Chapter 5 — Leukemia

Leukemia is the ninth most prevalent cancer among new cases. Moreover, it is also the ninth most common cause of cancer-related death in Canada, accounting for 2.3% of new cancer cases in women and 2.9% of new cases in men. Nationally, it is the sixth ranked cancer in terms of potential years of life lost (33).

This review assessed a total of 23 studies on leukemia and pesticide exposure, categorized as follows:

- Cohort studies: 6 (5 positive, 4 with statistical significance, 1 negative)
- Case-control studies: 8 (8 positive, 8 with statistical significance)
- Ecological studies: 1 (0 positive)
- Lab study: 1 (1 positive)
- Excluded: 7 (5 positive, 4 with statistical significance, 2 negative)

Nearly all the acceptable studies were rated 4 or 5 out of 7 by both readers; Heacock et al. (11), a negative study, received one 6, and Ma et al. (18), a positive study, received a 6 and 7 from the assessors.

Cohort Studies

Of the 6 cohort studies, 5 showed positive associations (4 with statistical significance) and 1 showed a negative association. None had direct exposure histories due to the large number of subjects. Two of the studies (13, 12) showed increased rates of leukemia in workers with exposure to livestock. The first (13) showed an increase of acute leukemia (subtype undefined) in men engaged in dairy farming (RR 1.76, CI 1.02–3.05). The second (12) showed an increase in leukemia in children of farming parents engaged in pig farming (RR 2.26). This association between animal husbandry and cancers has often been found, and is thought to be due either to insecticide exposure or animal viruses. The study by Beard et al. (10) showed an increase in leukemia in a cohort of outdoor workers in Australia with an SIR of 20.90 (CI 1.54–284.41) for the most highly exposed group. The one negative study, Heacock et al. (11), the study given 6 by one of the readers, did not find a relationship between childhood leukemia and paternal exposure to chlorophenate fungicides among sawmill workers, though the total number of all cancers found was only 40. Waterhouse et al. (23) found an elevated SIR (1.4, CI 1.03–1.86) for chronic lymphocytic leukemia (CLL) and lymphomas (classed together) in a cohort study, and a nested case-control study showed an elevated though not significant OR. Kross et al. (14) was the only study looking at the mortality rates of golf course superintendents. These people encounter many occupational hazards such as sunlight and exposure to pesticides, fertilizers, and diesel exhaust. The PMR for leukemia was 162 (CI 83–316).

Case-Control Studies

All 8 case-control studies were positive. The study by Ciccone et al. (15) was one of the few studies looking at women. It showed an OR of 4.4 (CI 1.7–11.5) for acute and chronic myelocytic leukemia (AML and CML) in women exposed to pesticides; however specific pesticides were not named or quantified.

The study by Infante-Rivard et al. (16) showed increased rates of acute lymphocytic leukemia (ALL) in children whose parents used insecticides in the garden and on interior plants, especially when the mother was exposed while pregnant. The cases were derived from an urban area of Montreal, which would have excluded farm children who may have had higher pesticide exposures than the urban children, and whose data may have shown an even stronger association. In addition, a case-only cytogenetic study was done which found that an increased number of the children with ALL had specific metabolic mutations that were involved in carcinogen metabolism. This supports other studies that show that people with alterations in the cytochrome P-450 metabolic pathway ("slow metabolizers") are susceptible to certain illnesses with exposure to chemicals such as pesticides (discussed in Chapter 6, Genetic Polymorphisms).

Leiss et al. (17) found a strong association (OR 1.7–3.0) between use of pest strips containing dichlorvos (an insecticide) and ALL in children. Ma et al. (18), the study given 6 and 7 by the readers, showed increased rates of childhood leukemia with exposure to insecticides, with certain time periods of exposure being critical (pre-pregnancy, and both pre- and post-natal). Interestingly, the most crucial exposure period for later development of leukemia was found to be during pregnancy. Meinert conducted two studies, in 1996 (19) and in 2000 (20). Both showed increased rates of childhood leukemia with pesticide use on farms and in gardens. A study by Nanni et al. (21) showed an increase in CLL and low-grade non-Hodgkins lymphoma in farm animal breeders in Italy. Rates were increased with exposure to insecticides in general (OR 2.46, CI 1.07–5.63), to carbamates (OR 3.08, CI 1.05–9.00), and to organophosphates (OR 2.97, CI 1.28–6.91), with the latter showing a dose–response relationship. Richardson et al. (22) found increased rates of leukemia with exposure to weed killers (OR 3.5, CI 1.1–10.8) and insecticides (OR 1.7, CI 1.0–3.1), though specific types of pesticides were not identified.

Laboratory Study

The laboratory study of Cuneo et al. (24) examined a group of patients with AML and used questionnaires to obtain information about pesticide use. They divided the patients into two groups: those exposed and those not exposed to pesticides or organic solvents (although covariates were not measured). Chromosomal aberrations, cytologic features, peripheral blood and bone marrow indices, and the clinical picture of the illness were examined for both groups. The patients exposed to pesticides had the same recurring chromosomal aberrations and cytological features, which were different from those found in the unexposed group. In addition, the clinical picture differed considerably between the two groups. The exposed group had lower leukocyte counts and lower blast cell percentages in the bone marrow. The exposed group was refractory to treatment, with few attaining remission. This is in contrast to the unexposed group that attained almost 50% remission. The mean survival of the exposed group was 2 months and of the non-exposed group 9 months. What is most interesting is that the features found in the exposed group (cytologic and chromosomal changes, and a distinct clinical picture with poor prognosis) resemble those found in patients with secondary leukemia (leukemia caused by an insult such as radiation, chemotherapy, or some chemical exposures). This may implicate pesticides as an etiologic factor in the development of leukemia.

Ecological Study

The selected ecological study was by Reynolds et al. (25), who examined cancer cases in children and pesticide use from 1988 to 1994 in each of several thousand geographic areas into which California was divided for the study. No preponderance of childhood cancer was found in areas of heavy pesticide use; however, pesticide use was gauged by indirect database measures,

such as quantity applied, number of acres treated, and type of crop treated. Also, the study measured only agricultural and not home use of pesticides.

Excluded Studies

Seven studies were excluded, 5 of which were positive (4 with statistical significance) and 2 of which were negative. Scheele et al. (31) found similar concentrations of PCB and DDT in the bone marrow of children both with and without leukemia, though this could be confounded by the presence of less fat in the marrow of people with leukemia. That study was eliminated because these chemicals were not included in our list of pesticides. Smith et al. (32) studied cases of soft tissue sarcoma and lymphoma and found increased relative risks up to 2.7 with exposure to chlorphenoxy herbicides but without statistical significance. This study was excluded because it did not deal with leukemia. Deschamps et al. (26) did a case-control study on a cluster of childhood leukemia cases in a city in British Columbia; the study did not show a relationship between leukemia and pesticide exposure. It was, however, excluded because the exposure history was very poor, the number of cases was small, the results could have arisen from cluster analysis, and no adjustment was made for any of the covariates mentioned. Mulder et al. (29) looked at a cluster of hematopoietic malignancies that occurred in a horticultural community in the Netherlands, but the sample size was too small to allow any conclusions to be drawn (8 leukemia and 7 lymphoma cases). El-Sadek et al. (27) found that a group of farm workers had significantly higher lymphocyte, white blood cell, and platelet counts than a group of workers that were not exposed to pesticides. The study was eliminated because there were no details of exposure history and the methodology was poor, though the findings are interesting. Safi et al. (30) found increasing rates of cancer in the 1990–1999 period, corresponding to increasing use of pesticides in the Gaza Governorates; however, the study was excluded because the methodology was so poor and the cancer rate measurements were not reliable. Fagioli et al. (28) was excluded because it reported on the same data as Cuneo et al. (24), included in the Lab Studies section above.

Conclusions

In conclusion, it is clear from the findings of these studies that a positive association exists between pesticide exposure and leukemia. Of 16 studies included in this review, 14 show associations between pesticide exposure and leukemia, all but one with statistical significance — despite the limitations of cohort, case-control, and ecological studies. This is consistent with many previous studies that showed similar relationships. The dose–response effect found by some of the studies also corroborates this conclusion. In addition, Infante-Rivard explored the issue of gene polymorphisms which may predispose “slow metabolizers” to chemical-related illness; this issue was found in other studies, for example with respect to Parkinson’s disease (see Chapter 8, Neurological and Mental Health). The laboratory study (24) is particularly compelling, even though its study design is not the best. This implication of pesticides in the development of leukemia warrants further investigation and also political action to address this public health issue. In addition, the public should try to minimize occupational and environmental exposure to pesticides. Ways to do this would include: avoiding use at home, on pets, and in the garden; avoiding — if possible — exposure via purchased food; and wearing protective gear if pesticide use is deemed necessary.

Chapter 5 — Leukemia

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Chapter 5 — Leukemia

Table

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cohort Studies						
Beard 2003	Retrospective cohort; looked at about 20 different health conditions (leukemia was one of these); Males having worked as field officers or lab staff for the Board of Tick Control between 1935–1996; 1999 exposed, 1984 not exposed.	Exposure categorized into 'modern chemical use,' but specifics not given; period of employment was used to estimate exposure and dose (in 3 or 5 yr periods); employment records used.	Age, smoking history, alcohol consumption neuropsych score.	OR, SMR, SIR; Poisson regression	There are a number of values given on p. 726 and 727; nonsignif increases in SMR for leukemias as a group in modern era period; when exposure lag removed increase of borderline signif (SMR 3.62, CI 0.99–9.26); highest doses of pest resulted in higher SIRs (SIR 20.90, CI 1.54–284.41).	4,5
Heacock 2000	Retrospective cohort; children born in BC b/t 1952–1988, younger than 20 yrs at dx and dx b/t 1969–1993 who were offspring off fathers who worked in BC sawmills between 1950-1985; fathers 23, 829, children 19,674	Chlorophenates; exposure based on records from sawmills and interviews to determine pesticide use in mill; created 3 categories of exposure (low, medium, high) and an index of cumulative duration of exposure based on job history at the mill.	Age, gender	SIR, OR; regression analysis	No clear relationship b/t paternal occ exposure to chlorophenate fungicide and risk of childhood cancer; SIR 1.0 CI 0.5–1.8; risks for developing childhood cancer (all types) ranged from OR 0.8–1.7 for varying windows of parental exposure; For leukemia, the OR's ranged between 0.8–1.8 for different ages of dx.	5,6
Kristensen 1996	Retrospective cohort; all offspring born 1952–1991 to farm holders in agricultural censuses in Norway in 1969–1989; 323, 292 children and 1275 children had cancer.	Exposure taken from agricultural censuses done every 3 yrs; exposure presented as dichotomy (present/absent); from variables including location of farm, area, $$	Age, gender	SIR, RR Poisson regression	Rates were not elevated for pesticide exposure but were elevated for cattle, dairy, chicken and pig farming with statistical significance for pig farming only (RR 2.26, 1.07–4.12).	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
		spent on pesticides, spraying equip on farm, type of crop.				
Kristensen 1996	Retrospective cohort; all people who were farm holders and born later than 1924; 136,463 men and 109,641 women, total 3333 men and 2145 women with cancer.	Agricultural census data used to gather exposure info; exposure presented as dichotomy (present/absent) from variables including location of farm, area, $ spent on pesticides, spraying equipment on farm, type of crop.	Age, gender	OR, Poisson regression	There was a relationship b/t increased rates of leukemia and men and dairy cattle; RR 1.76 (CI 1.02–3.05); the tables only included values for positive associations – this was the only one for leukemia, therefore we cannot provide other RR values or ranges.	4,4
Kross 1996	Retrospective cohort of white male golf course superintendents, members of a professional association, died between 1970 and 1992, total of 203 cancer deaths.	No exposure histories, no comment on specific pesticides, but high use of insecticides, fungicides and herbicides with large differences in volume depending on region.	No covariates	PMR, compared to white males in the U.S. population, CI calculated by method of Jensen et al (1991)	PMR 162 (CI 83–316)	4,4
Waterhouse 1996	Cohort study; individuals over the age of 16 yrs in Tecumseh, Michigan; 6702 residents.	All acres within the county were assigned an exposure level according to annual number of acres and % treated with chemicals.	Smoking history, alcohol, exposure to radiation, occupational & household exposure, history of similar neoplasms in relatives	SIR, OR, Poisson	Census block groups with high use of propargite did have signif elevated levels of childhood leukemia, but no dose-response trend (RR 1.48, CI 1.03–2.13); otherwise, no assocations; RR's ranged between 0.68–1.48 for propargite, methyl bromide, metam sodium, trifluralin, simazine, dicofol, and chlorothalonil; when they examine leukemias by block group for organochlorines, organophosphates,	4,4

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
					carbamates, and dithiocarbamates the RR's ranged between 0.70–1.07.	
Case-Control Studies						
Ciccone 1993	Case-control; newly dx cases of acute or myeloid leukemia treated in the main hospital in Torino, Italy b/t 1989–1990, b/t ages of 15–74 yrs; 50 with AML, 17 CML, 19 MDS; 246 controls.	Exposure categorized as 'pesticides' but no further info provided; collected with questionnaires; occ hygienist then divided exposure as exposed to some, not exposed, possibly exposed, probably exposed.	Smoking habits, age, area of residence	OR, logistic regression	OR for AML and CML in women 4.4. 95% CI (1.7-11.5); no value given for men.	4,4
Clavel 1996	Case-control; all cases dx b/t 1980–1990 from 18 French hospitals; controls selected from people hospitalized at the same time; 226 cases (farmers) and 425 controls.	Questionnaire; all pesticides, divided into chemical categories; designated definite or possible exposures and low, medium or high exposure depending on number of days per yr, spray height, equipment, exposure route.	Smoking habits, education, ses, dx before or after 1984 (b/c mortality lower after 1984)	OR, conditional logistic regression	Increased risk of HCL with farmers compared to non-farmers; only positive association was for organophosphorous insecticides (OR 7.5, 95% CI 0.9–61.5); overall OR's for insecticide, fungicide, and herbicide ranged from 1.5 to 2.4.	5,4
Infante-Rivard 1999	Case-control; cases dx b/t 1980–1993 in Quebec and b/t ages 0–9 yrs from tertiary care centres; 491 cases and 491 controls; also looked at gene polymorphisms in cases and controls.	Questionnaire (only mothers had questions about pesticides); number of exposure events divided into categories – 1 month before pregnancy to birth and birth to dx.	Maternal age, age, sex	OR, conditional logistic regression	Indoor use of some insecticides by the owners and pesticide use in the garden and on interior plants associated with increased risk of leukemia; OR herbicide 3.72 (CI 0.72–19.06); plant insect OR 4.01 (CI 1.12–14.32); several pages of tables in the text with many OR ranges; "slow metabolizers" (with gene polymorphisms) had higher rates of AML.	5,5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Leiss 1995	Case-control; all cases of childhood cancers (age 0–14) dx among residents of the Denver 1970 standard metro area b/t 1976–1983; 252 cases and 222 controls.	Questionnaire to determine home exposure; Dichotomized 'use' vs 'no use;' 3 exposure periods: 3 months prior to birth, birth thru 2 yrs prior to dx, 2 yrs prior to dx thru dx.	Age at dx, fathers ed, mothers age, ses, residential stability, maternal smoking, race, magnetic exposure	OR, Mantel-Hanzel	Relationship b/t increased rate of leukemia and use of pest strips; OR 3.0 (first exposure category), OR 1.7 (second exposure cat), OR 2.6 (third exposure cat); OR's ranged from 0.3–3.0 for pesticide exposure from home extermination, yard treatment, and pest strips.	5,5
Ma 2002	Case-control; all newly dx with leukemia ages 0–14 yrs residing in the area, no hist of cancer; California; 162 cases and 162 controls.	Home exposure thru questionnaire; 3 time windows (did not use, used less than 5 times, 5 or more times); all pesticides – recorded name of product.	Age, gender, race, income, maternal education, maternal age	OR, conditional logistic regression	E xposure to household pesticides is assoc with increased risk of leukemia; esp use of professional pest. services (OR 2.8); OR's ranged between 1.0–3.6 for different types of pesticide exposure (please refer to table on page 958).	6,7
Meinert 1996	Case-control; born after 1975, age at dx less than 15 yrs, dx b/t 1988–1993, residing in state at dx; Germany; 173 cases – 2 groups of controls; also 175 children with other solid tumours.	Questionnaire for home exposure; all pesticides; Parents had to specify if hazard present yr before pregnancy, during pregnancy, and/or after child's birth.	Age, gender, ses, degree of urbanization	OR, conditional logistic regression	Only stat. signif finding was a more frequent use of pesticides in garden when leukemia cases compared with local controls (OR 2.52); several tables and large range of OR's; for exposure from 2 yrs before birth to date of dx OR's ranged between 0.83–2.55.	4,4
Meinert 2000	Case-control; included all children younger than 15 yrs who have lived in community for at least 6 months; in Germany; 234 cases with NHL, 940 with solid tumours, 1184 with leukemia.	Home exposure assessed by interview of parents; parents had to specify if hazard present yr before pregnancy, during pregnancy, and/or after child's birth.	Age, gender, ses, degree of urbanization	OR, conditional logistic regression	U se of pesticides on farms was weakly related to childhood leukemia (OR 1.5, CI 1.0–2.2); occ exp to herbicides, insecticides, and fungicides showed signif higher OR's that ranged between 1.3–3.6; use of pesticides in gardens, farms, and homes had OR's between 1.0–1.8.	5, 5

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Nanni 1996	Case-control; all incident cases of NHL and CLLs in a province of Italy b/t 1987–1990; 187 cases and 977 controls.	Occupational exposure assessed by questionnaires; estimates of pesticide use based on criteria: usual dose, number of trtmts, surface area cultivated, period in yrs cultivation; all pesticides.	Age, sex, altitude of municipality, first degree family cancer history, work hist, use of drugs, exposure to radiation	OR, unconditional logistic regression	When the analysis was limited to CLLs and low grade NHLs a positive signif assoc emerged for insecticides in general, carbamates, and phosphates; OR's varied between 1.17–3.18 for different types of pesticides (i.e. herbicides, fumigates, fungicides, carbamates, phosphates).	5,4
Richardson 1992	Case-control; cases admitted to hospitals in France, over 30 yrs of age; 185 cases and 513 controls.	Occ exposure assessed by questionnaire; occ hygienist then coded exposure as low, medium, high based on time exposed; all pesticides included.	Age, sex, place of residence; occ and health probs of family, med hist, drug use	OR, conditional logistic regression	Signif positive relationship b/t leukemia and exposure to weedkillers (OR 3.5, CI 1.1–10.8) and insecticides (OR 2.1, CI 0.8–5.4); OR for acute lymphoblastic leukemia was 2.82 and for acute myelogenous leukemia was 1.38.	4,4
Ecological Studies						
Reynolds 2002	Cross-sectional ecological study; all cases of invasive cancer dx in children under 15 yrs b/t 1988–1994 in California; 7143 cancer cases.	Home exposure determined by database info – PUR (pesticide reporting database); combined with GIS info and divided into blocks; estimated average annual pesticide use for each block by summing the average pounds applied and then divide by block area; they selected the 7 most widely used pesticides for evaluation.	Ses, degree of urbanisation, race, sex, age	RR, Poisson regression	Census block groups with high use of propargite did have signif elevated levels of childhood leukemia, but no dose-response trend (RR 1.48, CI 1.03–2.13); otherwise, no assocations; RR's ranged between 0.68–1.48 for propargite, methyl bromide, metam sodium, trifluralin, simazine, dicofol, and chlorothalonil; when they examine leukemias by block group for organochlorines, organophosphates, carbamates, and dithiocarbamates the RR's ranged between 0.70–1.07.	4,4
Lab Studies						

Reference	Population Description	Pesticides Type and Exposure Assessment	Covariates	Statistical Analysis	Measures of Association and Values	Global Rating
Cuneo 1992	Type of case report or case series; 70 people with AML divided into exposed and unexposed to pesticides and chromosomes analyzed; consecutive pts admitted to hospital b/t 1986–1991 in Italy.	Questionnaire; all pesticides; exposure index developed where hours per day X days per yr X years.	None mentioned	Number and type of chromosomal aberrations	Clonal chromosome aberrations were more frequently encountered among exposed pts than unexposed, blood and bone marrow counts differed and the exposed group had poorer clinical outcomes; exposed patients resembled what is seen in secondary leukemia.	4,4