the patterns of diseases, signs and symptoms summarised portray a broad picture of potential disorders and conditions that may be experienced after exposure to 2,4,5-T, 2,4-D and/or 2,3,7,8-TCDD. However, in contrast to the epidemiological case-control and cohort studies investigating defined diseases or conditions as reviewed in the first section of this report, conclusions on a causal link between patterns of disease, sign and symptoms and exposure to the compounds of interest cannot be drawn from descriptive studies.
This review investigated the association between a set of cancer and non-cancer endpoints and exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD. Outcomes from previous assessments regarding these associations were summarised and, together with evaluations of Literature Updates, considered for an overall evaluation. This overall evaluation was based on the total available epidemiological and toxicological evidence and set evaluation criteria.

The following table summarises the evaluation categories of the present Review and the Key Reviews considered. If a particular health effect was not evaluated and assigned an evaluation criterion by a Key Review, a summary of the general conclusion is given (unshaded areas). Formal evaluations according to defined criteria are shaded red.

### Table 16. Summary of evaluation outcomes or conclusions from the present review and provided by the five Key Reviews considered.

<table>
<thead>
<tr>
<th>CANCER ENDPOINTS</th>
<th>This review</th>
<th>IARC</th>
<th>ATSDR</th>
<th>US EPA</th>
<th>WHO</th>
<th>NAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cancer</strong></td>
<td>Probable</td>
<td>Carcinogenic to humans Group 1</td>
<td>May be human carcinogen</td>
<td>Human carcinogen</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Gastrointestinal cancer</strong></td>
<td>Evidence of no causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited or suggestive evidence of no association</td>
</tr>
<tr>
<td><strong>Hepatobiliary cancer</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Head and neck cancers</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Larynx cancer</strong></td>
<td>Possible causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td><strong>Lung cancer</strong></td>
<td>Possible causal link</td>
<td>Elevated in occupational cohorts, unlikely due to chance or confounding</td>
<td>Some data suggests a possible relationship</td>
<td>Significant risk in occupational and Yusho cohorts</td>
<td>N/A</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td><strong>Bone cancer</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Soft tissue sarcoma</strong></td>
<td>Probable causal link</td>
<td>Significantly increased risk in occupational cohorts</td>
<td>Some data suggests a possible relationship</td>
<td>Direct linkage could not be made</td>
<td>N/A</td>
<td>Sufficient evidence</td>
</tr>
<tr>
<td><strong>Skin Cancer Melanoma and non-melanoma</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td>Possible causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Weak human evidence Some animal evidence</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td><strong>Testicular cancer</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited data available</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Urinary bladder cancer</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Renal cancer</strong></td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td><strong>Brain tumours</strong></td>
<td>Evidence of no causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited or suggestive evidence of no association</td>
</tr>
<tr>
<td>Condition</td>
<td>Probable/Causal Link</td>
<td>Human Data</td>
<td>Some Data</td>
<td>No Consistent Picture</td>
<td>N/A</td>
<td>Sufficient Evidence</td>
</tr>
<tr>
<td>-----------------------------------</td>
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<td>------------------------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>Probable causal link</td>
<td>Human data show weak evidence of an association</td>
<td>Some data suggests a possible relationship</td>
<td>No consistent picture at the present time</td>
<td>N/A</td>
<td>Sufficient evidence</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Sufficient evidence</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Insufficient evidence (leukaemia) possible causal link (CLL)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence (leukaemia) Sufficient evidence (CLL)</td>
</tr>
</tbody>
</table>

NON-CANCER ENDPOINTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probable/Causal Link</th>
<th>Human Data</th>
<th>Some Data</th>
<th>No Consistent Picture</th>
<th>N/A</th>
<th>Sufficient Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurobehavioral Disorders</td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>Effects may occur in adults exposed to high levels; TCDD may be a neurological hazard to developing organisms</td>
<td>Acute effects</td>
<td>No causal relationship could be deduced from human data</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td>Chloracne</td>
<td>Established causal link</td>
<td>N/A</td>
<td>Data suggests that TCDD is a dermal toxicant</td>
<td>Positive relationship</td>
<td>N/A</td>
<td>Sufficient evidence</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>Acute effects may cause respiratory effects</td>
<td>Acute effects</td>
<td>N/A</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>No clear relationship</td>
<td>No consistent information in humans but immune system is a target for TCDD in many animal species</td>
<td>Inconclusive</td>
<td>Alterations of human immune parameters are in line with animal studies but mechanism of action is unknown</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>Reproductive effects may occur</td>
<td>Reproductive relationship (reproductive hormones) inconclusive (semen changes)</td>
<td>Inadequate human data but strong biological plausibility</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td>Male Reproductive Disorders</td>
<td>Insufficient evidence</td>
<td>Human studies have limited power but developmental and reproductive toxicity in animals</td>
<td>Reproductive effects may occur</td>
<td>Reproductive relationship (reproductive hormones) inconclusive (semen changes)</td>
<td>Inadequate human data but strong biological plausibility</td>
<td>Inadequate or insufficient evidence</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>Exposure to high levels may induce alterations in glucose metabolism</td>
<td>Possible</td>
<td>N/A</td>
<td>Limited or suggestive evidence</td>
</tr>
<tr>
<td>Lipid and Lipoprotein Disorders</td>
<td>Possible causal link</td>
<td>N/A</td>
<td>Possible</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
<td></td>
</tr>
<tr>
<td>Thyroid Homeostasis</td>
<td>Insufficient evidence</td>
<td>N/A</td>
<td>Exposure to high levels may</td>
<td>Possible</td>
<td>N/A</td>
<td>Inadequate or insufficient evidence</td>
</tr>
</tbody>
</table>
In addition to defined and diagnosed adverse health endpoints, this review considered studies that describe the patterns of symptoms, signs, symptoms or death after exposure to the herbicides 2,4,5-T and 2,4-D and/or 2,3,7,8-TCDD has occurred. These studies are descriptive and often did not encompass statistical ascertainment of an association. Patterns observed in the exposed individuals and groups showed a wide range of possible health effects that may be association with the exposure to the compounds investigated. The most frequently observed signs and symptoms in all long-term exposure groups related to gastrointestinal, cognitive, motor-sensory, neuropsychiatric and skin disorders and diseases. Generally similar signs and symptoms were observed in individuals or groups that were exposed to the compounds of interest for relatively short periods of time. Signs and symptoms reported from acute exposure (mainly poisoning) differed from long- and short-term exposure disease categories mainly with respect to greater frequency of circulatory, respiratory and hematologic disorders and conditions. Overall, the patterns of diseases, signs and symptoms summarised portray a broad picture of potential disorders and conditions that may be experienced after exposure to 2,4,5-T, 2,4-D and/or dioxins.
Normative data for cancer in Australians have been sourced from the Australian Institute of Health and Welfare (AIHW). Normative data for other conditions and diseases have been sourced from either the AIHW, the Australian Bureau of Statistics (ABS), or population surveys published in the scientific literature.

1 GASTROINTESTINAL TRACT TUMOURS

Normative data for this group of cancers were sourced from (AIHW, 1999). Colon cancer accounts for 8.4% of all new cases of cancer and 9% of cancer deaths in males. Men have a 1 in 31 lifetime risk of developing colon cancer. Rectal cancer accounts for 5.3% of all new cancer cases and 3.6% of cancer deaths in males. Men have a 1 in 45 lifetime risk of developing rectal cancer. Stomach cancer accounts for 2.9% of all new cases of cancer and 3.8% of all cancer deaths for males. Men have a 1 in 91 lifetime risk of developing stomach cancer. Pancreatic cancer accounts for 2.1% of all new cases of cancer and 4.4% of all cancer deaths in males. Men have a 1 in 129 lifetime risk of developing pancreatic cancer.

Table 17. Incidence and mortality for cancer of the Colon in the Australian population in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
<td>0.0</td>
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</tr>
<tr>
<td>15–19</td>
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</tr>
<tr>
<td>20–24</td>
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<td>0.6</td>
</tr>
<tr>
<td>25–29</td>
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</tr>
<tr>
<td>30–34</td>
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<td>3.1</td>
</tr>
<tr>
<td>35–39</td>
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<td>5.8</td>
</tr>
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<td>40–44</td>
<td>6.9</td>
<td>10.2</td>
</tr>
<tr>
<td>45–49</td>
<td>16.1</td>
<td>20.1</td>
</tr>
<tr>
<td>50–54</td>
<td>36.8</td>
<td>27.5</td>
</tr>
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<td>55–59</td>
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<td>60–64</td>
<td>118.8</td>
<td>87.8</td>
</tr>
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<td>65–69</td>
<td>167.9</td>
<td>134.2</td>
</tr>
<tr>
<td>70–74</td>
<td>242.8</td>
<td>178.8</td>
</tr>
<tr>
<td>75–79</td>
<td>286.8</td>
<td>218.8</td>
</tr>
<tr>
<td>80–84</td>
<td>305.9</td>
<td>272.6</td>
</tr>
<tr>
<td>85 and over</td>
<td>391.4</td>
<td>308.9</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source (AIHW, 1999).

Table 18. Incidence and mortality from cancer of the rectum in the Australian population in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.0</td>
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<td>10–14</td>
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<td>15–19</td>
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<td>20–24</td>
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<td>25–29</td>
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<td>1.1</td>
</tr>
<tr>
<td>30–34</td>
<td>0.9</td>
<td>2.0</td>
</tr>
<tr>
<td>35–39</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>40–44</td>
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<td>5.8</td>
</tr>
<tr>
<td>45–49</td>
<td>14.4</td>
<td>10.3</td>
</tr>
</tbody>
</table>
Table 19. Incidence and mortality from cancer of the stomach in the Australian population in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
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<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15–19</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>20–24</td>
<td>0.3</td>
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<td>0.9</td>
</tr>
<tr>
<td>35–39</td>
<td>3.8</td>
<td>1.7</td>
</tr>
<tr>
<td>40–44</td>
<td>7.8</td>
<td>3.3</td>
</tr>
<tr>
<td>45–49</td>
<td>11.2</td>
<td>5.2</td>
</tr>
<tr>
<td>50–54</td>
<td>20.5</td>
<td>5.3</td>
</tr>
<tr>
<td>55–59</td>
<td>34.6</td>
<td>12.4</td>
</tr>
<tr>
<td>60–64</td>
<td>59.2</td>
<td>21.9</td>
</tr>
<tr>
<td>65–69</td>
<td>82.1</td>
<td>31.2</td>
</tr>
<tr>
<td>70–74</td>
<td>98.9</td>
<td>39.4</td>
</tr>
<tr>
<td>75–79</td>
<td>127.7</td>
<td>52.8</td>
</tr>
<tr>
<td>80–84</td>
<td>149.9</td>
<td>74.5</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source: (AIHW, 1999).

Table 20. Incidence and mortality from cancer of the pancreas in the Australian population in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
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<td>10–14</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>15–19</td>
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<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>25–29</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>30–34</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>35–39</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>40–44</td>
<td>2.5</td>
<td>1.4</td>
</tr>
<tr>
<td>45–49</td>
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<td>1.9</td>
</tr>
<tr>
<td>50–54</td>
<td>9.1</td>
<td>4.5</td>
</tr>
<tr>
<td>55–59</td>
<td>18.3</td>
<td>8.3</td>
</tr>
<tr>
<td>60–64</td>
<td>27.0</td>
<td>19.2</td>
</tr>
<tr>
<td>65–69</td>
<td>38.0</td>
<td>26.8</td>
</tr>
<tr>
<td>70–74</td>
<td>55.7</td>
<td>48.8</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source: (AIHW, 1999).
75–79 67.8 60.7 63.8 67.3 55.4 60.5
80–84 92.2 72.9 80.2 83.3 77.8 79.9
85 and over 105.5 85.4 91.5 140.2 87.8 103.7

Note: all rates are expressed per 100,000 population. Source: (AIHW, 1999).

2 HEPATOBILIARY, PANCREAS AND STOMACH CANCERS

Normative data for this group of cancers were sourced from (AIHW, 1999). Liver and intrahepatic bile duct account for 1.1% of new cases of cancer and 1.6% of all cancer deaths for males. Men have a 1 in 223 lifetime risk of developing liver and intrahepatic bile duct cancer. Cancer of the gallbladder and extrahepatic bile ducts, account for 0.6% of new cases of cancer and 0.6% of all cancer deaths for males. Males have a 1 in 445 lifetime risk of developing cancer of the gallbladder and extrahepatic bile ducts.

Table 21. Incidence and mortality of Australian males and females from cancer of the liver and intrahepatic bile ducts in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0–4</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>5–9</td>
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<tr>
<td>10–14</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>15–19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>25–29</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>30–34</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>35–39</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>40–44</td>
<td>2.3</td>
<td>0.6</td>
</tr>
<tr>
<td>45–49</td>
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<td>50–54</td>
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<td>2.3</td>
</tr>
<tr>
<td>55–59</td>
<td>9.8</td>
<td>2.6</td>
</tr>
<tr>
<td>60–64</td>
<td>14.6</td>
<td>3.6</td>
</tr>
<tr>
<td>65–69</td>
<td>26.0</td>
<td>6.1</td>
</tr>
<tr>
<td>70–74</td>
<td>27.7</td>
<td>10.5</td>
</tr>
<tr>
<td>75–79</td>
<td>38.6</td>
<td>11.4</td>
</tr>
<tr>
<td>80–84</td>
<td>28.4</td>
<td>12.0</td>
</tr>
<tr>
<td>85 and over</td>
<td>27.8</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

Table 22. Incidence and mortality of Australian males and females from cancer of the gallbladder and extrahepatic bile ducts in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0–4</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
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<tr>
<td>15–19</td>
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<td>0.0</td>
</tr>
<tr>
<td>30–34</td>
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<td>0.0</td>
</tr>
<tr>
<td>35–39</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>40–44</td>
<td>1.3</td>
<td>0.6</td>
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<tr>
<td>45–49</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>50–54</td>
<td>2.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)
### 3 Cancers of the Head and Neck

Normative data for this group of cancers were sourced from (AIHW, 1999). Cancers of the head and neck account for 2.7% of all new cases of cancer and 2.3% of cancer deaths in males. Men have a 1 in 87 lifetime risk of developing colon cancer.

**Table 23. Incidence and mortality rates for cancer of the head and neck (ICD10 C01-14) in Australian males in 1999.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.0</td>
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<td>10–14</td>
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<td>0.2</td>
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<tr>
<td>15–19</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>20–24</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>25–29</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>30–34</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>35–39</td>
<td>3.6</td>
<td>2.4</td>
</tr>
<tr>
<td>40–44</td>
<td>8.8</td>
<td>4.2</td>
</tr>
<tr>
<td>45–49</td>
<td>12.0</td>
<td>4.9</td>
</tr>
<tr>
<td>50–54</td>
<td>26.0</td>
<td>10.7</td>
</tr>
<tr>
<td>55–59</td>
<td>40.1</td>
<td>13.6</td>
</tr>
<tr>
<td>60–64</td>
<td>36.4</td>
<td>16.8</td>
</tr>
<tr>
<td>65–69</td>
<td>44.8</td>
<td>18.8</td>
</tr>
<tr>
<td>70–74</td>
<td>57.1</td>
<td>16.8</td>
</tr>
<tr>
<td>75–79</td>
<td>50.4</td>
<td>13.1</td>
</tr>
<tr>
<td>80–84</td>
<td>49.7</td>
<td>28.8</td>
</tr>
<tr>
<td>85 and over</td>
<td>56.9</td>
<td>26.0</td>
</tr>
</tbody>
</table>

Note: Rates are per 100,000 population. Source: (AIHW, 1999)

### 4 Laryngeal Cancer

Normative data for this group of cancers were sourced from (AIHW, 1999). Laryngeal cancer accounts for 1.1% of new cases of cancer and 1.1% of cancer deaths in males. Men have a 1 in 201 lifetime risk of developing cancer of the larynx.

**Table 24. Incidence and mortality from cancer of the larynx in Australian males and females by age.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>5–9</td>
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<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15–19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>25–29</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>30–34</td>
<td>0.3</td>
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</table>
35–39 0.3 0.0 0.1 0.0 0.0 0.0
40–44 1.0 0.3 0.6 0.1 0.0 0.1
45–49 3.6 0.7 2.2 0.5 0.0 0.2
50–54 8.5 1.3 4.9 3.6 0.3 2.0
55–59 12.8 1.5 7.2 3.6 0.4 2.1
60–64 21.1 3.4 12.2 6.8 0.8 3.8
65–69 26.0 3.2 14.4 10.5 1.7 6.0
70–74 26.0 4.5 14.6 12.8 2.4 7.3
75–79 31.1 3.9 15.6 14.6 1.1 6.9
80–84 21.3 0.5 8.4 20.4 1.6 8.8
85 and over 9.7 1.8 4.2 18.0 3.6 8.0

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999).

5 LUNG CANCER

Normative data for this group of cancers were sourced from (AIHW, 1999). Lung cancer is the third most common cancer after prostate and colorectal cancer (excluding non-melanotic skin cancer). It is the most common cause of death from cancer among Australian males, affecting one man in every eighteen over the course of a lifetime. Lung cancer accounts for 11.9% of all new cases of cancer and 23.7% of cancer deaths in males. Men have a 1 in 21 lifetime risk of developing cancer of the trachea, bronchus and lung.

Table 25. Incidence and mortality from cancer of the trachea, bronchus and lung (ICD-10 C22-C34) for Australian males in 1994.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>10–14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15–19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>25–29</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>30–34</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
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<td>2.4</td>
</tr>
<tr>
<td>40–44</td>
<td>7.3</td>
<td>6.8</td>
</tr>
<tr>
<td>45–49</td>
<td>18.4</td>
<td>12.3</td>
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<tr>
<td>50–54</td>
<td>38.9</td>
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<tr>
<td>55–59</td>
<td>85.7</td>
<td>45.4</td>
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<td>60–64</td>
<td>158.4</td>
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<tr>
<td>65–69</td>
<td>271.0</td>
<td>103.9</td>
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<tr>
<td>70–74</td>
<td>371.4</td>
<td>151.0</td>
</tr>
<tr>
<td>75–79</td>
<td>463.9</td>
<td>164.1</td>
</tr>
<tr>
<td>80–84</td>
<td>436.2</td>
<td>138.7</td>
</tr>
<tr>
<td>85 and over</td>
<td>452.4</td>
<td>102.4</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source: (AIHW, 1998).

6 BONE CANCER

Normative data for this group of cancer were sourced from AIHW (1999). In Australia, bone Cancer accounts for 0.2% of new cases of cancer and 0.3% of cancer deaths in males. Men have a 1 in 1446 lifetime risk of developing cancer of the bone and articular cartilage..

Table 26. Incidence and mortality in Australians from cancer of the bone and articular cartilage in 1999.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males Rate</td>
<td>Females Rate</td>
</tr>
</tbody>
</table>
### 7 SOFT-TISSUE SARCOMAS

Normative data for this group of cancer were sourced from AIHW (1999). Soft-tissue sarcomas include neoplasm of connective and other soft tissue and malignant neoplasm of thymus, heart and mediastinum. Cancer of other connective and soft tissue accounts for 0.7% of new cases of cancer and 0.5% of all cancer deaths for males. Men have a 1 in 413 lifetime risk of developing cancer of other connective and soft tissue. Cancer of the thymus, heart, mediastinum and pleura, account for 0.1% of new cases of cancer and 0.1% of all cancer deaths in males. Men have a 1 in 2257 lifetime risk of developing cancer of the thymus, heart, mediastinum and pleura.

#### Table 27. Incidence and mortality from cancer of the connective and soft tissue in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0–4</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>5–9</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>10–14</td>
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<td>0.9</td>
</tr>
<tr>
<td>15–19</td>
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<td>1.1</td>
</tr>
<tr>
<td>20–24</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>25–29</td>
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<td>0.7</td>
</tr>
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<td>30–34</td>
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<td>1.3</td>
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<td>35–39</td>
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<td>0.7</td>
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<td>40–44</td>
<td>2.0</td>
<td>1.8</td>
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<td>45–49</td>
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<td>1.5</td>
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<td>1.7</td>
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<td>6.3</td>
</tr>
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<td>70–74</td>
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<td>75–79</td>
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<td>9.6</td>
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<td>80–84</td>
<td>28.4</td>
<td>9.2</td>
</tr>
<tr>
<td>85 and over</td>
<td>27.8</td>
<td>15.7</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)
Table 28. Incidence and mortality from cancer of the thymus, heart, mediastinum and pleura (ICD-10 C37-C38) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0– 4</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>5– 9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10– 14</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>15– 19</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>20– 24</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>25– 29</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30– 34</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>35– 39</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>40– 44</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>45– 49</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>50– 54</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>55– 59</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>60– 64</td>
<td>0.5</td>
<td>0.5</td>
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<td>65– 69</td>
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<td>0.6</td>
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<td>70– 74</td>
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<td>1.2</td>
</tr>
<tr>
<td>75– 79</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>80– 84</td>
<td>5.3</td>
<td>2.7</td>
</tr>
<tr>
<td>85 and over</td>
<td>5.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

8 MELANOMA

Normative data for this group of cancer were sourced from AIHW (1999). Melanoma accounts for 10.4 of all new cases of cancer and 3.3% of all cancer deaths in males. Men have a 1 in 25 lifetime risk of developing melanoma.

Table 29. Incidence and mortality from melanoma (ICD-10 C43) in Australian males and females by age.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0– 4</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>5– 9</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>10– 14</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>15– 19</td>
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<td>5.5</td>
</tr>
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<td>20– 24</td>
<td>10.5</td>
<td>18.2</td>
</tr>
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<td>25– 29</td>
<td>16.7</td>
<td>19.6</td>
</tr>
<tr>
<td>30– 34</td>
<td>23.7</td>
<td>28.1</td>
</tr>
<tr>
<td>35– 39</td>
<td>32.2</td>
<td>36.5</td>
</tr>
<tr>
<td>40– 44</td>
<td>41.5</td>
<td>41.5</td>
</tr>
<tr>
<td>45– 49</td>
<td>58.7</td>
<td>57.5</td>
</tr>
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<td>50– 54</td>
<td>72.1</td>
<td>62.2</td>
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<tr>
<td>55– 59</td>
<td>92.8</td>
<td>64.5</td>
</tr>
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<td>60– 64</td>
<td>119.9</td>
<td>65.5</td>
</tr>
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<td>65– 69</td>
<td>145.5</td>
<td>81.4</td>
</tr>
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<td>70– 74</td>
<td>191.1</td>
<td>89.9</td>
</tr>
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<td>75– 79</td>
<td>213.3</td>
<td>95.6</td>
</tr>
<tr>
<td>80– 84</td>
<td>252.7</td>
<td>111.5</td>
</tr>
<tr>
<td>85 and over</td>
<td>230.4</td>
<td>104.2</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999).
9  **BASAL AND SQUAMOUS CELL (NON-MELANOMA) SKIN CANCER**

**Australian Normative Data**

Normative data for this group of cancer were sourced from AIHW (1999). Each year approximately 270,000 new cancer cases of non-melanocytic skin cancer are diagnosed in Australia. Incidence data for this cancer are not collected on a routine basis by cancer registries. Estimates for the incidence numbers are derived from data collected by a national market research company in 1985, 1990 and 1995, and analysis by Staples, Marks and Giles (1998)(AIHW, 1998). The lifetime mortality risk for males is 1 in 645. Non-melanoma skin cancer accounts for 1.4% of all cancer deaths for males.

**Table 30. Incidence and mortality from non-melanocytic cancers (ICD-10 C44) in Australian males and females by age.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males Rate</td>
<td>Females Rate</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15–19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>25–29</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30–34</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>35–39</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>40–44</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>45–49</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>50–54</td>
<td>2.0</td>
<td>0.5</td>
</tr>
<tr>
<td>55–59</td>
<td>3.0</td>
<td>0.4</td>
</tr>
<tr>
<td>60–64</td>
<td>3.1</td>
<td>0.8</td>
</tr>
<tr>
<td>65–69</td>
<td>9.0</td>
<td>2.3</td>
</tr>
<tr>
<td>70–74</td>
<td>12.8</td>
<td>1.5</td>
</tr>
<tr>
<td>75–79</td>
<td>26.4</td>
<td>5.0</td>
</tr>
<tr>
<td>80–84</td>
<td>47.0</td>
<td>11.4</td>
</tr>
<tr>
<td>85 and over</td>
<td>65.2</td>
<td>32.7</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

10  **PROSTATE CANCER**

**Australian Normative Data**

Normative data for this group of cancer were sourced from AIHW (1998). Other than non-melanotic skin cancer, this is the most common form of cancer in Australian men. Over the course of a lifetime, 1 in 8 Australian men will develop prostate cancer. It is the second most common cause of cancer death in Australian males.

**Table 31. Incidence and mortality rates for Australian males in 1994 for prostate cancer.**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5-9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10-14</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>15-19</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20-24</td>
<td>0.0</td>
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<td>25-29</td>
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<td>0.0</td>
</tr>
<tr>
<td>30-34</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>35-39</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>40-44</td>
<td>1.7</td>
<td>0.0</td>
</tr>
<tr>
<td>45-49</td>
<td>8.1</td>
<td>1.1</td>
</tr>
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<td>50-54</td>
<td>48.4</td>
<td>3.8</td>
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<tr>
<td>55-59</td>
<td>179.2</td>
<td>13.2</td>
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<tr>
<td>60-64</td>
<td>418.9</td>
<td>38.3</td>
</tr>
<tr>
<td>65-69</td>
<td>803.5</td>
<td>81.5</td>
</tr>
<tr>
<td>70-74</td>
<td>1,149.3</td>
<td>184.2</td>
</tr>
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<td>75-79</td>
<td>1,374.3</td>
<td>351.5</td>
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<tr>
<td>80-84</td>
<td>1,525.2</td>
<td>572.3</td>
</tr>
</tbody>
</table>
Note: The rate provided is the rate per 100,000 per year, standardised to the Australian 1991 population standard. Source: (AIHW, 1998).

11 **TESTICULAR CANCER**

Normative data for this group of cancer were sourced from AIHW (1999). Testicular cancer accounts for 1.3% of new cases of cancer and 0.2% of cancer deaths for males. Men have a 1 in 241 lifetime risk of developing testicular cancer.

Table 32. Incidence and mortality from cancer of the testis (ICD-10 C62) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
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</tr>
<tr>
<td>0–4</td>
<td>1.1</td>
</tr>
<tr>
<td>5–9</td>
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<td>10–14</td>
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<td>15–19</td>
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<tr>
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<td>45–49</td>
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<tr>
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<td>3.7</td>
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<td>55–59</td>
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</tr>
<tr>
<td>60–64</td>
<td>2.3</td>
</tr>
<tr>
<td>65–69</td>
<td>0.9</td>
</tr>
<tr>
<td>70–74</td>
<td>2.7</td>
</tr>
<tr>
<td>75–79</td>
<td>1.9</td>
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<tr>
<td>80–84</td>
<td>2.7</td>
</tr>
<tr>
<td>85 and over</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

12 **URINARY BLADDER CANCER**

Normative data for this group of cancer were sourced from AIHW (1999). Urinary bladder cancer accounts for 4.7% of all new cases of cancer and 3.1% of all cancer deaths in males. Australian males have a 1 in 60 lifetime risk of developing bladder cancer.

Table 33. Incidence and mortality from cancer of the bladder (ICD-10 C67) in Australian males and females by age in 1999.

<table>
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<tr>
<th>Incidence</th>
<th>Mortality</th>
</tr>
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<tbody>
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</tr>
<tr>
<td>0–4</td>
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</tr>
<tr>
<td>5–9</td>
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<tr>
<td>20–24</td>
<td>0.2</td>
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<tr>
<td>25–29</td>
<td>0.8</td>
</tr>
<tr>
<td>30–34</td>
<td>1.4</td>
</tr>
<tr>
<td>35–39</td>
<td>1.5</td>
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<td>45–49</td>
<td>6.9</td>
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<tr>
<td>Age group</td>
<td>Incidence Rate</td>
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<td>-----------</td>
<td>----------------</td>
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<tr>
<td>80–84</td>
<td>64.7</td>
</tr>
<tr>
<td>85 and over</td>
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</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

13 RENAL CANCER

Normative data for this group of cancer were sourced from AIHW (1999). Cancer of the kidney accounts for 3.3% of all new cases of cancer and 2.7% of all cancer deaths for males. Men have a 1 in 74 lifetime risk of developing cancer of the kidney. Cancer of renal pelvis accounts for 0.3% of new cases of cancer and 0.1% of all cancer deaths for males. Men have a 1 in 1089 lifetime risk of developing renal pelvis cancer. Cancer of ureter accounts for 0.2% of new cancer cases and 0.1% of cancer deaths in males. Men have a lifetime risk of 1 in 452 of developing cancer of the ureter.

Table 34. Incidence and mortality from cancer of the kidney (ICD-10 C64) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Persons Rate</td>
<td>Rate</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Persons Rate</td>
<td>Rate</td>
</tr>
<tr>
<td>0–4</td>
<td>1.8</td>
<td>4.1</td>
</tr>
<tr>
<td>5–9</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>10–14</td>
<td>0.1</td>
<td>0.2</td>
</tr>
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<td>15–19</td>
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<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>25–29</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>30–34</td>
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<td>1.5</td>
</tr>
<tr>
<td>35–39</td>
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<td>1.6</td>
</tr>
<tr>
<td>40–44</td>
<td>5.8</td>
<td>3.5</td>
</tr>
<tr>
<td>45–49</td>
<td>12.9</td>
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<td>15.1</td>
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<td>60–64</td>
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<td>65–69</td>
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<td>66.9</td>
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<td>75–79</td>
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<td>40.5</td>
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<tr>
<td>80–84</td>
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<td>27.7</td>
</tr>
<tr>
<td>85 and over</td>
<td>59.7</td>
<td>23.0</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

Table 35. Incidence and mortality from cancer of the renal pelvis (ICD-10 C65) in Australian males and females by age in 1999.
Table 36. Incidence and mortality from cancer of the ureter (ICD-10 C66) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence Males Rate</th>
<th>Incidence Females Rate</th>
<th>Incidence Persons Rate</th>
<th>Mortality Males Rate</th>
<th>Mortality Females Rate</th>
<th>Mortality Persons Rate</th>
</tr>
</thead>
<tbody>
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<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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</tr>
<tr>
<td>5–9</td>
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<td>0.0</td>
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</tr>
<tr>
<td>10–14</td>
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</tr>
<tr>
<td>15–19</td>
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<td>0.0</td>
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</tr>
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<td>60–64</td>
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<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<td>0.9</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>70–74</td>
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<td>3.3</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>75–79</td>
<td>4.7</td>
<td>2.8</td>
<td>3.6</td>
<td>0.9</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>80–84</td>
<td>11.5</td>
<td>5.4</td>
<td>7.8</td>
<td>1.8</td>
<td>0.5</td>
<td>1.0</td>
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<tr>
<td>85 and over</td>
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</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

14 BRAIN CANCER

Normative data for this group of cancer were sourced from AIHW (1999). Brain cancer accounts for 1.7% of new cases of cancer and 3.0% of all cancer deaths. Men have a 1 in 153 lifetime risk of developing brain cancer.

Table 37. Incidence and mortality from cancer of the brain (ICD-10 C71) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence Males Rate</th>
<th>Incidence Females Rate</th>
<th>Incidence Persons Rate</th>
<th>Mortality Males Rate</th>
<th>Mortality Females Rate</th>
<th>Mortality Persons Rate</th>
</tr>
</thead>
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<td>0.3</td>
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<td>1.8</td>
<td>1.9</td>
<td>1.3</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>10–14</td>
<td>1.9</td>
<td>2.2</td>
<td>2.0</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>15–19</td>
<td>2.8</td>
<td>1.7</td>
<td>2.3</td>
<td>0.9</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>20–24</td>
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<td>1.2</td>
<td>1.7</td>
<td>0.3</td>
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<td>1.9</td>
<td>2.6</td>
<td>1.6</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Age group</td>
<td>Number of new cases</td>
<td>% of all new cancer cases</td>
<td>Lifetime risk*</td>
<td>Number of deaths</td>
<td>% of all cancer deaths</td>
<td>Potential Years of Life lost</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
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<td>----------------</td>
<td>-----------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td>30–34</td>
<td>4.7</td>
<td>2.2</td>
<td>3.5</td>
<td>1.7</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>35–39</td>
<td>3.6</td>
<td>2.2</td>
<td>2.9</td>
<td>2.4</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>40–44</td>
<td>6.8</td>
<td>3.6</td>
<td>5.2</td>
<td>4.8</td>
<td>2.2</td>
<td>3.5</td>
</tr>
<tr>
<td>45–49</td>
<td>8.4</td>
<td>3.9</td>
<td>6.2</td>
<td>7.1</td>
<td>3.7</td>
<td>5.4</td>
</tr>
<tr>
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<td>10.1</td>
<td>4.7</td>
<td>7.4</td>
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<td>16.0</td>
<td>7.9</td>
<td>12.0</td>
</tr>
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<td>17.4</td>
<td>11.4</td>
<td>14.4</td>
<td>17.2</td>
<td>9.8</td>
<td>13.5</td>
</tr>
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<td>65–69</td>
<td>26.6</td>
<td>17.3</td>
<td>21.9</td>
<td>20.0</td>
<td>15.0</td>
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<td>21.1</td>
<td>22.3</td>
<td>21.9</td>
<td>22.1</td>
</tr>
<tr>
<td>75–79</td>
<td>33.0</td>
<td>23.1</td>
<td>27.3</td>
<td>27.8</td>
<td>18.8</td>
<td>22.7</td>
</tr>
<tr>
<td>80–84</td>
<td>23.1</td>
<td>21.2</td>
<td>21.9</td>
<td>16.8</td>
<td>15.8</td>
<td>16.2</td>
</tr>
<tr>
<td>85 and over</td>
<td>26.4</td>
<td>17.6</td>
<td>20.2</td>
<td>26.4</td>
<td>17.6</td>
<td>20.2</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

## 15 Non-Hodgkin’s Lymphoma

Normative data for this group of cancer were sourced from AIHW (1998). NHL is the most commonly occurring bone marrow disorder in Australia, with 1 in 75 people being diagnosed with the disease, mainly in the over 45 years age bracket. Australian men have experienced a 30% increase in incidence in NHL between 1983-1994, the rate of increase being most marked in the 45-59 age range. Male incidence of NHL in 1988 and 1994 has increased in the relevant age categories eg 45-49yrs from 15.2 to 17.8; 50-54yr from 16.2 to 29.2; and 55-59yrs from 27.5 to 32.0 per 100,000 and lifetime risk for NHL in men has moved from 1 in 80 to 1 in 70 across this period.


<table>
<thead>
<tr>
<th></th>
<th>Number of new cases</th>
<th>% of all new cancer cases</th>
<th>Lifetime risk*</th>
<th>Number of deaths</th>
<th>% of all cancer deaths</th>
<th>Potential Years of Life lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1,468</td>
<td>3.4</td>
<td>1 in 70</td>
<td>790</td>
<td>4.1</td>
<td>9,195</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1,217</td>
<td>3.7</td>
<td>1 in 98</td>
<td>639</td>
<td>4.5</td>
<td>4,505</td>
</tr>
</tbody>
</table>

Source: (AIHW, 1998)

## 16 Hodgkin’s Disease

Normative data for this group of cancer were sourced from AIHW (1999). Hodgkin’s disease accounts for 0.5% of all new cases of cancer and 0.2% of cancer deaths for males. Men have a 1 in 551 lifetime risk of developing Hodgkin’s disease.

### Table 39. Incidence and mortality from Hodgkin’s disease (ICD-10 C81) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>0–4</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
<td>1.6</td>
<td>0.6</td>
</tr>
<tr>
<td>15–19</td>
<td>3.3</td>
<td>4.1</td>
</tr>
<tr>
<td>20–24</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>25–29</td>
<td>3.8</td>
<td>4.5</td>
</tr>
<tr>
<td>30–34</td>
<td>4.0</td>
<td>3.4</td>
</tr>
<tr>
<td>35–39</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>40–44</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>45–49</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>50–54</td>
<td>1.8</td>
<td>1.0</td>
</tr>
<tr>
<td>55–59</td>
<td>1.7</td>
<td>0.4</td>
</tr>
<tr>
<td>60–64</td>
<td>1.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

### 17 MULTIPLE MYELOMA

Normative data for this group of cancer were sourced from AIHW (1999). Multiple Myeloma accounts for 1.3% of new cases of cancer and 1.8% of all cancer deaths in males. Men have a 1 in 203 lifetime risk of developing multiple myeloma.

Table 40. Incidence and mortality from multiple myeloma (ICD-10 C90) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>Rate</td>
</tr>
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<td>0–4</td>
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<td>0.0</td>
</tr>
<tr>
<td>5–9</td>
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<td>0.0</td>
</tr>
<tr>
<td>10–14</td>
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</tr>
<tr>
<td>15–19</td>
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<td>0.0</td>
</tr>
<tr>
<td>20–24</td>
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<td>0.0</td>
</tr>
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<td>25–29</td>
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<td>0.0</td>
</tr>
<tr>
<td>30–34</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>35–39</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>40–44</td>
<td>2.5</td>
<td>1.3</td>
</tr>
<tr>
<td>45–49</td>
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<td>3.3</td>
</tr>
<tr>
<td>50–54</td>
<td>8.0</td>
<td>3.3</td>
</tr>
<tr>
<td>55–59</td>
<td>10.7</td>
<td>6.4</td>
</tr>
<tr>
<td>60–64</td>
<td>16.1</td>
<td>9.1</td>
</tr>
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<td>65–69</td>
<td>23.3</td>
<td>19.9</td>
</tr>
<tr>
<td>70–74</td>
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<td>20.4</td>
</tr>
<tr>
<td>75–79</td>
<td>41.9</td>
<td>29.5</td>
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<td>80–84</td>
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<td>21.2</td>
</tr>
<tr>
<td>85 and over</td>
<td>52.7</td>
<td>36.9</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

### 18 LEUKAEMIA

Normative data for this group of cancer were sourced from AIHW (1999). Acute lymphocytic leukaemia accounts for 0.4% of new cancer cases and 0.5% of all cancer deaths for males. Men have a 1 in 803 lifetime risk of developing acute lymphoblastic leukaemia. Chronic lymphocytic leukaemia accounts for 0.9% of all new cancer cases and 0.8% of all cancer deaths in males. Men have a 1 in 277 lifetime risk of developing chronic lymphocytic leukaemia. Acute myeloid (or granulocytic) leukaemia accounts for 0.8% of new cases of cancer and 1.6% of cancer deaths for males. Men have a 1 in 329 lifetime risk of developing acute myeloid leukaemia. Chronic myeloid (or granulocytic) leukaemia accounts for 0.3% of new cancer cases and 0.4% of cancer deaths in males. Men have a 1 in 800 lifetime risk of developing chronic myeloid leukaemia. All leukaemias account for 3.1% of new cases of cancer and 3.9% of all cancer deaths in males. Men have a 1 in 90 lifetime risk of developing leukaemia.

Table 41. Incidence and mortality from lymphoblastic leukaemia (ICD-10 C91.0) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>Rate</td>
</tr>
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</tr>
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<td>5–9</td>
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</tr>
<tr>
<td>10–14</td>
<td>1.8</td>
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<tr>
<td>Age group</td>
<td>Incidence</td>
<td>Mortality</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
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<tr>
<td>5–9</td>
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<td>10–14</td>
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<td>15–19</td>
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<td>0.2</td>
</tr>
<tr>
<td>20–24</td>
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</tr>
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<td>25–29</td>
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<td>30–34</td>
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<td>0.4</td>
</tr>
<tr>
<td>35–39</td>
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<td>0.4</td>
</tr>
<tr>
<td>40–44</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>45–49</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>50–54</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>55–59</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>60–64</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>65–69</td>
<td>2.7</td>
<td>1.5</td>
</tr>
<tr>
<td>70–74</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>75–79</td>
<td>3.5</td>
<td>2.7</td>
</tr>
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<td>80–84</td>
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</tr>
<tr>
<td>85 and over</td>
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</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)
<table>
<thead>
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<tbody>
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<td>1.7</td>
<td>1.6</td>
<td>1.8</td>
<td>3.6</td>
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<td>13.1</td>
<td>22.6</td>
<td>31.1</td>
<td>33.7</td>
<td>31.9</td>
</tr>
<tr>
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<td>1.2</td>
<td>1.5</td>
<td>1.6</td>
<td>3.2</td>
<td>3.9</td>
<td>3.9</td>
<td>10.1</td>
<td>11.4</td>
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<td>1.7</td>
<td>3.4</td>
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<td>5.8</td>
<td>9.9</td>
<td>16.7</td>
<td>22.5</td>
<td>24.3</td>
<td>25.7</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

Table 44. Incidence and mortality from chronic myeloid leukaemia (ICD-10 C92.1) in Australian males and females by age in 1999.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.3</td>
<td>0.1</td>
<td>0.0</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
<td>0.7</td>
<td>1.1</td>
<td>1.8</td>
<td>5.2</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>9.8</td>
<td>15.3</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
<td>0.3</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
<td>1.2</td>
<td>4.9</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>6.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Persons</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
<td>1.2</td>
<td>3.8</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>19.5</td>
<td>8.3</td>
</tr>
</tbody>
</table>

Note: All rates are expressed per 100,000 population. Source: (AIHW, 1999)

Table 45. Incidence and mortality from all leukaemias (ICD-10 C91-C95) in Australian males and females by age in 1999.
19 **NEUROBEHAVIORAL DISORDERS**

**Australian Normative Data**

Normative data for this group of cancer were sourced from AIHW (2002e). Cognitive effects include memory problems and dementia. Dementia affects 5.6% of males aged 65 and over and 7.1% of females aged 65 and over. A National Survey of Mental Health of Adults was conducted throughout Australia in 1997 (ABS, 1998). It consisted of representative sample of residents of private dwellings in all States and Territories. The estimates are based on information obtained from approximately 10600 people. Neuropsychiatric effects investigated include neurasthenia, depression, post-traumatic stress disorder and suicide. Depression affects 3.4% of males, 6.8% of females and 5.1% of all people. Post-traumatic stress disorder affects 2.3% of males, 4.2% of females and 3.3% of all people (ABS, 1998). The rates for suicide for males and females are shown in the Figure 2 -1. Motor and coordination dysfunction includes Parkinson’s disease and amyotrophic lateral sclerosis.

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0.50</td>
<td>0.53</td>
</tr>
<tr>
<td>5–9</td>
<td>0.00</td>
<td>0.53</td>
</tr>
<tr>
<td>10–14</td>
<td>0.50</td>
<td>0.00</td>
</tr>
<tr>
<td>15–19</td>
<td>0.51</td>
<td>0.54</td>
</tr>
<tr>
<td>20–24</td>
<td>0.00</td>
<td>0.48</td>
</tr>
<tr>
<td>25–29</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>30–34</td>
<td>0.00</td>
<td>0.46</td>
</tr>
<tr>
<td>35–39</td>
<td>0.94</td>
<td>2.05</td>
</tr>
<tr>
<td>40–44</td>
<td>0.50</td>
<td>2.84</td>
</tr>
<tr>
<td>45–49</td>
<td>0.00</td>
<td>4.53</td>
</tr>
<tr>
<td>50–54</td>
<td>3.36</td>
<td>14.20</td>
</tr>
<tr>
<td>55–59</td>
<td>14.75</td>
<td>33.86</td>
</tr>
<tr>
<td>60–64</td>
<td>33.88</td>
<td>95.02</td>
</tr>
<tr>
<td>65–69</td>
<td>130.34</td>
<td>191.31</td>
</tr>
<tr>
<td>70–74</td>
<td>404.97</td>
<td>589.52</td>
</tr>
<tr>
<td>75–79</td>
<td>1188.58</td>
<td>1667.44</td>
</tr>
<tr>
<td>80–84</td>
<td>3136.78</td>
<td>4730.12</td>
</tr>
<tr>
<td>85+</td>
<td>8505.97</td>
<td>17208.11</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source: (AIHW, 2002f).
Figure 2. Age-specific suicide rates for Australian males, 1998.
Source: (AIHW, 2002b)

Table 47. Age-specific and age-standardised mortality rates for Parkinson’s disease, Australia, 1994–1998.

<table>
<thead>
<tr>
<th>Rates Age</th>
<th>Rates Males</th>
<th>Rates Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>5–9</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10–14</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>15–19</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>20–24</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>25–29</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>30–34</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>35–39</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>40–44</td>
<td>0.00</td>
<td>0.29</td>
</tr>
<tr>
<td>45–49</td>
<td>0.31</td>
<td>0.32</td>
</tr>
<tr>
<td>50–54</td>
<td>0.76</td>
<td>1.18</td>
</tr>
<tr>
<td>55–59</td>
<td>2.38</td>
<td>2.45</td>
</tr>
<tr>
<td>60–64</td>
<td>19.53</td>
<td>11.09</td>
</tr>
<tr>
<td>65–69</td>
<td>63.85</td>
<td>23.24</td>
</tr>
<tr>
<td>70–74</td>
<td>195.34</td>
<td>76.90</td>
</tr>
<tr>
<td>75–79</td>
<td>469.67</td>
<td>243.36</td>
</tr>
<tr>
<td>80–84</td>
<td>1019.83</td>
<td>460.48</td>
</tr>
<tr>
<td>85+</td>
<td>1536.50</td>
<td>647.80</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source: (AIHW, 2002f)


<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>0.30</td>
<td>0.64</td>
</tr>
<tr>
<td>5–9</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>10–14</td>
<td>0.30</td>
<td>0.00</td>
</tr>
<tr>
<td>15–19</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>20–24</td>
<td>1.13</td>
<td>0.29</td>
</tr>
<tr>
<td>25–29</td>
<td>1.69</td>
<td>0.00</td>
</tr>
<tr>
<td>30–34</td>
<td>2.50</td>
<td>0.55</td>
</tr>
<tr>
<td>35–39</td>
<td>4.43</td>
<td>1.93</td>
</tr>
<tr>
<td>40–44</td>
<td>8.27</td>
<td>2.35</td>
</tr>
<tr>
<td>45–49</td>
<td>11.84</td>
<td>7.64</td>
</tr>
<tr>
<td>50–54</td>
<td>25.78</td>
<td>15.00</td>
</tr>
<tr>
<td>55–59</td>
<td>40.96</td>
<td>25.98</td>
</tr>
</tbody>
</table>
Note: all rates are expressed per 100,000 population. Source: (AIHW, 2002f)

20 **Respiratory Disorders**

The National Health Survey of the Australian Bureau of Statistics reported that in 1995, 37% of Australians (6.7 million people) had a respiratory condition (ABS, 2002e). This Survey included the residents of 23 800 dwellings across Australia. The information in the survey was essentially ‘as reported’ by respondents, reported information on medical conditions was not medically verified and was not necessarily based on diagnosis by a medical practitioner. 4.3% of the population or 777 800 people had bronchitis and/or emphysema which included chronic obstructive pulmonary disease. Other respiratory conditions, which include acute respiratory infections, other disease of the upper respiratory tract, pneumonia, pleurisy, and pneumoconiosis, affected 2.6% of people (475 800 people). Influenza affected 3.2% of people (573 000) (ABS, 2002e). The overall rate for respiratory conditions was higher for females (39%) than for males (36%). In Western Australia, 40.8% (standardised) of people had a respiratory condition compared to 37.4% for all of Australia (ABS, 2002e).

In 1996, 8% of all deaths (10 298 deaths) were identified as being caused by a respiratory condition. Bronchitis and/or emphysema which includes chronic obstructive pulmonary disease accounted for 67% of male and 53% of female deaths due to respiratory conditions (ABS, 2002e). Influenza and pneumonia accounted for 2.1% of all deaths in 2001 (ABS, 2002b).

Table 49. Australians with respiratory conditions in 1995.

<table>
<thead>
<tr>
<th>Type of condition</th>
<th>'000</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayfever</td>
<td>2 515.4</td>
<td>13.9</td>
</tr>
<tr>
<td>Asthma</td>
<td>2 041.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1859.0</td>
<td>10.3</td>
</tr>
<tr>
<td>Common cold</td>
<td>1 028.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Bronchitis and/or emphysema</td>
<td>777.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Influenza</td>
<td>573.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Cough and/or sore throat</td>
<td>540.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Other respiratory conditions (b)</td>
<td>475.8</td>
<td>2.6</td>
</tr>
<tr>
<td>All respiratory conditions(c)</td>
<td>6 748.7</td>
<td>37.4</td>
</tr>
<tr>
<td>Total persons</td>
<td>18 061.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Source: (ABS, 2002e)

In 2001, 417 900 males and 616 400 females were affected by ‘allergy (undefined)’ (ABS, 2002d). Data on asthma and hayfever are summarised in section 5 Respiratory Disorders. Autoimmune diseases include conditions such as type 1 diabetes and rheumatoid arthritis. In 2001, there were 48900 males and 46300 females affected by type 1 diabetes and 180200 males and 258000 females affected by rheumatoid arthritis (ABS, 2002d). Primary immunodeficiency disorders (PID) are uncommon conditions that require specialised immunologic services for diagnosis and management (Baumgart et al., 1997). The prevalence

21 **Immune System Disorders**

In 2001, 417 900 males and 616 400 females were affected by ‘allergy (undefined)’ (ABS, 2002d). Data on asthma and hayfever are summarised in section 5 Respiratory Disorders. Autoimmune diseases include conditions such as type 1 diabetes and rheumatoid arthritis. In 2001, there were 48900 males and 46300 females affected by type 1 diabetes and 180200 males and 258000 females affected by rheumatoid arthritis (ABS, 2002d). Primary immunodeficiency disorders (PID) are uncommon conditions that require specialised immunologic services for diagnosis and management (Baumgart et al., 1997). The prevalence
of primary immunodeficiency was ascertained from a national register of PID. Results showed that the national prevalence of all primary immunodeficiency disorders was 2.1/100,000.

22 MALE REPRODUCTIVE DISORDERS

It is estimated that male fertility affects about one Australian man in 20. In approximately 60% of infertile men, no cause is found for low sperm counts or inadequate production of sperm" (McLachlan and de Kretser, 2001). Between 1981 and 1997 the rate of congenital malformations of the genital organs was 24.6 per 10,000 births (although there was not a differentiation for male or female genital organs) (AIHW, 2002a).

23 DIABETES

The National Health Survey of the Australian Bureau of Statistics reported 2.9% of the Australian population (554,200 persons, self-reported) that have been diagnosed with diabetes mellitus in 2001 (ABS, 2002c). Of these, 78% reported Type 1, 17% Type 2 diabetes. It is, however, estimated that approximately half of the Australian diabetes population is undiagnosed (Diabetes Australia, 2003). Death rates for diabetes in the Australian population are shown in Table 8.1 – 1. A national study involving 11,247 participants aged > or =25 years living in 42 randomly selected areas from the six states and the Northern Territory were examined in a cross-sectional survey. The prevalence of diabetes in Australia was 8.0% in men and 6.8% in women, and an additional 17.4% of men and 15.4% of women had IGT or IFG. Even in the youngest age group (25-34 years), 5.7% of subjects had abnormal glucose tolerance. The overall diabetes prevalence in Australia was 7.4%, and an additional 16.4% had IGT or IFG (Dunstan David et al., 2002). Australia’s indigenous population suffers the fourth highest rate of Type II diabetes in the world. Five percent of Indigenous Australians self-reported diabetes as a condition (ABS, 2002a). The prevalence of NIDDM in Aborigines is more than twice that of non-Aboriginal Australians and a prevalence of higher than 20% has been observed in some communities (Guest and O’Dea, 1992; Thompson and Gifford, 2000).

### Table 50. Death rates for diabetes by age in the Australian population.

<table>
<thead>
<tr>
<th>Disease as the underlying cause of death</th>
<th>SEX</th>
<th>25–29</th>
<th>30–44</th>
<th>45–64</th>
<th>65–74</th>
<th>75+</th>
<th>All ages*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Males</td>
<td>3.9</td>
<td>2.6</td>
<td>0.8</td>
<td>3.4</td>
<td>2.3</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>3.2</td>
<td>2.1</td>
<td>0.7</td>
<td>3.2</td>
<td>2.2</td>
<td>7.9</td>
</tr>
<tr>
<td>All causes of death</td>
<td>Males</td>
<td>5.8</td>
<td>3.7</td>
<td>1.3</td>
<td>2.6</td>
<td>2.4</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>4.3</td>
<td>2.6</td>
<td>0.7</td>
<td>2.0</td>
<td>1.6</td>
<td>6.6</td>
</tr>
</tbody>
</table>

* Rates should be interpreted with caution as the relative standard errors are between 25% and 50%.

** Rates are not presented as relative standard errors are greater than 50%.

(a) Age-standardised to the 1991 Australian population.

Source: (AIHW, 2002c).

24 LIPID AND LIPOPROTEIN DISORDERS

In 1999-00, over six million Australians aged 25 years and over (50% of the population) had total blood cholesterol levels higher than 5.5mmol/L (AIHW, 2002d). Total blood cholesterol levels above 5.5mmol/L are an indication of an increased risk of developing coronary heart disease (hypercholesterolemia). The Australian Diabetes study reported that 50.2% of Australian males and 49.6% of females had hypercholesterolemia (AIHW, 2002c).

“There are no national data on blood cholesterol levels among Aboriginal and Torres Strait Islander peoples. A New South Wales survey in 1987-88 on cardiovascular risk factors showed that a greater proportion of Indigenous women in Wilcannia had cholesterol levels above 6.5mmol/L compared with other Australian women. However, other studies have shown no difference in cholesterol levels between Indigenous Australians and other Australians (AIHW, 2001).”

A comprehensive investigation under the Australian diabetes, Obesity and Lifestyle Study, shows that 3.8% of Australian males and 1.5% of females aged 25 and over have fasting hypertriglyceridemia. Fasting hypertriglyceridemia was defined as triglycerides >4.0mmol/L (recommended level: < 2.0mmol/L). The rates were age-standardised to the Australian population as at 30 June 1991 and included adults aged 25 years and above from 42 randomly selected urban and non-urban areas in Australia. Self-reported data and physical health check information was collected from 11,000 participants Australia-wide (AIHW, 2002c).
25 Thyroid Homeostasis

The prevalence of thyroid diseases in Australian males was reported by the Australian Institute of Health and Welfare with an age-standardised rate per 1000 population of 5.2 for males and 27.3 for females (Dunn et al., 2002).

Table 51. Age-specific and age-standardised mortality rates for thyroid disorders, Australia, 1994–1998

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0.301194</td>
<td>0</td>
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<tr>
<td>5-9</td>
<td>0</td>
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<tr>
<td>10-14</td>
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<td>0</td>
</tr>
<tr>
<td>15-19</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>0.28174</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>0.277794</td>
<td>0.553927</td>
</tr>
<tr>
<td>35-39</td>
<td>0.276569</td>
<td>0.551055</td>
</tr>
<tr>
<td>40-44</td>
<td>0.295217</td>
<td>0.588487</td>
</tr>
<tr>
<td>45-49</td>
<td>0.622942</td>
<td>0.636578</td>
</tr>
<tr>
<td>50-54</td>
<td>0.379185</td>
<td>1.973967</td>
</tr>
<tr>
<td>55-59</td>
<td>1.905314</td>
<td>0.490274</td>
</tr>
<tr>
<td>60-64</td>
<td>1.116133</td>
<td>4.436166</td>
</tr>
<tr>
<td>65-69</td>
<td>2.386799</td>
<td>7.937282</td>
</tr>
<tr>
<td>70-74</td>
<td>5.083301</td>
<td>17.22538</td>
</tr>
<tr>
<td>75-79</td>
<td>11.07713</td>
<td>30.11438</td>
</tr>
<tr>
<td>80-84</td>
<td>32.34534</td>
<td>53.70397</td>
</tr>
<tr>
<td>85+</td>
<td>36.34742</td>
<td>155.2458</td>
</tr>
</tbody>
</table>

Note: all rates are expressed per 100,000 population. Source (Dunn et al., 2002).

26 Circulatory Disorders

In 2001, 22% of adult Australians (3.1 million people) were affected by circulatory conditions. Hypertension was the most prevalent condition, affecting 1.9 million people (13.4%), with females more likely than males to report the disease (14.4% compared with 12.5%). According to the Heart, Stroke and Vascular Diseases Australian Facts 2001, there are no national data available on the number of Australians who have heart failure. Heart failure accounted for 0.6% of all problems managed by
General Practitioner consultations, 0.7% of all hospitalisations and 10% of all hospitalisations for cardiovascular diseases. (AIHW, 2001).

A National Health Survey included the residents of 17 918 private dwellings across Australia. Within each selected household, a random sub-sample of usual residents was selected for inclusion in the survey as follows: one adult (> 18 years), all children (0-6 years) and one child (7-17 years). The information in the survey was essentially ‘as reported’ by respondents (ABS, 2002d). Arteriosclerotic heart disease or ischaemic heart disease affected 2.5% of the population aged 18 years and over (2.9% males and 2.1% females). Peripheral vascular disease affected 627 800 people or 4.4% of the population, 2.7% of males and 6.1% of females. Cerebrovascular diseases affected 0.7% of the population, 0.8% of males and 0.6% of females (ABS, 2002d).

Table 52. Circulatory conditions* in Australians aged 18 years and over (2001)

<table>
<thead>
<tr>
<th>Type of condition</th>
<th>Males '000</th>
<th>Males %</th>
<th>Females '000</th>
<th>Females %</th>
<th>Persons '000</th>
<th>Persons %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disease</td>
<td>886.2</td>
<td>12.5</td>
<td>1,039.5</td>
<td>14.4</td>
<td>1,905.7</td>
<td>13.4</td>
</tr>
<tr>
<td>Ischaemic heart diseases</td>
<td>199.6</td>
<td>2.9</td>
<td>152.2</td>
<td>2.1</td>
<td>351.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>6.0</td>
<td>0.1</td>
<td>6.3</td>
<td>0.1</td>
<td>12.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>142.2</td>
<td>2.0</td>
<td>190.8</td>
<td>2.6</td>
<td>333.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>55.9</td>
<td>0.8</td>
<td>46.2</td>
<td>0.6</td>
<td>102.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Oedema</td>
<td>87.2</td>
<td>1.3</td>
<td>208.2</td>
<td>2.9</td>
<td>295.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Diseases of the arteries/arterioles/capillaries</td>
<td>123.6</td>
<td>1.8</td>
<td>72.8</td>
<td>1.0</td>
<td>196.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Diseases of veins, lymphatic vessels etc.</td>
<td>187.0</td>
<td>2.7</td>
<td>440.8</td>
<td>6.1</td>
<td>627.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Other diseases of the circulatory system</td>
<td>23.7</td>
<td>0.3</td>
<td>41.3</td>
<td>0.6</td>
<td>65.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Symptoms/signs involving the circulatory system</td>
<td>153.8</td>
<td>2.2</td>
<td>221.8</td>
<td>3.1</td>
<td>375.6</td>
<td>2.6</td>
</tr>
<tr>
<td>All circulatory conditions (a)</td>
<td>1,349.8</td>
<td>19.4</td>
<td>1,765.2</td>
<td>24.4</td>
<td>3,115.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Note: Each person may have reported more than one type of condition; therefore components may not add up to totals. Source: (ABS, 2002d).

Mortality data are obtained from Australian death certificates. Registration of deaths in Australia is the responsibility of the State and Territory Registrars of Births, Deaths and Marriages. Registrars provide the deaths data to the Australian Bureau of Statistics for coding of cause of death and compilation into aggregate statistics. The AIHW also holds these data in a National Mortality Database.

In 2000, almost 40% (49,687) of all deaths were due to diseases of the circulatory system. Ischaemic heart disease or arteriosclerotic heart disease accounted for 21% of all deaths, and cerebrovascular diseases a further 9.6% (ABS, 2002f). In 2000, the age-standardised rate per 100,000 persons for deaths due to hypertension was 4.9 for males and 5.0 for females. In 2001, heart failure was the cause of death for 14.1 males per 100,000 population and the rates for peripheral vascular disease was 15.1 for males and 7.8 for females (ABS, 2002b). Between 1990 and 2000, age-standardised death rates for diseases of the circulatory system declined by 36% for males (from 400 to 254 per 100,000 persons), 35% for females (from 263 to 172) and 35% in total (from 325 to 210). In 2000, data on causes of death for Aboriginal and Torres Strait Islander peoples were considered to be of publishable quality for New South Wales, Victoria, Queensland, Western Australia, South Australia and the Northern Territory. In that year, the leading cause of death among the Indigenous population was diseases of the circulatory system, which accounted for 28% of all Indigenous deaths, compared to 39% of all non-Indigenous deaths. In 1998-2000, the median age at death for Indigenous persons from cardiovascular disease was 60 years compared with 81 years for the non-Indigenous population (ABS, 2002f).

27 GASTROINTESTINAL DISORDERS

In 2001, there were 103,800 males and 214,400 females who were affected by ‘all disease of the digestive system’ (ABS, 2002d). In 2001, there was a death rate of 20.4 for males, 13.9 for females and 17.0 for all persons for diseases of the digestive tract (ABS, 2002b).

Diseases of oesophagus, stomach and duodenum had a death rate of 3.1 for males, 2.1 for females and 2.5 for all persons. Gastric and duodenal ulcers had a death rate of 2.1 for males, 1.5 for females and 1.8 for all persons. (Rates are based on standardised death rate per 100,000 of the mid-year 1991 population.) (ABS, 2002b). In 2001, 2.7% of males, 2.6% of females and 2.7% of all persons suffered from diseases of the digestive system including stomach/duodenal/gastrointestinal ulcer (ABS, 2002d).

The rates of mortality from appendicitis for males per 100,000 was 0.2 and for females 0.1. The incidence for appendicitis for males was 137.7 and 123.4 for females, per 100,000 population (Mathers et al., 1999). 2.5% of males, 1.6% of females and 2.0% of all persons were affected by hernia of the abdominal cavity (ABS, 2002d).
In 2001, there were 42 100 females and 40 900 males with ‘signs or symptoms involving the digestive system’ (ABS, 2002d). In 2001, mortality rate from disease of the liver was 7.9 for males, 3.1 for females and 5.4 for all persons. (Rates are based on standardised death rate per 100 000 of the mid-year 1991 population.) (ABS, 2002b).
**APPENDIX 2 LITERATURE UPDATES**

Copies of full publications of papers reviewed and evaluated for this report are provided with the hardcopy submission.
Based on the exclusion criteria defined for Literature Updates, 38 papers that addressed associations between the chemicals of interest (2,4,5-T, 2,4-D and TCDD) and human health effects were excluded from this review (18 reviews, 6 letters, 3 case reports/series, 2 studies investigating biochemical effects, 1 commentaries, 1 correlation study, 3 mixtures of undefined chemicals, 3 without reported measures of effect and 1 study was included in the NAS 2002 Update). A short summary of these papers, including the rationale for exclusion is provided in here.

**Reference:** (Acquavella et al., 2003) Epidemiological studies of occupational pesticide exposure and cancer: regulatory risk assessments and biologic plausibility

**Summary:** Reviews the toxicology and exposure data that are developed as part of the pesticide regulatory process and discusses applicability of this data to epidemiological research. Provides generic example of how worker pesticide exposures might be estimated and compared to relevant toxicological dose levels. Provides guidance for better characterisation of exposure and for consideration of biological plausibility

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Ahmad, 2002) Agent Orange no longer linked to childhood AML

**Summary:** Comments on a National Academy of Sciences’ rework of its report in 2001 which linked parental dioxin exposure to acute myelogenous leukaemia (AML) in children.

**Rationale for selection/exclusion:** Letter not providing new epidemiological data

**Reference:** (Blodgett et al., 2002) Miscellaneous Pesticides with Action on the Nervous System

**Summary:** Provides a summary of various pesticide groups that may have neurotoxic effects, including clinical evidence of neurotoxicity and mechanisms of action.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Butler, 2003) Flight records full extent of Agent Orange contamination

**Summary:** Comments on new data available for the estimation of the quantity of herbicides sprayed during the Vietnam War.

**Rationale for selection/exclusion:** Letter not providing new epidemiological data

**Reference:** (Carli and Maynadie, 2002) Non-Hodgkin’s lymphoma: Epidemiology and aetiology

**Summary:** Review on the results from different studies evaluating the role of various factors in the etiology of non-Hodgkin’s lymphoma

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Domingo, 2002) Public fear of dioxins from modern municipal waste incinerators is not justified

**Summary:** Comments on the moratorium on construction of new municipal waste incinerators and more stringent controls on existing units due to the fear from dioxin emissions. Notes that due to the reduction of dioxin emissions in recent years, countries with stringent regulations are now only a minor contributor to a national inventory and highlights that diet is the main route of dioxins exposure.

**Rationale for selection/exclusion:** Letter not providing new epidemiological data

**Reference:** (Ehrlich et al., 2002) Chronic acquired dyskeratotic papulopapulosis of the face

**Summary:** Case report on a Vietnam veteran who had been exposed to Agent Orange and showed a history of papulonodular disease mainly affecting the face. Multiple biopsies of both fresh and mature papulonodules were performed for routine histopathology and electron microscopy. Results were positive for spongiosis with exocytosis, acanthosis, dyskeratotic keratinocytes, and marked incontinence of pigment, which together are suggestive of a previously unreported clinical entity that we term chronic acquired dyskeratotic papulopapulosis

**Rationale for selection/exclusion:** Case report not providing any measure of effect

**Reference:** (Garabrant and Philbert, 2002) Review of 2,4-Dichlorophenoxyacetic acid (2,4-D) Epidemiology and Toxicology

**Summary:** Update review of 2,4-D toxicity in humans and animals relating to cancer risks, neurologic disease, reproductive risks and immunotoxicity. Focuses on evidence accumulated between 1995-2001. Details of 11 cohort studies of phenoxy herbicide manufacturers and/or applicators are reviewed. Case-control studies of soft tissue sarcoma (10 studies), Non-Hodgkin’s Lymphoma (12 studies) and Hodgkin’s disease (2 studies). The review focuses on human cohort studies in which herbicide use or exposure was believed to involve direct contact with chemicals in their concentrated form. The review of cohort studies and case-
control studies concluded that overall the studies did not provide adequate evidence to conclude exposure to 2,4-D is associated with Soft Tissue Sarcoma, Non-Hodgkin’s Lymphoma, Hodgkin’s Disease or any other cancer. The authors acknowledge TCDD (as the contaminant of phenoxy herbicides) may be an important confounder of associations between phenoxy herbicides and cancer.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Geusau et al., 2002) Clinical and Laboratory follow up in two patients severely contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin

**Summary:** Case report of two females severely contaminated with TCDD (unknown cause, but most likely oral exposure). Initial serum TCDD blood levels were 144,000 ppt in patient 1 and 26,000 ppt in patient 2. The clinical course, including skin manifestations, and the laboratory parameters were evaluated over a four year time period. The authors concluded that severe TCDD intoxication was associated with chloracne and gastrointestinal symptoms, but no single routine laboratory parameter was clearly indicative of dioxin poisoning in the first four years of observation. Only direct measurement of dioxins serum concentrations allowed to corroborate the suspicion of TCDD intoxication.

**Rationale for selection/exclusion:** Case report not providing any measure of strength of evidence

**Reference:** (Greene et al., 2003) Basis for a proposed reference dose (RfD) for dioxin of 1-10pg/kg-day: a weight of evidence evaluation of the human and animal studies.

**Summary:** Reviewed published studies including laboratory experimental and epidemiological studies that address non-cancer effects associated with dioxins in order to derive a reference dose on a combination of human and animal data. Reviewed cohorts include occupationally, accidentally and environmentally exposed groups (including 2,4,5-T, 2,4-D and TCDD). Developmental toxicity was chosen as the most sensitive effect of TCDD consistently seen in mice and rats. A reference dose between 1 and 10 pg/kg/day TCDD TEQ was proposed.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Kayajanian, 2002) The J-shaped dioxin curve

**Summary:** Commentary on statistical treatment of cancer incidence data in selected workers exposed to dioxin from NIOSH chemical plant study and in Seveso (acute and long-term occupational and environmental exposure including 2,4,5-T, 2,4-D and TCDD). This paper describes difficulties in assessing exposure to single chemical in a complex mixture of chemicals and the problems with extrapolating back from high dose exposure to low dose exposure. Serum TCDD concentration was provided by the studies, ranging from 2 to 6500 ppt. A J-shaped dioxin dose response curve was suggested: cancer incidence at high dose exposure is preceded at low and medium doses by a significant decrease in the expected incidence of cancers including primary liver cancer in men. The authors highlight that cancer incidence at high dose exposure is preceded at low and medium doses by a significant decrease in the expected incidence of cancers including primary liver cancer in men.

**Rationale for selection/exclusion:** Commentary not providing new epidemiological data

**Reference:** (Katsnel’son et al., 2002) Dioxins: facts and conjectures

**Summary:** Review of general dioxin and dioxin-like effects on humans. The authors conclude that the most characteristic and constant indicators of intoxication with dioxin-containing substances are altered body weight, chloracne, hepatic damage, thyroid involution, structural changes in the adrenal cortex, spleen, genitals, immunodeficiency. There is evidence for a role of these agents in the development of infertility and neonatal pathology.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Kerkvliet, 2002) Recent advances in understanding the mechanisms of TCDD immunotoxicity

**Summary:** Reviewed published studies including laboratory experimental and epidemiological studies that address non-cancer effects associated with dioxins in order to derive a reference dose on a combination of human and animal data. Reviewed cohorts include occupationally, accidentally and environmentally exposed groups (including 2,4,5-T, 2,4-D and TCDD). Developmental toxicity was chosen as the most sensitive effect of TCDD consistently seen in mice and rats. A reference dose between 1 and 10 pg/kg/day TCDD TEQ was proposed.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Kern et al., 2002) The stimulation of tumour necrosis factor and inhibition of glucose transport and lipoprotein lipase in adipose cells by 2,3,7,8-Tetrachlorodibenzo-p-dioxin

**Summary:** Examined the effects of TCDD in adipocytes to examine associations with diabetes. The authors demonstrated that the addition of TCDD to adipocyte cultures resulted in an increase in TNF secretion and a decrease in glucose transport and LPL activity. Because TCDD is concentrated in adipose tissue, this provides a possible physiologic mechanism for epidemiological studies that link dioxin to diabetes.

**Rationale for selection/exclusion:** Biochemical study not providing new epidemiological data

**Reference:** (Langford and Ferner, 2002) Episodes of environmental poisoning worldwide.

**Summary:** Reviews major chemical incidents with immediate impact, and causing insidious exposure to a variety of compounds. Highlights the need for appropriate risk assessment and management and concludes that if managed appropriately, the impact of chemical spills on the environment and human life may be minimised.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Leikauf, 2002) Hazardous air pollutants and asthma.

**Summary:** Reviews major chemical incidents with immediate impact, and causing insidious exposure to a variety of compounds. Highlights the need for appropriate risk assessment and management and concludes that if managed appropriately, the impact of chemical spills on the environment and human life may be minimised.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data
Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Marwick, 2003) Link found between Agent Orange and chronic lymphocytic leukaemia.
Summary: short letter summarising the U.S. Institute of Medicine conclusion that a positive association exists between exposures to herbicides used as defoliants during the Vietnam war and the risk of developing chronic lymphocytic leukaemia.

Rationale for selection/exclusion: Letter not providing new epidemiological data

Reference: (Massaad et al., 2002) How can chemical compounds alter human fertility?
Summary: Review summarising recent findings on the molecular mechanisms of action of xenohormones, dioxins and glycol ethers. Comparison of animal and cell experimental models with epidemiological studies. The authors conclude that the effects of xenoestrogens on human and animals remain controversial. With respect to dioxins, the authors highlight that these compounds constitute a major threat on reproduction, and that, in a similar manner to xenohormones, TCDD exerts its effects by disrupting the endocrine system, but acts by means of the Ah Receptor.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Meyer, 2002b) Incidence of Cutaneous T-Cell Lymphoma in Vietnam veterans
Summary: Case series investigating cutaneous T-cell lymphoma (CTCL) in 7 Vietnam veteran patients who recalled military exposure to Agent Orange (2,4,5-T, 2,4-D and TCDD). An informal exploratory questionnaire was obtained including information on potential exposure to agent orange in Vietnam. 6 or 7 patients recalled having some possible contact with herbicides in Vietnam.

Rationale for selection/exclusion: Case series not providing any measure of strength of evidence

Reference: (Michalek et al., 2003b) Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of Operation Ranch Hand
Summary: TCDD elimination rates were estimated using previous pharmacokinetic study of repeated blood TCDD measurements in the same cohort of 343 Vietnam Veterans of Operation Ranch Hand exposed to Agent Orange. The diagnosis of diabetes was verified by medical records. Information on confounding parameters was obtained (body mass index, smoking, family history of diabetes, age, diabetes prior to exposure). Using multivariate statistical modelling, the results suggest an increased risk of diabetes with decreased elimination rate without adjustment for age, body mass index and family history. After adjustment, no significant relationship between the rate of TCDD elimination and the occurrence or time to onset of diabetes was found.

Rationale for selection/exclusion: study that does not provide any measure of effect

Reference: (Nagayama et al., 2002) Effects of organochlorine compounds such as pesticides, PCB’s and dioxins on immune response system in Japanese mothers.
Summary: cohort study investigating immune responses of Japanese mothers (N=124) with uncomplicated pregnancies and no signs of serious illness. Environmental exposure to organochlorine pesticides, PCBs and dioxins. Breast milk was sampled 2-4 months after childbirth to determine concentrations of organochlorine pesticides, PCB’s and dioxins. After ~1 year after childbirth, blood samples were collected from 45 mothers to measure lymphocyte sub-populations. Spearman rank correlation coefficients were employed; statistical significance was evaluated using Student’s t-test.

Summary: contaminations level of dioxins as TEQ concentration was 100 to 10,000 times lower than those of the pesticides and PCBs in Japanese breast milk (PCB and PCDD/F TEQ (wet weight basis) median 0.94 ppt, ranging from 0.15-2.92 ppt). Significant correlations were observed between CD3 and dieldrin, between CD4 and dieldrin or HCE, between CD16 and dieldrin, and between CD20 and DDT and PCBs (rank correlation coefficient = 0.356, p = 0.022). No results on a correlation were reported for dioxins or dioxin-like compounds separately of other mixtures.

Rationale for selection/exclusion: study that does not provide any measure of effect

Summary: short review/commentary on the association of cancers in residents of Angers with waste incineration.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Neubert, 2002) Reproductive toxicology: the science today
Summary: review article discussing the process and difficulties of determining risk assessment of endocrine disruptors and possible mechanism hypotheses. The review investigates adverse effects on reproduction induced directly by damaging the semen producing epithelium, or indirectly, by interfering with sex hormonal homeostasis.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Summary: Review the of the final evaluation report by the Science Advisory Board of the draft report of the2001 EPA reassessment of the risks posed by TCDD and related chemicals. The authors conclude that given the uncertainty in approaches for identifying safe levels of TCDD exposure and the peculiar toxicity of the dioxins, it is prudent for all nations to continue to work toward reducing dioxin emissions and to monitor the expected continued reduction in blood levels in the general population.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Pohl et al., 2002) Public Health Perspectives on Dioxin Risks: Two Decades of Evaluations
Summary: A general discussion of dioxin risk assessment as performed by different agencies over the past 20 years. Numerous different cohort studies with varying exposure are discussed. The authors conclude that US EPA’s reassessment of dioxin and related compounds may place too much confidence in the ability to accurately predict cancer risks at low doses. This approach dramatically increases cancer risk.
estimates that are not based on compelling new data but rather on the application of statistical models applied to results of occupationally exposed cohorts that have been associated with significant uncertainty regarding actual exposure. This is further confounded by the fact that these models are not yet fully validated and that we still have knowledge gaps with respect to the mechanism of action and interaction for the dioxin like groups of chemicals. Emphasises caution when predicting cancer risk at low exposure doses.

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Pavuk et al., 2002a; Pavuk et al., 2002b) Alterations in thyroid metabolism in US Air Force sprayers of Agent Orange (full paper) & Effects of TCDD on thyroid metabolism in US Air Force herbicide sprayers (conference paper)

**Summary:** cohort study investigating U.S. Air Force veterans who participated in Operation Ranch Hand (participants of the Air Force Health Study) compared to of Air Force veterans of Southeast Asia not involved in herbicide spraying (matched by age, race, occupation). Periodical medical examinations and interviews were conducted in 1982, 1985, 1987, 1992 and 1997. Thyroid disease was verified using medical records. Blood serum analysis for T4 and TSH, calculation of T3% uptake and FTI were performed. Serum TCDD analysis was carried out in 1987, 1992 and 1997. Veterans were divided into high exposure (TCDD ≥ 94 ppt), low exposure (TCDD ≥10 ppt ≤ 94 ppt) and background (TCDD ≤ 10 ppt) (extrapolated to time of exposure). Statistical analyses were performed using covariance analysis (adjustment for age, occupation, race). Mean TSH increased with TCDD exposure category at each examination. No significant differences were found between any exposure category and mean T4, T3% uptake or FTI at any examination. Significant increase of mean TSH with exposure category and a significant difference in mean TSH in both high and low exposure groups compared to comparison group (p=0.008 and p=0.04) were observed. No significant mean differences between any exposure category and comparison group were found in longitudinal analysis of total T4 and T3% uptake. Consistently elevated odds of abnormally high TSH levels in high exposure category at all examinations were observed, but were not statistically significant. The odds ratio for specific thyroid disease was not statistically significant in any exposure category but non-statistically significant. The odds ratio for specific thyroid disease was reported. No significant mean differences between any exposure category and a significant difference in mean TSH in both high and low exposure groups compared to comparison group (p=0.008 and p=0.04) were observed. No significant mean differences between any exposure category and comparison group were found in longitudinal analysis of total T4 and T3% uptake. Consistently elevated odds of abnormally high TSH levels in high exposure category at all examinations were observed, but were not statistically significant. The odds ratio for specific thyroid disease was not statistically significant in any exposure category but non-statistically significant. The odds ratio for specific thyroid disease was reported.

**Rationale for selection/exclusion:** Results have been included in the assessment of (NAS, 2002) update

**Reference:** (Remillard and Bunce, 2002a) Linking dioxins to diabetes: epidemiology and biologic plausibility.

**Summary:** Review of epidemiological studies and theoretical study proposing biologically plausible connection between dioxins and diabetes. The authors conclude that the Aryl Hydrocarbon (Ah) receptor functions may antagonize peroxisome proliferator-activated receptor (PPAR) functions, and hence the Ah receptor may promote diabetogenesis through a mechanism of PPAR antagonism.

**Rationale for selection/exclusion:** study that does not provide any measure of effect


**Summary:** This study investigated cases of human malignancy and recorded information on pesticide use (grouped into insecticides, herbicides, fungicides, nematicides and others) and cases of human malignancy during 1990-1999 (hospital records). Tumour types were grouped by sex and age group. Pesticide usage ranged from 216.9t-393.3t from 1990-1999, respectively; no distinction was made between occupational and general public exposure. The average annual cancer incidence was 5.32/10,000 and age-adjusted rate of 10.53/10,000. Lung cancer, lymphomas, leukaemia, cancers of the urinary bladder, prostate, brain, colon, stomach and liver were the most abundant among males. Breast cancer, leukaemia, lymphomas, cancers of the brain, uterus, lung, thyroid gland and liver were the most abundant in females. Significant positive correlations between type of pesticide groups and cancer incidence for male, female and both sexes.

**Rationale for selection/exclusion:** Study investigating mixtures of pesticides, grouping 2,4,5-T and 2,4-D exposure into the groups of herbicides, which also includes Diquat and Paraquat.

**Reference:** (Suzuki et al., 2003 in press) Association of the genetic polymorphism in cytochrome P450 (CYP) 1A1 with risk of familial prostate cancer in a Japanese population: a case-control study.

**Summary:** investigates the association between genetic polymorphisms of CYP1A1 and familial prostate cancer risk using a case-control design of 185 individuals. The results indicate that CYP1A1 polymorphism has an association with prostate cancer risk, especially with progression of prostate cancer.

**Rationale for selection/exclusion:** Biochemical study not reporting epidemiological data.

**Reference:** (Tsutsu, 2002) Endocrine disruptors and reproductive mechanism

**Summary:** review on endocrine disruptors and effects on female exposure and possible effects such as endometriosis and effects on pre-implantation embryonic development of offspring

**Rationale for selection/exclusion:** Review article not providing new epidemiological data

**Reference:** (Washam, 2002) Profiles in cancer

**Summary:** Letter reporting on the genetic profiling of several of the most common sarcomas that may enable pathologists to accurately diagnose most soft-tissue sarcomas

**Rationale for selection/exclusion:** Letter not providing new epidemiological data

**Reference:** (Watanuki, 2002) Origin of dioxin causalties

**Summary:** Reports on the US-Vietnam Joint Scientific Conference on Human Health and Environmental Effects of Agent Orange/ Dioxin held in March 2002.

**Rationale for selection/exclusion:** Letter not providing new epidemiological data

Summary: Historical review on milestones in environmental health and their regulatory responses in banning of certain persistent organic pollutants. Comments on advances in epidemiological and practical implications for clinical practice and scientific studies to identifying and managing adverse environmental health effects.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Weiss, 2002) Sexually Dimorphic Non-reproductive Behaviours as Indicators of Endocrine Disruption

Summary: Reviews the literature on the dimorphism of responses of males and females to toxic compounds, showing that the developing male and female respond differently to many chemical agents, with subsequent expression in behaviour. Highlights the importance of including outcome measures based on sexual dimorphism in non-reproductive behaviour studies.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Weber et al., 2002) Environmental influences on male reproduction

Summary: review article discussing various effects of endocrine disruptors and possible mechanism hypotheses. Highlights that the critical issue is whether there are sufficiently high levels of endocrine disrupters in the ambient environment to exert adverse health effects on the general population.

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Young, 2002) Vietnam and Agent Orange Revisited

Summary: An Historical Overview of the issues relating exposure to Agent Orange (and associated TCDD contaminant) and health problems reported by Vietnam Veterans. Recognises current shift of focus to the potential impacts of Agent Orange and dioxin on the environment and people of Vietnam. Lists the ten diseases or conditions for which the US Department of Veterans Affairs currently assumes service connection. Recognised cancers are: STS, HD, NHL, prostate and respiratory cancers (lung, bronchus, larynx or trachea, which occur within 30 years of exposure to Agent Orange).

Rationale for selection/exclusion: Review article not providing new epidemiological data

Reference: (Zhou et al., 2002) Utility of the WHO Neurobehavioral Core Test Battery in Chinese Workers - A Meta-Analysis

Summary: Meta-analysis was performed to summarise the results of WHO Neurobehavioral Core Test Battery (NTCB) in Chinese workers and to describe the most sensitive subtests for different exposure agents. Data was extracted from previous studies. The authors conclude that for organic solvents-exposure, Digit Span, Pursuit Aiming II and Digit Symbol were the most sensitive subsets.

Rationale for selection/exclusion: Study investigating mixtures of pesticides, no specific investigation of 2,4,5-T, 2,4-D or TCDD exposure was undertaken.
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