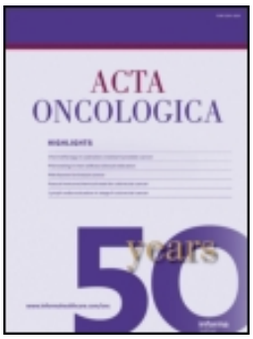

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INVITED ARTICLE

Pesticides, soft-tissue sarcoma and non-Hodgkin lymphoma – historical aspects on the precautionary principle in cancer prevention

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Abstract

Background. After the 2nd World War a long range of chemical agents have been introduced on the market, both in Sweden and most other countries. From the 1950's several pesticides gained increasing use in agriculture and forestry. In the 1970's public concern increased in Sweden especially regarding use of phenoxy herbicides to combat deciduous wood, although statements from different authorities were reassuring of the safety. *Materials and methods.* At the end of the 1970's the author and his colleagues published the first scientific evidence of an association between exposure to phenoxyacetic acids, chlorophenols and certain malignant tumours, i.e., soft-tissue sarcoma and malignant lymphoma. The study subjects were also exposed to contaminating dioxins such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Later studies showed also an association between certain persistent organic pollutants such as polychlorinated biphenyls and non-Hodgkin lymphoma (NHL) with an interaction with titers of antibodies to Epstein-Barr virus early antigen. These results have been corroborated in other studies. *Discussion.* Over the years industry and its allied experts have attacked our studies, but in 1997 IARC classified TCDD as a human carcinogen, Group I. The increasing incidence of NHL in Sweden levelled off about 1990. The author postulated that the regulation or ban of the use of chlorophenols, certain phenoxy herbicides and some persistent organic pollutants in Sweden back in the 1970s has contributed to the now decreasing incidence of NHL. Unfounded criticism from industry experts may prohibit the precautionary principle and early warnings of cancer risk can be ignored. Cancer risks by certain chlorinated phenols may serve as a model of how the precautionary principle should be used by taking early warnings seriously.

In 1973 I met a patient with an abdominal tumour living in the county of Norrbotten in northern Sweden. He was first diagnosed as having liver cancer but at autopsy it turned out to be pancreatic cancer. This 64-year-old man had worked as a forestry foreman. In the 1950's and 1960's he used a mixture of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) to spray hardwoods. He used no protective equipment. His relatives were of the opinion that his cancer was caused by exposure to these chemicals. This case history initiated my interest in research about a potential association between herbicides and cancer.

The most common combined preparation for the control of deciduous forest in Sweden since the early 1950's was a 2:1 mixture of 2,4-D and 2,4,5-T (Hormoslyr®). Of the total sprayed area 41% was located in the county of Norrbotten. The phenoxy herbicides 2,4-D and 4-chloro-2-methylphenoxyacetic acid (MCPA) were the most commonly used weed killers in farming. The most potent phenoxy herbicide for killing of hardwoods was 2,4,5-T.

In the early 1970's there was public concern in Sweden regarding the use of phenoxy herbicides in forestry. In humans teratogenic and carcinogenic properties were discussed, as well as adverse health effects in animals. A suspected high incidence of cancer was reported among persons living in the village of Jutis in Norrbotten. In Torsby, in the county of Värmland, a group of environmentalists presented an extensive report of persons having malignant or teratogenic diseases with suspected link to exposure to Hormoslyr®. Diseases not previously noted in animals were reported and it was suspected that they were related to exposure to phenoxy herbicides.

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Early in the 1950's, while introducing the phenoxyacetic acids, employers claimed that they could be used safely and that no protective equipment was necessary [1]. Still, there was concern among some of those who were occupationally exposed. In 1963, a letter regarding the safety of spraying with Hormoslyr® was sent by representatives for the labour union to one of the manufacturers. In the reply dated March 25, 1963 it was stated that this chemical "cannot in any way be considered to be carcinogenic. The chemical is characterized by low toxicity and no cases of toxic damage of human beings or animals have been reported to us".

The hygienic conditions during spraying were often poor. The sprayers did not regularly wash their hands before eating or taking oral snuff. The same clothes were used during several days. Soiled clothes were later shown to be a significant cause of exposure. Exposure was oral, dermal and by inhalation.

In the 1970's there were almost opposite opinions between some laymen and representatives of the Swedish Environmental Protection Agency (EPA) regarding the potential toxicity of phenoxy herbicides. The Swedish EPA issued a report with reassuring conclusions on the safety of the use of phenoxy herbicides [2]. I received that publication from the agency upon my request for documentation on 2,4-D and 2,4,5-T. This request was initiated by the exposure history of the patient described above. The occurrence of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at ppm levels in 2,4,5-T was described. At that time TCDD was certainly already documented to be a toxic chemical and thus, at least due to the impurities of TCDD in 2,4,5-T, that herbicide had to be suspected to be a toxic chemical.

Chloracne is caused only by contact with chlorinated organic chemicals and is thus a chemical disease. It has been associated with exposure to 2,4,5-trichlorophenol and 2,4,5-T [3]. In a confidential industry report TCDD was identified as a contaminant in 2,4,5-tricholorphenol and 2,4,5-T already in 1964 [4]. It was identified to be the acnegenic chemical in trichlorophenol. It was not until 1970 that the public became aware that 2,4,5-T was contaminated by TCDD, as reported by independent university researchers [5]. The public awareness of dioxins in Agent Orange®, a 1:1 mixture of 2,4-D and 2,4,5-T, was an important factor that forced the U.S. military to stop spraying with Agent Orange® in Vietnam in 1970.

Thus, in the early 1970's TCDD had been reported to be a contaminant of 2,4,5-T and TCDD had been found to be a toxic chemical. There were, however, no reports of malignant diseases in human beings associated with exposure to phenoxyacetic acids, the chemically related chlorophenols, or TCDD.

Clinical observations on soft-tissue sarcoma

In September 1976, I met a patient with a soft-tissue sarcoma (STS) at the Department of Oncology, University Hospital, Umeå, Sweden. His occupational exposure to phenoxy herbicides reminded me of the patient described above and provoked my further interest in the potential carcinogenicity of phenoxyacetic acids. STS is a rare malignant disease of the connective tissue comprising less than 1% of all malignant diseases in Sweden. The next male patient with STS admitted to the ward was also exposed to phenoxy herbicides. Within three months a third case of STS and similar chemical exposure appeared at the department. In the medical records, another four patients with STS and exposure or potential exposure to phenoxyacetic acids were identified. These case histories were published in Swedish [6] and a summary is given in Table I.

In addition to these seven cases another two patients, who had worked temporarily near sprayed areas in the 1950's and 1960's were found. One of them had also picked sprayed berries for consumption. Histopathological diagnoses were two types of

Table I. Clinical observation of seven male cases with soft-tissue sarcoma and exposure to phenoxyacetic acids [6].

Age	Occupation	Diagnosis	Exposure history	Latency
62 years	Forestry worker	Leiomyosarcoma	1963–1976, 2,4,5-T during 14 weeks	13 years
57 years	Forestry worker	Mesenchymal tumour, probably liposarcoma	1950's–1960's, 2,4,D and 2,4,5-T during 21 weeks	>17 years
49 years	Owner of workshop	Mesenchymal tumour, probably neurofibrosarcoma	1961–1972, stored and handled phenoxy herbicides during 11 months per year	15 years
60 years	Forestry worker	Leiomyosarcoma	1961–1966, phenoxy herbicides during 20 weeks	10 years
44 years	Agriculture, forestry	Rhabdomyosarcoma	1960–1968, phenoxy herbicides during 16 weeks	14 years
76 years	Farmer	Myxofibrosarcoma	1950's, phenoxy herbicides	>13 years
67 years	Forestry worker	Polymorphcellular sarcoma, possibly rhabdomyosarcoma	1956–early 1960's, phenoxy herbicides	14 years

STS, rhabdomyosarcoma and neurofibrosarcoma, respectively.

The Swedish case-control studies on STS

These clinical observations initiated case-control studies to further investigate a potential association between STS and exposure to phenoxy herbicides, chlorophenols and contaminating dioxins and in total four studies were performed [7–10]. These studies were performed in different geographical areas in Sweden in close collaboration with Professor Olav Axelson, Department of Occupational Medicine in Linköping, Sweden.

In principle, the same study methods were used in the various studies and further details can be obtained in the publications. In short, the male cases were drawn from existing cancer registers and the controls were extracted from the population register. Since all persons in Sweden have a unique 10-digit personal identification number it is easy to trace present postal address.

For deceased cases, deceased controls were obtained from the National Register on Causes of Death. The next of kin of all deceased subjects, cases and controls, was traced from the local parish.

Information on the complete working history for each case and control was obtained by using extensive self-administered questionnaires. Many questions were asked on specific job categories, exposures, smoking habits, etc. whereby the hypotheses under investigation were obscured. Use of pesticides during work or leisure time was asked for as well as use of impregnating agents such as tar, chlorophenols etc. Further information was obtained over the phone by specially trained interviewers using a structured instruction form. Thereby, e.g. type of chemical, years of use, number of working days, etc were asked for.

The same exposure criteria were used in all four studies on STS. Thus, a minimum exposure time of one day was required for cases and controls to be classified as exposed to phenoxyacetic acids or chlorophenols. For solid tumours the induction period is at least a number of years. For that reason, all exposure to phenoxy herbicides and chlorophenols within five years before the diagnosis of STS was excluded. For the matched controls the year for diagnosis of the respective case was used. Exposure to chlorophenols for one week or more continuously or at least one month totally over the years was classified as high-grade. Exposure for less time was classified as low grade.

We performed a meta-analysis of our four STS studies [11]. This was justified since the same study methods were used in all investigations in a uniform population. The data were stratified on age, vital status and study. In one study [9] in addition to population controls patients with other types of malignant diseases were used as controls. In the meta-analysis these cancer controls were excluded so that only population controls were included. The results were based on data for 434 cases with STS and 948 controls.

The results are displayed in Table II. Exposure to phenoxyacetic acids or chlorophenols gave odds ratio (OR) = 2.8, 95% confidence interval (CI) = 2.1–4.4. Exposure to all types of phenoxy herbicides yielded OR = 2.7, 95% CI = 1.9–4.7 and exposure to 2,4,5-T in any combination gave OR = 3.5, 95% CI = 2.3–6.7. No significant association was found for 2,4-D or MCPA. Exposure to chlorophenols gave OR = 3.3, 95% CI = 1.8–6.1 and exposure to the most common type, pentachlorophenol, yielded OR = 2.8, 95% CI = 1.5–5.4.

Based on knowledge of dioxin contamination in phenoxyacetic acids and chlorophenols cases and controls were classified regarding exposure to all types of dioxins, TCDD, and other dioxin types than TCDD. Highest risk was obtained for TCDD yielding OR = 3.0, 90% CI = 2.0–4.5 for cumulative exposure <1 year increasing to OR = 7.2, 90% CI = 2.6–20 for cumulative exposure ≥ 1 year (Table III). Also exposure to other types of dioxins gave an increased risk for STS [12].

Clinical observation on malignant lymphoma

In May 1978, a patient with a tumour in his left thigh was admitted to the Department of Oncology at the University Hospital in Umeå. The clinical picture was similar to a soft-tissue sarcoma. Furthermore, this male patient reported a massive exposure to

Table II. Mantel-Haenszel odds ratio (OR) and 95% confidence interval (CI) for soft-tissue sarcoma and exposure to phenoxyacetic acids or chlorophenols. Stratification was made by age, vital status and study. Median number of days for controls was used as cut-off in dose-response calculations. Meta-analysis of four case-control studies on soft-tissue sarcoma including 434 cases and 948 controls [7–10].

Agent	Number of exposed cases/controls	OR	CI
Phenoxyacetic acids	59/59	2.7	1.9–4.7
1–24 days	19/30	1.7	0.9–3.5
>24 days	40/29	3.7	2.4–7.8
2,4,5-T and combination	46/41	3.5	2.3–6.7
2,4-D only	5/9	1.4	0.4–5.1
MCPA only	8/9	1.6	0.6–5.3
Chlorophenols	34/34	3.3	1.8–6.1
1–77 days	22/15	3.0	1.1–7.3
>77 days	22/19	3.4	1.7–7.8

Table III. Mantel-Haenszel odds ratio (OR) and 90% confidence interval (CI) for exposure to dioxins in four case-control studies on soft-tissue sarcoma including 434 cases and 948 controls [7–10,12]. Stratification was made according to study.

	Exposure <1 year			Exposure ≥1 years		
Substance	Number of exposed cases/controls	OR	CI	Number of exposed cases/controls	OR	CI
All dioxins	58/74	2.4	1.7–3.4	24/9	6.4	3.5–12
TCDD	40/39	3.0	2.0–4.5	6/2	7.2	2.6–20
Other dioxins	18/35	1.7	0.98–2.9	18/7	6.2	2.9–13

phenoxyacetic acids. Histopathological examination showed, however, a non-Hodgkin lymphoma (NHL). All male patients with the same diagnosis admitted to our Department during January–September 1978, in total 17 cases, were asked about their occupational history. Exposure to phenoxyacetic acids or chlorophenols was reported by 11 patients [13].

The Swedish case-controls studies on malignant lymphoproliferative diseases

This clinical observation initiated a case-control study on malignant lymphoma [14]. The same technique was used as in the studies on soft-tissue sarcoma. The study consisted of 60 men with Hodgkin lymphoma (HL), 105 men with NHL and 4 unclassifiable lymphoma cases. No exposure data was obtained for three of the 338 controls. Exposure to phenoxy herbicides yielded OR = 4.8, 95% CI = 2.9–8.1 and chlorophenols OR = 4.3, 95% CI = 2.7–6.9 for malignant lymphoma. Also organic solvents showed increased risk.

In further analysis increased risk was found for HL [15]. Thus exposure to phenoxy herbicides yielded OR = 5.0, 95% CI = 2.4–10, high-grade exposure to chlorophenols OR = 6.5, 95% CI = 2.2–19 and low-grade exposure to chlorophenols OR = 2.4, 95% CI = 0.9–6.5. Regarding NHL exposure to phenoxyacetic acids yielded OR = 5.5, 95% CI = 2.7–11 and exposure to chlorophenols resulted in OR = 4.8, 95% CI = 2.7–8.8, Table IV [16].

A new case-control study from Sweden further analyzed the association between phenoxy herbicides or chlorophenols and NHL [17]. The study included 442 male cases and twice as many population-based controls. Increased risk was found for exposure to herbicides and fungicides. Regarding phenoxy herbicides an OR of 1.5, 95% CI = 0.9–2.4, was obtained with increased risk both for MCPA (OR = 2.7, 95% CI = 1.0–7.0) and 2,4-D + 2,4,5-T (OR = 1.3, 95% CI = 0.7–2.3). The highest OR was calculated for exposure to phenoxyacetic acids during the 1970s (OR = 2.8, 95% CI = 1.3–5.6) and 1980s (OR = 4.0, 95% CI = 1.2–13), whereas no increased risk was found for exposure during the 1940s and 1950s. For exposure during the 1960's OR = 1.6, 95% CI = 0.9–2.8 was calculated.

A decreasing risk following a long time period since last exposure also reflected the effect of tumor induction period. Chlorophenols were banned in Sweden in January 1978 and no significantly increased risk was found for exposure in this respect, although an effect of the tumour induction period was shown also for these chemicals with highest risk for the most recent exposure. The use of 2,4,5-T and thereby Hormoslyr® was stopped in Sweden in 1977. Thus, these results suggest a rather short malignant lymphoma induction period for exposure

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for non-Hodgkin lymphoma and exposure to different agents. Mantel-Haenszel method stratified by age was used in the first study [16], conditional logistic regression analysis in the second study [17], and unconditional logistic regression analysis with adjustment for age, sex and year of diagnosis (cases) or enrolment (controls) in the third study [unpublished data]. The analysis in study I was based on 105 cases and 335 controls [16], in study II on 404 cases and 741 controls [17], and in study III on 910 cases and 1016 controls [unpublished data]. Numbers of exposed cases and controls are given (Ca/Co).

	Study I [16]			Study II [17]			Study III [unpublished]		
Agent	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Phenoxyacetic acids	25/24	5.5	2.7–11	51/71	1.5	0.9–2.4	47/26	2.0	1.2–3.4
2,4,5-T and combination	18/23	4.1	1.9–8.6	43/62	1.3	0.7–2.3	29/18	1.6	0.9–3.0
MCPA	4/0	–	–	12/11	2.7	1.0–7.0	21/9	2.8	1.3–6.2
Chlorophenols	35/35	4.8	2.7–8.8	57/92	1.1	0.7–1.8	40/36	1.2	0.8–2.0
Organic solvents	45/88	2.4	1.4–3.9	199/349	1.1	0.8–1.4	299/271	1.4	1.1–1.7

to these chemicals. Another conclusion from this study seems to be that restriction of the use of these and related chemicals may have had a preventive effect on NHL.

Hairy cell leukemia is a rare subtype of NHL with a marked male predominance. A Swedish study encompassing 121 male cases with hairy cell leukemia and 484 controls found an increased OR of 2.7 (95% CI 1.3–5.7) for exposure to phenoxy herbicides [18]. Exposure to pentachlorophenol gave OR = 2.6 (95% CI = 1.1–6.2). Interestingly, these risks were further increased in cases with elevated levels of antibodies to Epstein-Barr virus (EBV) early antigen (EA).

Multiple myeloma is a lymphoproliferative malignancy related to malignant lymphoma. Several reports have described an association with farming. A Swedish case-control study on multiple myeloma found an increased realtive risk (RR) for exposure to phenoxyacetic acids (RR = 2.0, 90% CI = 1.2–4.7), but not to chlorophenols (RR = 1.1, 90% CI = 0.6–1.9) [19].

A more recent study from our research group included cases and controls from the time period December 1, 1999 until April 30, 2002 [unpublished data]. All cases and controls were included and reported in the SCALE study that was performed at the same time period, for further details see [20]. The questionnaire was answered by 910 (91%) of the cases and 1 016 (92%) of the controls of those included in the SCALE study. There was no overlap between that study and our regarding e.g. pesticide exposure and use of wireless phones [21]. Exposure to phenoxy herbicides gave OR = 2.0, 95% CI = 1.2–3.4, Table IV. When subdivided, exposure to MCPA gave OR = 2.8, 95% CI = 1.3–6.2, whereas 2,4,T- in any combination gave OR = 1.6, 95% CI = 0.9–3.0. Also other herbicides than phenoxyacetic acids increased the risk for NHL, OR = 1.8, 95% CI = 1.1–3.1. Chlorophenol exposure did not increase the risk significantly, OR = 1.2, 95% CI = 0.8–2.0.

Persistent organic pollutants

Persistent organic pollutants (POPs) are a group of chemicals that accumulate in the ecological chain. They are environmentally persistent and humans are exposed following their accumulation in the food chain. It has been suggested that exposure to certain POPs is of etiologic significance for NHL [22]. An interaction between EBV and pesticides has been shown in some studies. These results have been discussed elsewhere [23–25].

In a recent study we found significantly increased concentrations for the sum of polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and sum of chlordanes in NHL cases [26]. An interaction between elevated EBV EA IgG and these chemicals was found (Table V). Furthermore, in the high concentration group of 1,1-dichloro-2,2bis(p-chlorophenyl)ethylene (p,p′-DDE) and high titer to EBV EA IgG OR = 3.3, 95% CI = 1.4–7.7 was obtained. When analyzing the chemicals only without considering titer to EA IgG lower ORs were obtained. This suggests an interaction between these chemicals and EBV. These results are similar to our previous study on this topic [22]. For

Table V. Odds ratio (OR) and 95% confidence interval (CI) for different organohalogen compounds and NHL in relation to titre to Epstein-Barr virus early antigen (EA) IgG [26]. As cut-off the median concentration of the chemicals and titre to EA in the controls was used. Numbers (expressed in ng/g lipid) are shown for cases and controls. Adjustment was made for age, sex and body mass index. For abbreviations of chemicals, see text.

	EA ≤40			EA >40		
Exposure	Cases/controls	OR	CI	Cases/controls	OR	CI
Sum of PCBs						
≤median 646	14/25	(1.0)	–	24/24	2.5	0.97–6.4
>median 646	20/29	2.1	0.7–6.1	39/20	5.2	1.9–14
HCB						
≤median 24	9/24	(1.0)	–	34/26	3.9	1.5–10
>median 24	25/30	2.5	0.9–6.7	31/19	5.3	1.9–15
p,p′-DDE						
≤median 271	20/28	(1.0)	–	26/22	1.8	0.8–4.1
>median 271	14/26	1.0	0.4–2.7	39/23	3.3	1.4–7.7
Sum of chlordanes						
≤median 19	13/23	(1.0)	–	24/27	1.8	0.7–4.7
>median 19	21/31	1.8	0.6–5.1	41/18	6.8	2.3–20
PBDE						
≤median 1.8	17/24	(1.0)	–	43/26	2.7	1.2–6.2
>median 1.8	17/30	0.9	0.4–2.3	22/19	1.8	0.7–4.5

polybrominated diphenylether (PBDE) no significantly increased risk was found [26].

Towards understanding of the aetiology of NHL

The incidence of NHL increased substantially during the second half of the 20th century in Sweden and in other Western countries. However, during the last decade the increasing incidence has levelled off in many countries [24]. According to The National Board of Health and Welfare in Sweden the annual change in incidence was for men 0% and for women –0.5% during the time period 1996–2005. This finding may be explained by decreasing exposure to certain risk factors in the population.

The established risk factors for development of NHL include different immunosuppressive conditions, e.g., HIV, autoimmune diseases as Sjögren's syndrome and SLE, immunosuppressive drugs used after organ transplantation and some inherited disorders [23]. However, these factors cannot explain the change of the incidence. Instead it is of interest that exposure to certain persistent organic pollutants, pesticides and organic solvents has been implicated to be of etiologic significance.

EBV is a human herpes virus prevalent in B-lymphocytes. The virus is found worldwide and the majority of the adult population has antibodies to EBV antigens. The primary infection occurs usually in childhood and is mainly sub clinical. A latent infection is established that is balanced by the host immune response. EBV has been associated with certain types of NHL such as Burkitt lymphoma and lymphomas in immunologically compromised or HIV-infected subjects. Immunosuppression is a risk factor for NHL and exposure to organochlorines has been reported to compromise the immune system in humans. Immunosuppression may lead to loss of cell-mediated immune control of reactivated EBV and give clonal expansion of cells.

Risk estimates and exposure frequencies in our studies enable calculation of the attributable fraction; that is the proportion of cases that can be attributed to the particular exposure. This is calculated as the exposed case fraction multiplied by [(OR − 1)/OR]. The use of Hormoslyr® was prohibited in Sweden in 1977 and chlorophenols January 1, 1978. The attributable fraction was for phenoxy herbicides = 19%, for 2,4,5-T in any combination (e.g., Hormoslyr®) = 13% and for chlorophenols = 26% in our first case-control study on NHL with cases diagnosed in 1974–1978 [14,16].

Our next epidemiological study on NHL [17] encompassed diagnoses during the time period 1987–90. Lower odds ratios for exposure to the phenoxyacetic acids 2,4-D and 2,4,5-T (Hormoslyr®) were now obtained. The risk was highest with a latency period of 10–20 years and decreased with longer tumour induction period. The attributable fraction was for phenoxyacetic acids = 4.2%, for 2,4,5-T in any combinations (e.g., Hormoslyr®) = 2.5%. For chlorophenols an attributable fraction of 1.3% was calculated.

In our most recent study on NHL with cases diagnosed during December 1, 1999 and April 30, 2002 these attributable fractions were even lower. Thus phenoxyacetic acids yielded attributable fraction = 2.6%, 2,4,5-T in any combination = 1.2% and chlorophenols = 0.7% [unpublished data].

Regarding polychlorinated biphenyl (PCB) we found an interaction with EBV EA IgG and the attributable fraction was calculated as 25%. The attributable fraction was of the same magnitude for hexachlorobenzene and chlordanes. Also for dioxins calculated as toxic equivalents a similar attributable fraction was found. TCDD was in 1997 classified as a human carcinogen Group I (sufficient evidence) by IARC [27]. It should be noted, that in our latest study on POPs as risk factors for NHL [26] similar attributable fraction was calculated. In the latest study cases were diagnosed during December 1, 1999 and April 30, 2002 [26] compared with the time period 1994–1997 in the earlier study, as discussed elsewhere [24,25]. Thus these two studies covered a rather short time span for diagnosis of NHL as compared with the case-control studies on exposure to phenoxy herbicides and chlorophenols. This might have an impact on the attributable fraction.

Most of the chemicals discussed here were introduced during or shortly after the 2nd World War. Exposure to the population increased until restrictions during the 1970's for e.g., 2,4,5-T, chlorophenols and PCBs. The highest exposure occurred during the 1970's for persistent organic pollutants such as dioxins, chlorophenols and PCBs. After that the concentrations in the environment and thus also in the food chain have declined although the decline has levelled off since the 1990's. The reduction of the attributable fraction for NHL is obviously due to both a reduction in the odds ratios but also of the fraction of exposed cases. Latency seems to be important; that should neither be too short nor too long. The risks seems to increase with time since first exposure and then to drop again.

The Swedish studies on pesticide exposure as risk factor for NHL were the first epidemiological studies in this area and initiated similar research in other countries. These results have been reviewed in many papers and pesticide exposure is now an established risk factor for NHL [23–25]. Changing exposure to pesticides as a factor to explain the decline of the incidence has been discussed elsewhere [24].

The decline over time of attributable fraction for pesticides in lymphomagenesis, as discussed above, is noteworthy.

Epidemiologic evidence indicates that TCDD increases the risk for malignant lymphoma but also for all cancers combined. Higher odds ratios are present in several studies for NHL and STS. It is, as concluded by IARC, unlikely that these findings are due to chance [27]. The purpose of this article has not been to make a thorough review of this research area and the reader is referred to other publications [e.g., 23–25,28].

The precautionary principle

Preventing hazards from known risks is relatively easy, e.g. banning smoking or asbestos. However, it would have needed precaution to avoid exposure to asbestos in the 1930's–1950's or tobacco smoke in the 1950's because of not sufficient evidence of the carcinogenic risks. On the other hand such precaution would have saved many lives [29,30]. Prevention is justified to restrict exposure to known causes, IARC category I carcinogen, whereas precaution is necessary to restrict exposure to suspected or less clear risk factors, Category 2A or 2B carcinogen, as has recently been discussed [31].

Our studies have been criticized by different persons including those employed by the chemical industry and its allied experts, who have postulated various *ad hoc* hypotheses as explanations for the results [32]. These *ad hoc* hypotheses could certainly be easily rejected by using information in our published papers. Rebutting all these statements is, however, an almost impossible task since it is time consuming and not all editors are willing to give space for rebuttals. Thus, such rumours tend to gain their own life to dismiss the results propagated by persons whose own agenda is not disclosed. In this matter some uneducated journalists with their own conflicting interests may take part. It is not within the scope of this paper to discuss in more detail this scientific controversy, but the reader may find more details elsewhere [32]. It should be noted that the time from first results about the carcinogenicity of TCDD and regulatory activities is in the range of 20 years [27], and thus far shorter than for certain other carcinogens, e.g., asbestos [33].

The scientific community should certainly have a critical attitude toward results, especially with the publication of new findings. Any debate must, however, be based on facts. This has not always been the case regarding our studies. One example is the hypothesis that recall bias, i.e. influence by potential knowledge of studies by our research group on an association between phenoxy herbicides and cancer, might explain our results on the association between pesticide exposure and STS. This hypothesis was somewhat tested in one of our four STS studies [9]. Thus, part of the questionnaires from the controls was returned to the research team, another part to an independent statistical research bureau, however yielding no significant difference of reported exposure. The same procedure was also undertaken for some of the cases. It turned out that exposure to phenoxy herbicides gave crude OR = 2.5, 95% CI = 0.7–7.6 if these questionnaires were returned to our research group *versus* crude OR = 2.8, 95% CI = 0.6–9.4 when returned to the statistical research bureau. Again, the results were not significantly different indicating no recall bias associated with the study team.

Vested interests constitute the main reason to ignore the precautionary principle [32]. Furthermore, in these circumstances society gets an unbalanced and unfair view of scientific results. Thus, objective information is essential so that people can prudently avoid exposure. To conceal scientific evidence and even denigrate research groups whose results may be in conflict with corporate or orthodox thinking in society makes such personal precautions almost impossible. Furthermore, such behavior makes cancer prevention the privilege of an educated elite since it is the well-educated persons who have easier access to information sources and can make their own conclusions.

There are many historical examples of the long time period between scientific results showing cancer risk and the following regulation of toxic substances. TCDD is just one example with scientific publications indicating a carcinogenic effect in the 1970's and a gap of almost 30 years before the classification in 1997 as a human carcinogen [27]. Regarding NHL, based on our results, many cases would have been avoided annually in Sweden without exposure to phenoxy herbicides, chlorophenols and certain POPs.

Total cancer rates in both children and adults are still increasing in the Western world. Much research is devoted to understanding the biological mechanisms for carcinogenesis and developing new treatment modalities. Promising new treatment options of several malignant diseases have been achieved, but the new drugs are very expensive. For prevention it is necessary to take thorough occupational and environmental exposure histories at the oncological clinic and it is important to keep a watchful attitude for suspicious relationships between exposure and malignant diseases.

Research on risk factors for cancer does not have the glamour associated with the development of complicated and profitable new drugs for cancer treatment. But cancer prevention, on the other hand,

is cost-effective and research to identify risk factors should be of equal importance as laboratory studies in molecular biology. As well, while cancer patients are effective pressure groups for better patient care and treatment, individuals avoiding cancer due to preventive measurements are clinically invisible and so have no voice to protest against cancer policy. When we consider the precautionary principle and while planning policy, these cultural, economic and political factors should be given consideration alongside the scientific facts.

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References

[1] Fransson P. Control of birch in Northern Sweden with weed killers. Statens skogsforskningsinstitut, Sverige. 1952; Vol 42, No 1. In Swedish.
[2] Nilsson R. Chlorinated phenoxyacetic acids. Evaluation of toxic effects on mammals including human beings. Produktkontrollbyrån. Statens Naturvårdsverk SNV PM 527, oktober 1974. In Swedish.
[3] Kimmig J, Schultz KH. Occupational chloracne caused by aromatic cyclic ethers. Dermatologica 1957;115:540–6.
[4] Skelly NE. Isolation and identification of possible acnegens from the caustic-insoluble portion of the products from the 2,4,5-trichlorophenol process. The Dow Chemical Company, Report No. ALS 54–474, December 8, 1964.
[5] Meselson MS, Westing AH, Constable JD, Cook RR. Preliminary Report of the Herbicides Assessment Commission of the American Association for the Advances of Science. Washington D.C., December 30, 1970.
[6] Hardell L. Soft-tissue sarcomas and exposure to phenoxy acids: A clinical observation. Läkartidningen 1977;74: 2753–4.
[7] Hardell L, Sandström A. Case-control study: Soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 1979;39:711–7.
[8] Eriksson M, Hardell L, Berg NO, Möller T, Axelson O. Soft-tissue sarcomas and exposure to chemical substances: A case-referent study. Br J Ind Med 1981;38:27–33.
[9] Hardell L, Eriksson M. The association between soft-tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer 1988;62:652–6.
[10] Eriksson M, Hardell L, Adami HO. Exposure to dioxins as a risk factor for soft tissue sarcoma: A population based case-control study. J Natl Cancer Inst 1990;82:486–90.
[11] Hardell L, Eriksson M, Degerman A. Meta-analysis of four Swedish case-control studies on exposure to pesticides as risk-factor for soft-tissue sarcoma including the relation to tumour localization and histopathological type. Int J Oncol 1995;6:847–51.
[12] Hardell L, Eriksson M, Axelson O, Fredriksson M. Dioxin and mortality from cancer. N Engl J Med 1991;324:1810–1.
[13] Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet 1979;i:55–6.
[14] Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids; A case-control study. Br J Cancer 1981;43:169–76.
[15] Hardell L, Bengtsson NO. Epidemiological study of socioeconomic factors and clincial findings in Hodgkin's disease, and reanalysis of previous data regarding chemical exposure. Br J Cancer 1984;48:217–25.
[16] Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 1994;54:2386–9.
[17] Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesiticides. Cancer 1999;85: 1353–60.
[18] Nordström M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukemia evaluated in a case-control study. Br J Cancer 1998;77:2048–52.
[19] Eriksson M, Karlsson M. Occupational and other environmental factors and multiple myeloma: A population based case-control study. Br J Ind Med 1992;49:95–103.
[20] Ekström-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma – a review. Acta Oncol 2006;45:258–71.
[21] Hardell L, Eriksson M, Carlberg M, Sundström C, Hansson Mild K. Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. Int Arch Occup Environ Health 2005;78:625–32.
[22] Hardell L, Eriksson M, Lindström G, van Bavel B, Linde A, Carlberg M, et al. Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens in the etiology of non-Hodgkin lymphoma. Leuk Lymphoma 2001;42:619–26.
[23] Hardell L, Axelson O. Environmental and occupational aspects on the etiology of non-Hodgkin's lymphoma. Oncol Res 1998;10:1–5.
[24] Hardell L, Eriksson M. Is the decline of the increasing incidence of non-Hodgkin lymphoma in Sweden and other countries a result of cancer preventive measures? Environ Health Perspect 2003;111:1704–6.
[25] Hardell L, Eriksson M, Axelson O, Flesch-Janys D. Epidemiological studies on cancer and exposure to dioxins and related compounds. In: Schecter A, Gasiewicz TA, editors. Dioxins and Health. John Wiley & Sons; 2003. p. 729–64.
[26] Hardell L, Björnfoth H, Hardell K, van Bavel B, Lindström G, Carlberg M, et al. Concentrations of organohalogen compounds and titers of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. Organohalogen Compounds 2006;68:2535–8.
[27] IARC Monographs on the evaluation of carcinogenic risks to humans. Polychlorinated-*para*-dioxins and polychlorinated dibenzofurans. Volume 69. Lyon, France: IARC; 1997.
[28] Dreiher J, Kordysh E. Non-Hodgkin lymphoma and pesticide exposure: 25 years of research. Acta Heamatol 2006; 116:153–64.
[29] European Environment Agency. Late lessons from early warnings: The precautionary principle 1896–2000. Copenhagen: European Environment Agency, 2001.
[30] Gee M. Late lessons from early warnings: Towards realism and precaution with EMF? http://www.bioinitiative.org/ (assessed September 4, 2007).
[31] Martuzzi M. The precautionary principle: In action for public health. Occup Env Med 2007;64:569–70.
[32] Hardell L, Walker M, Walhjalt B, Friedman LS, Richter ED. Secret ties to industry and conflicting interests in cancer research. Am J Ind Med 2007;50:227–33.
[33] IARC Monographs on the evaluation of carcinogenic risk of chemicals to humans. Asbestos. Volume 14. Lyon, France: IARC; 1997.