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Leukemias and Blood Dyscrasias Following Exposure to Chlordane and Heptachlor

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We present 25 new cases of blood dyscrasia, including leukemias, production defects, and thrombocytopenic purpura, generally following home termite treatment with the chlorinated hydrocarbon pesticides chlordane and heptachlor (C/H). These newly reported cases are consistent with 34 previously published case reports associating blood dyscrasias with CIH exposure. Additionally, the newly reported leukemias are consistent with epidemiologic evidence of excess risk of leukemia and other cancers in CIH-exposed populations and with the carcinogenic action of CIH in animals. The importance of case reports in warning of the association of blood dyscrasias to C/H exposure is emphasized. Until the voluntary halt in production in July 1987, millions of homes in the United States were treated with chlordane and heptachlor for termites even though their agricultural uses were phased out in 1978, largely on the grounds of "imminent hazard" because of carcinogenicity. In view of the recognized myelotoxicity, carcinogenicity, and other chronic toxic effects of these pesticides, a national program for monitoring all homes treated is urgently needed to detect persistent contamination.

Key words: aplastic anemia, termiticides, pesticides, thromobocytopenia

INTRODUCTION

The literature on the association between blood dyscrasias and exposure to the chlorinated cyclodiene pesticides chlordane and heptachlor (CM) was last reviewed in 1978 when six new cases of blood dyscrasias in children (along with five cases of neuroblastoma) following prenatal or postnatal chlordane exposure were presented [1]. In approximately one half of the 34 cases of blood dyscrasias (including five

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leukemias) then reported, there was also exposure to ocher potentially myelotoxic agents.

The very low incidence of most blood dyscrasias limits the feasibility of epidemiologic study [2,3], so the association of these diseases with specific toxic agents depends largely on observations and case reports by alert clinicians. The importance of such reports is illustrated by results of a large population-based, case-control study on the relation between analgesic use and agranulocytosis and aplastic anemia that confirms associations previously accepted on the basis of case reporting [2].

The present communication presents a series of 25 previously unpublished cases of blood dyscrasias following C/H exposure, including two illustrative case reports. Additionally, the epidemiological and other literature relevant to the myelotoxic hazards of C/H is briefly reviewed.

New Cases of Chlordane/Heptachlor-Associated Blood Dyscrasias

The myelotoxic hazards of C/H have been well-recognized for over three decades [4][1]. Chlordane was judged to be "one of the most hazardous hydrocarbon insecticides" in 1955 after aplastic anemia was reported following exposure to this agent [4]. Chlordane vaporizing devices were specially singled out as a "serious health menace" [5]. In addition to reports in the medical literature, industry files[2] contain information on unpublished cases resulting from physician inquiries about blood disorders in patients who had been exposed to C/H. Other unpublished cases in industry files include complaints and personal injury claims filed by patients developing blood disorders following exposure to C/H.

Tables I and II, respectively, list 12 litigated and 13 nonlitigated previously unpublished cases of C/H-associated blood dyscrasias; most of these cases do not appear to have been disclosed to the Environmental Protection Agency (EPA) and listed in their voluntary reporting system [6,7]. More than one half of the 25 cases occurred prior to 1975. Tables I and II summarize all of the available data.

Table III reviews the 34 previously published case reports of blood dyscrasia and C/H exposure. The distribution of the major categories of dyscrasias is similar in the published and unpublished sources, with the exception of a greater prevalence of thrombocytopenia in the latter (Table IV). Thrombocytopenia was as common in the unlitigated series (three cases) as in the litigated series (two cases).

In 15 of the 25 unpublished cases (60%), no potentially myelotoxic exposures besides C/H were reported. Among the 16 cases for which exposure data are available, the majority, 75%, involved homeowners and their families following home, lawn, and garden applications, particularly after home termite treatment. The remain-

[1]Despite these reports, a review of available labels for pesticides containing chlordane shows they contain no references to agranulocytosis, aplastic anemia, thrombocytopenia, leukemia, or any other disorder of the blood.

[2]These involve the files of Velsicol Chemical Co., Chicago, IL, the sole manufacturer of C/H; formulators such as Chevron and Chemagro; and applicators such as Orkin. We have been unable to obtain independent verification of all diagnoses.

TABLE I. Some Litigated Cases of Blood Dyscrasias Associated With Exposure to Chlordane/Heptachlor that Apparently Have N d Been Reported in the Scientific Literature

Case (Year)	Litigation reference	C/H exposure[a]	Blood dyscrasia	Comments
C.N. (1959)	Dist. Ct., Upton, TX Case No. 1360	+	Aplastic anemia	Nil
S. (1962)	Memphis, TN	+	Aplastic anemia	Nil
J.B. (1962)	Wisconsin State Circuit Court, Eau Claire Country	+	Thrombocytopenic purpura	Exposure in office following contamination from spraying in adjacent store premises
S.W. (1969)	California State court	+	Aplastic anemia	Exposure following home treatment for termites
C.S. (1971)	U.S. Dist. Court. 4th Div.. Minnesota 4–71, CIV. No. 318	+	Aplastic anemia	Exposure following sprayings of garden; suit not prosecuted
R.H. (1972)	Oklahoma City, OK	a	Acute disseminated hemorrhages and ? leukemia	Recent exposure following extensive sprayings of garden; suit not prosecuted
J.R. (1975)	U.S. Dist. Ct., E. Michigan Case No. 76-71904	+	Myelomonocytic leukemia	Nil
T.R. (1975)	Superior Court, California Case No. 468-446-C	+	Hemolytic anemia and ? leukemia	Developed in baby girl following home termite treatment
R.K. (1978)	State of N.Y. Supr. Ct. Index No. 4937-79	+	Leukemia	Nil
R.B. (1980)	U.S. District Court, Massachusetts Case No. 83-0927-S	b	Thrombocytopenic purpura	Exposure following spraying of own home: fatal
C.L. (1985)	U.S. District Court, West Michigan Case No. K-83-149-CAB-NP	c	Myelomonocytic leukemia	Nil
D.P. (1985)	17th Circuit Court, Michigan Case No. 85-46671-NI	+	Aplastic anemia	Exposure following home termite treatment: fatal

[a] +, No record other exposure; a, with aminopyrine; b, Teldrin exposure 6 months previously; c, with malathion.

ing 25% involved professional applicators. Of the classifiable dyscrasias, 14 were production defects, five were thrombocytopenic purpuras, and four were leukemias. A long-term follow-up of the production defect cases would be of particular interest in view of their high case-fatality rate [16] and the well-recognized sequential relationship between aplastic anemia and leukemia [13. Further details of most of these 25 cases cannot be evaluated in the absence of complete disclosure and reporting by the manufacturing, formulator, and applicator industries involved. Two cases for which additional information is available are presented for illustrative purposes.

TABLE II. Some Nonlitigated Cases of Blood Dyscrasias Associated With Exposure to Chlordane/Heptachlor That Apparently Have Not Been Reported in the Scientific Literature

Case (Year)	C/H exposure[a]	Blood dyscrasia	Comments
S.P. (1958)	+	Aplastic anemia	Nil
D.B. (1966)	a	Aplastic anemia	Worked as exterminator; fatal
Anon. (1969)	b	Aplastic anemia	Worked as exterminator; possible causality admitted in industry files
Anon. (1969)	+	Aplastic anemia	Exposure following extensive use for termite and eradication and garden applications; fatal (EPA, PIMS No. 360, 1980)
J.H. (1969)	+	Thrombocytopenic purpura	Nil
Anon. (1970)	+	Aplastic anemia	In young female child exposed to chlordane in garden yard; soil levels, 4 ppm; father who often used chlordane and other insecticides, died of aplastic anemia (reported in EPA, Pesticide Incident Monitoring System, Report No. 360, 1980)
B.P. (1974)	a	Aplastic anemia	Worked as groundskeeper
M.S. (1974)	+	Pernicious anemia	Nil
M.R. (1975)	+	Aplastic anemia	Developed in infant following home treatment for termites; remitted
R.S. (1976)	c	Thrombocytopenic purpura	Associated with myeloproliferative syndrome and pulmonary fibrosis; exposure following treatment of fruit trees in garden; serum chlordane, 250 ppb; soil levels, 234 ppm; patient assured by industry that chlordane causality was very unlikely
J.M. (1979)	a	Megaloblastic anemia	Worked as exterminator; possible causality admitted in industry files
J.M. (1982)	a	Chronic myeloid leukemia	Exposure following 5-year extensive use as pesticide in home
Anon. (1984)	+	Thrombocytopenic purpura	Remitted; patient's doctor told by industry that the only way of establishing causality was to see if patient relapsed following further exposure

[a] +, No record other exposure; a, with other unspecified exposures; b, with other "agricultural chemicals"; c, with other chlorinated hydrocarbon insecticides.

CASE REPORTS

Case 1

A white, 37-year-old commercial airline pilot (R.B., Table I) saw his FAA flight physician in May 1980 because of a 2-week history of backache, general malaise, and dizziness and a few days history of petechiae and ecchymoses over the lower extremities. Laboratory tests revealed a platelet count of 20,000/mm^3, and he was hospitalized with a working diagnosis of idiopathic thrombocytopenic purpura. He had previously been in good health except for mild "hayfever" for which he had

taken Teldrin once, 6 months previously, and a backache for which he had taken aspirin intermittently just prior to hospitalization in late April 1980.

On admission, his hematocrit was 37.6; hemoglobin, 13.2 gm%; white blood cell count, 6,700 cells/mm^3 with 46% polymorphonuclear leukocytes, 5% bands. 9% lymphocytes, 1% monocytes, 1% basophils. and 35% eosinophils; platelets, 19,000/mm^3; prothrombin time, 28 sec (patient)/27 sec (control); fibrinogen, 110 mg%. A tourniquet test was normal. Bone marrow aspiration of marginal quality showed adequate megakaryocytes but no evidence of platelet formation and an eosinophil hyperplasia with a shift toward immaturity. A stool guaiac test was positive.

The patient was placed on prednisone while awaiting further studies, but 2 days after admission he was found on the bathroom floor in hypotensive shock. Emergency laporatomy was performed and a ruptured. infarcted spleen removed. Transfusion with 20 units of platelet concentrate brought his platelet count level to about 200,000/mm^3, and multiple infusions of whole blood and fresh-frozen plasma were given in the perioperative period. Twenty-four hours postoperatively, he began to show signs of upper gastrointestinal and intraabdominal bleeding, and intensive platelet replacement therapy was again initiated. He was then transferred to a tertiary care hospital for further evaluation and treatment, at which time his platelet count had fallen to 75,000/mm^3. He followed a rapidly downhill course, with peritonitis and disseminated intravascular coagulation leading to death approximately 2 weeks after initial admission.

Before his fatal illness in late April 1980. the patient sprayed five cords of wood for carpenter ants with a half quart of chlordane formulation, which he diluted with water and applied with a hand sprayer without a nozzle. He had performed similar applications once or twice yearly since 1977, using a total of 1-2 quarts of chlordane concentrate.

case 2

A 41-year-old white male (C.L., Table I) was admitted for diagnostic work-up to a community hospital in November 1980 by his family physician after an office visit indicated mild anemia and thrombocytopenia. He had a 5-month history of easy bruising and slow wound healing, a 3-month history of easy fatiguability, and a 6-week history of sore throat. Just prior to admission he developed severe apthous ulcers. The patient had been rejected as a blood donor in July 1980 because of "low hemoglobin." He informed his physician that in July he had sprayed his house with chlordane. No history of other toxic exposures was then elicited. He worked as a diesel truck driver and had a 25 pack-year smoking history. Prior to his presenting illness he had been in goad health.

On admission his hemoglobin was 9 gm%; platelets, 40,000/mm^3, and WBC, 8,100/mm^3 with 69% lymphocytes and 10% monocytes. There were petechiae on his anterior chest and both legs and a diffuse hardening in the right axilla but no organomegaly. The physical examination was otherwise noncontributory. A bone marrow biopsy showed normal cellularity without blast infiltration and a relative increase in monocytes. Megakaryocytes were average in frequency but showed no significant platelet maturation. The pathologist's impression was of a reactive phase following toxic depression, "probably due to pronounced exposure to chlordane in July 1980." The patient was discharged to a university medical center for further

TABLE III. Some Cases Reported in the Scientific Literature of Blood Dyscrasisas Associated With Exposure to Chlordane/Heptachlor

Authors	Number of dyscrasia cases: Total	C/H alone	C/H with other agents: NS[a]	C/H with other agents: Specified	Blood dyscrasia	Comments
Conley [4]	2	0	0	[1]Sulfonamide and toxaphene	Aplastic anemia	Following repeated home spraying; fatal
			0	[2]As above	Aplastic anemia	Following repeated home spraying; fatal
Mendeloff and Smith [5]	1	0	0	DDT and lindane	Aplastic anemia	Following farm use; fatal
Muirhead et al (1959) [8]	1	0	0	Dieldrin and toxaphane	Hemolytic anemia	Following farm use; fatal
Gewin (1959) [9]	1	0	0	Lindane	Aplastic anemia	Following home spraying; fatal
Hugoly (1961) [10]	5	2	0	0	Aplastic anemias	Included in AMA 1965 series
			3	0	Aplastic anemias	Included in AMA 1965 series
AMA (1962) [11]	15	3	0	0	Aplastic anemias	Nil
			12	0	Aplastic anemias (9); agranulocytosis (2); thrombocytopenia	Six of the 12 "nonspecified agents" were myelotoxic

Williams et al (1973) [12]	4	0	0	DDT and lindane	Aplastic anemia	Following repeated farm use
Hayes and Pirkle (1966) [13]	1	0	0	DDT, Dieldrin, Pyrethrins	Aplastic anemia	Following repeated home spraying; fatal
Furie and Trubowitz (1976) [14]	1	1	0	0	Megaloblastic anemia	Following termite treatment of office; remitted (EPA, PIMS No. 360, 1980)
Collins (1976) [15]	2	1	0	0	Chronic monocytic leukemia	Following repeated home spraying
			0	Indomethacin	Chronic monocytic leukemia	Following repeated home spraying (husband and wife)
▮ fa te et al [1]	6	3	0	0	Aplastic anemia	Following home and garden spraying
					Acute monocytic leukemia	Following home and garden spraying
					Acute stem cell leukemia	Following repeated termite treatment of home
				1. Isotox	Aplastic anemia	Following repeated home and garden spraying
				2. Diazinon and paints	Aplastic anemia	Following repeated spraying; fatal
				3. Misc. pesticides and paint strippers	Acute lymphoblastic leukemia	Worked for lawn care firm

[a]NS, not specified.

TABLE IV. Major Categories of Blood Dyscrasias Associated With Chlordane Exposure Published in the Scientific Literature and From Unpublished Industry Files

Dyscrasia	Number of cases		
	Published	Unpublished	Total
Production defects[a]	27	14	41
Thrombocytopenia	1	5	6
Hemolytic anemia	1		1
Leukemia	5	4	9
Unclassifiable		2	2
Total	34	25	59

[a]Includes cases reported as aplastic anemia (pancytopenia), agranulocytosis, and megaloblastic anaemia.

therapy with a diagnosis of "bone marrow depression from chlordane . . . most likely currently in a pre-leukemic state."

A bone marrow aspirate 2 weeks later at the referral hospital was hypercellular, with the erythroid series decreased, an increase in the myeloid series with a left shift (57% myeloblasts, 11% progranulocytes), and a marked decrease of megakaryocytes. His disease was diagnosed as acute myelocytic leukemia, later specified as acute monomyelocytic leukemia on the basis of special studies. He was treated with chemotherapy and achieved remission, which has lasted to the present (April 1987).

The only other pesticide exposure the patient remembered was occasional malathion use in his garden. In the course of maintaining his automobile he very occasionally cleaned his hands with gasoline after working on the engine, but in his occupation as a truck driver he used a commercial detergent for this purpose. He was also exposed to diesel fumes and particulates and had unsuccessfully Ned a workers' compensation claim in 1981, alleging that his occupation conmbuted to his leukemia. He later filed complaints against the formulator and manufacturer of chlordane, but settled out of court.

A more detailed history revealed that in 1975, 5 years before the diagnosis of leukemia, he had bought a 1-gallon bottle of chlordane concentrate in a hardware store and used approximately half of it to treat a utility room, a crawl space, and the perimeter of his house for termites. At that time he used many gallons of a solution prepared by mixing one tablespoon of chlordane with a gallon of water in a pump sprayer. This work extended over several days. He used no protective clothing or mask, but showered after each application. In July 1980, he repeated spraying his garage and outside the house, using a large portion of the remaining half gallon.

Carcinogenicity of Chlordane/Heptachlor

Chlordane, heptachior, and its metabolite heptachlor epoxide are carcinogenic in mice and in rats, inducing hepatic and extrahepatic tumors following oral administration [17,18]. C/H has also been shown to promote hepatic and extrahepatic tumors in mice following initiation by diethylnitrosamine [19]. It should also be noted that commercial chlordane formulations contain carcinogenic "inert ingredients" and contaminants, such as propylene oxide, hexachlorobutadiene, and carbon tetrachloride, apart from some 40 other ingredients so far undisclosed by the manufacturer, formulators, and applicators of C/H.

Unfortunately animal bioassays are, in general, a poor model for myelotoxic effects in humans. A recent survey of a wide range of human leukemogens showed that all produced only solid tumors in mice or rats, including lymphomas, but no nonlymphatic leukemias [20]. This review noted that the lack of suitable animal models necessitates more reliance "on single case reports or clusters of cases in which chemical exposures are associated with acute leukemia." However, in an unpublished study sponsored by Velsicol. inhalation exposure of monkeys to chlordane, over a dose range from 100 to 1,000 $\mu g/m^3$ for a 90-day period, induced a statistically significant incidence of leukopenia and thromobocytopenia with effects at the lowest dose tested [21].

Epidemiological Studies Pertinent to C/H Exposure Effects

The current series brings the number of reported cases of leukemia or other blood dyscrasia following C/H exposure to 59. Many such blood disorders are uncommon. For instance, estimates of agranulocytosis incidence in a recent 6-nation study ranged from a low of $1.7/10^6$/year for Milan, Italy, to a high of $9.0/10^6$/year for Budapest, Hungary [2]. The population-weighted average of the age- and sex-standardized, region-specific agranulocytosis rates was $6.2/10^6$/year for the years 1980–1984 [2]; leukemia, by contrast, is more than one order of magnitude more frequent, occuring in the United States at a rate of approximately $1/10^4$/year [22]. Thus, cohort or cross-sectional studies to examine the relationship of C/H exposure to agranulocytosis would require extremely large populations with known domestic or occupational exposures together with a comparison group in whom such exposures could be excluded. Moreover, the validity of death certificate data for blood dyscrasias is questionable, making readily accessible routinely collected vital data of limited use.

The traditional method of studying rare diseases is by a case-control design. For adequate power, this requires sufficient numbers of cases and ascertainable exposure that is not too rare. The international cooperative study of aplastic anemia and agranulocytosis previously cited attempted to identify all cases in a total population of almost 15 million over a span of 2 to 5 years, depending on the country [2]. Intensive case-finding, achieved only with difficulty, was able to identify only 113 hospital admissions for aplastic anemia in this population. With this number of cases, the prevalence of known C/H exposure in the control population would have to exceed 25% to pick up a doubling of risk ($P = 0.05$, one-tailed, unmatched and equal sized control, 80% power). While past and unrecognized exposures of the general population to C/H is likely common (see below), the rate of recent *and* known exposure may not be. If, for example, 1% of the total U.S. population had a recent exposure of which they were aware, the same number of 113 cases would require an eightfold elevation of risk to be detectable under the same conditions [23].

Given such serious obstacles to investigation, it is not surprising that only one study, contracted by Velsicol, has specifically examined the relationship between aplastic anemia and exposure to chlorinated hydrocarbon pesticides [24]. Sixty cases of aplastic anemia among North Carolina males aged 15 to 65 years who died between 1968 and 1977 were matched for age and race with 120 controls. On death certificates usual occupations listed as farming, landscaping, gardening, or pest exterminating were taken as indicators of possible occupational exposure to unspecified chlorinated

hydrocarbon pesticides. The authors found no dosedependent relationship between pesticide exposure and aplastic anemia (RR = 0.67, 95% CI = 0.26–1.7), but were unable to exclude such an association "in view of the several case reports of aplastic anemia following exposure to pesticides . . . [which] may induce idiosyncratic bone marrow reactions in rare individuals" [24].

Velsicol has also funded a number of cohort studies of their employees by outside contractors. None, however. was of sufficient size even to consider the question of blood dyscrasia. A retrospective mortality study of C/H manufacturing workers showed significant excesses of both lung cancer in young workers and cerebrovascular disease, but had no separate classification for blood disorders [25]. With only 1,403 workers being followed, the expected number of aplastic anemia deaths, even with much longer follow-up than was possible here, would have been too few to have been detected. Even for the more common malignancies, the authors acknowledge that "the study population was too small and the period of follow-up too short to translate . . . into a statement that there is no excess risk of cancer" associated with C/H exposure [25]. Two more recent Velsicol-sponsored studies of these workers suffer from the same deficiencies and are further burdened by arithmetic discrepancies and inadequate presentation of data, preventing evaluation of the results [26,27]. An independent mortality study of this and three similar cohorts reported nonsignificant excesses of stomach and bladder cancer, but likewise recognized there were too few deaths to draw any meaningful conclusions [28]; short follow-up and rapid labor turnover added to the difficulties.

Pest-control operators (PCOs) have often been exposed to C/H. A cohort mortality study supported by Velsicol identified excess skin, bladder, and lung cancers [29]. While only the bladder cancer excess achieved statistical significance, the authors acknowledged the insensitivity of the study since too few person-years of observation were of workers with more than 5 years of employment and who were more than 10 years from first exposure. Additionally, there were insufficient numbers of workers to shed light on the question of blood dyscrasia or leukemia. Another retrospective cohort study of 3,827 licensed PCOs in Florida, followed-up at 10 years, revealed significantly elevated rates of lung cancer and excess deaths (O/E = 3/0.9) for acute myeloid leukemia [30].

Two case-control studies have examined the relationship of agricultural occupation to leukemia and related malignancies. One thousand eighty-four death certificates of leukemia cases among Nebraska residents during the years 1957–1974 were age-, sex-, race-, county-, and calendar year-matched with 2,168 control deaths from other causes [31]. These farmers exhibited an elevated risk of acute leukemia in countries where corn was grown in large quantities [31]. Similarly, death certificates from Iowa for 1,675 white males over age 30 years who died of leukemia were matched to two coritrols by age at death and country and year of death [32]. Iowa farmers had a higher risk for chronic or unspecified lymphatic leukemia in counties where there was extensive production of corn and soy bean. There was also an association of mortality from unspecified lymphatic leukemia with amount of corn produced per acre, as well as numbers of milk cows and egg-laying chickens. During the period of these studies, one of the major agricultural uses of chlordane was on corn crops.

A case-control study of children with brain tumors matched 84 cases with 76 normal controls and 112 children with other types of malignancies. More children

with brain tumors were found to have had pest exterminations in the household prior to diagnosis of the index child than had normal children (OR = **2.3, P = 0.10)** while there was no difference with the cancer controls [33].

Thus, the scanty epidemiological literature, in spite of its limitations and insensitivity, is consistent with an association between C/H exposure and leukemia and other cancers. However none of the studies has sufficient power to be meaningful with respect to blood dyscrasias such as aplastic anemia, agranulocytosis, or thrombocytopenia. For the foreseeable future, then, we will need to continue to rely. as we have in the past, on clinical reports associating C/H exposure with blood disorders.

Domestic Exposure to Chlordane/Heptachlor

The majority of C/H-associated case reports of blood dyscrasias, for which the circumstance of exposure is known, occurred following domestic application, particularly termite treatment (Table V). Such exposures continue to occur. In 1974, the U.S. Environmental Protection Agency proposed the cancellation of virtually all agricultural uses of C/H, largely on the basis of its demonstrated animal carcinogenicity, which was found to pose an "imminent hazard." An exception was made for subterranean use against termites by PCOs on the assumption that this entailed little or no exposure to the general population. However, subsequent information and experience has clearly proven the contrary.

There are no firm data on the number of homes in the United States that have been or are being treated for termites with C/H, although according to governmental estimates most of the nation's homes would have been or could be so treated [34]. The National Pest Control Association, which represents many structural pest control firms, estimates that 1.5 million homes per year are treated for termite control [35]. Available monitoring data have demonstrated that a high proportion of termite-treated homes become contaminated with C/H and that such contamination can persist for decades after treatment. In slab construction houses in which the heating and ventilation ducts are below the ground floor, C/H residues can be carried into the air and onto surfaces of the living areas [36]. In a survey of 435 U.S. Air Force homes treated from 1964 to 1978 and monitored in 1979, 60% had chlordane levels over 1 $\mu g/m^3$; the mean concentration in 77% of homes with detectable levels was 2 $\mu g/m^3$ [37]. Similarly, a recent survey of 1,110 air samples from 422 homes in 14 counties

TABLE V. Major Categories of Published and Unpublished Blood Dyscrasias Associated With Chlordane Exposure by Exposure Mode

		Occupational			
Dyscrasia	Domestic[1]	Pest control operator	Farming	Unknown	Total
Pmduction defects	16	5	2	18	41
Thrombocytopenia	4			2	6
Hemolytic anemia			1		1
Leukemia	5			4	9
Unclassifiable	a				2
Total	21	5	3	24	59

[1]Includes termiticide and other home, lawn, and garden applications by householder

of New York state showed that levels of chlordane in excess of 5 $\mu g/m^3$ were found in 33% of 289 nonliving area samples and 7% of 661 living area samples [38].

In 1985 the Commonwealth of Massachusetts banned termiticidal uses of chlordane, and in 1986 New York followed, adding the closely related cyclodiene pesticides Aldrin/Dieldrin to the list. Both states took note of the availability of noncarcinogenic alternatives to these termiticides. In March 1986, Japan banned the importation of all C/H-containing products because of their public health risks and high potential for contaminating the environment [39]. On December 31, 1986, the Environmental Protection Agency issued a new standard for C/H [40], restricting continued usage to licensed applicators on the unfounded assumption [41–43] that such application does not result in contamination. EPA also called for further studies on the hazards of C/H, notwithstanding the following considerations: Some 14 years earlier the Agency had found, on the basis of extensive hearings, that agricultural uses of C/H posed "imminent hazards" because of carcinogenicity and other toxic effects; that an extensive subsequent literature abundantly confirmed and extended data on such hazards; and that human exposure following termite treatment could be subsequently greater than that caused by food contamination following agricultural usage. In July 1987, following persistent pressure by environmental and consumer groups, the manufacturer of C/H termiticides entered into an agreement with the U.S. Environmental Protection Agency to halt production. The present case series of blood dyscrasias associated with C/H exposures lends weight to the urgent need for legislation creating a national program for monitoring homes known to have been treated to detect persistent contamination with these highly dangerous pesticides.

SUMMARY

1. We present 25 new cases of blood dyscrasias, including production defects, thrombocytopenic purpura, and leukemia, the majority following home termite treatment with chlordane/heptachlor.

2. These new cases are consistent with previous literature reports on the association between exposure to C/H and other chlorinated hydrocarbon pesticides and blood dyscrasias.

3. The new leukemia cases are consistent with epidemiological studies on associations between exposure to chlorinated hydrocarbon pesticides, including C/H, and leukemia and other cancers among pest control operators and in areas where corn and soy farming was prevalent.

4. The new leukemia cases are also consistent with numerous studies on the carcinogenicity of C/H in several strains of mice and rats, since there are no satisfactory animal models for blood dyscrasias and recognized human leukemogens induce solid tumors in rodents as opposed to leukemia.

5. In view of the many millions of U.S. homes that have been, and continue to be, treated for termites with C/H and the relatively high rate of subsequent persistent contamination, the U.S. government, and all other governments, should immediately institute a national monitoring program of all homes known to have been treated to detect persistent contamination with these highly dangerous pesticides.

REFERENCES

1. Infante PF, Epstein SS, Newton WA, Jr.: Blood dyscrasias and childhood tumors and exposure to chlordane and heptachlor. Scand J Work Environ Health 4:137–150, 1978.

2. International Agranulocytosis and Aplastic Anemia Study: Risks of agranulocytosis and aplastic anemia: A first report of their relation to drug use with special reference to analgesics. JAMA 256:1749–1757, 1986.
3. Sanchez-Medal L, Castanedo JP, Garcia-Rojas F: Insecticides and aplastic anemia. N Engl J Med 269:1365–1367, 1964.
4. Conley BE: The present status of chlordane. Council on Pharmacy and Chemistry. Committee on Pesticides. JAMA 158:1364–1367, 1955.
5. Mendeloff AI, Smith DE: Exposure to insecticides, bone marrow failure, gastrointestinal bleeding. and uncontrollable infections. *Am* J Med 19:274–284, 1955.
6. Environmental Protection Agency, Office of Pesticide Programs: "Summary of Reported Pesticide Incidents Involving Chlordane: Pesticide Incident Monitoring System (PIMS)." July 1980, Report No. 360. Unpublished, Washington, DC.
7. Environmental Protection Agency, Office of Pesticide Programs: "Summary of Reported Pesticide Incidents Involving Heptachlor: Pesticide Incident Monitoring System (PIMS)." February 1981. Report No. 359. Unpublished, Washington, DC.
8. Muirhead EE, Groves M, Guy R, Halden ER, Bass RK: Acquired hemolytic anemia, exposure to insecticides and positive Coombs test dependent on insecticide preparations. Vox Sang 4:277–292, 1959.
9. Gewin HM: Benzene hydrochloric and aplastic anemia. JAMA 171:1624–1625, 1959.
10. Huguley CM, Erslev AJ, Bergsagel DE: Drug-related blood dyscrasias. JAMA 177:23–26, 1961.
11. American Medical Association, Council on Drugs: Registry on blood dyscrasias. Report to the Council. IAMA 179:888–890, 1962.
12. Williams DM, Lynch RK, Cartwright GK: Drug-induced aplastic anemia. Sem Hem 10:185–223, 1973.
13. Hayes WJ, Pirkle CI: Mortality from pesticides in 1961. Arch Env Health 12:43–55. 1966.
14. Furie B, Trubowitz S: Insecticides and blood dyscrasias: chlordane exposure and self-limited refractory megaloblastic anemia. JAMA 235:1720–1722, 1976.
15. Collins TS: Monocytic leukemia in husband and wife following chronic exposure to chlordane. Aus New Zeal Jour Med 6:360, 1976.
16. Bottiger LE: Prevalence and etiology of aplastic anemia in Sweden. In Hibino S, Fumimaro T, Shahidi NT: "Aplastic Anemia." Baltimore: University Park Press, 1976, pp 171–180.
17. Epstein SS: Carcinogenicity of heptachlor and chlordane. Sci Total Environ 6:103–154, 1976.
18. Japanese Research Institute for *Animal* Science in Biochemistry and Toxicology:" 24-Month Chronic Toxicity and Tumorogenicity Test in Mice by Chlordane Technical; 30-Month Chronic Toxicity and Tumorogenicity Test in Rats With Chlordane Technical." Reports to Velsicol. December 1, 1983. Unpublished.
19. Williams, GM, Numoto S: Promotion of mouse liver neoplasms by the organochlorine pesticides chlordane and heptachlor in comparison to dichlorodiphenyltrichloroethane. Carcinogenesis 5:1689–1696, 1984.
20. Adamson RH, Seiber SM. Chemically induced leukemia in humans. Environ Health Perspect 39:93–103, 1981.
21. Huntingdon Research Laboratories: "Chlordane: A Ninety-Day Inhalation Toxicity Study in the Rat and the Monkey." Unpublished report to the Velsicol Company, June 1984.
22. Silverberg, E, Lubera J: Cancer statistics. CA 37:2–19, 1987.
23. Schlesselman JJ: "Case Control Studies." New York: Oxford University Press. 1982.
24. Wang HH, Grufferman S: Aplastic anemia and occupational pesticide exposure: A case-control study. J Occup Med 23:364–366, 1981.
25. Wang HH. MacMahon B: Mortality of workers employed in the manufacture of chlordane and heptachlor. J Occup Med 21:745–748, 1979.
26. Shindell S, Ulrich S, Giefer EE: Epidemiology and chlorinated hydrocarbon insecticides. In Khan MAQ. Stanton RH: "Toxicology of Halogenated Hydrocarbons." New York: Pergamon Press. 1981, pp 50–65.
27. Shindell S, Ulrich S: Mortality of workers employed in the manufacture of chlordane: An update. J Occup Med 28:497–501, 1986.
28. Ditraglia D, Brown DP. Namekata T, Iverson N: Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand J Work Environ Health 7:140–146, 1981.
29. Wang HH. MacMahon B: Mortality of pesticide applicators. J Occup Med 21:741–744. 1979.

30. Blair A, Grauman DJ, Lubin JH, Fraumeni JF, Jr.: Lung cancer and other causes of death among licensed pesticide applicators. JNCI 71:31-37, 1982.
31. Blair A, Thomas TL: Leukemia among Nebraska farmers: A death certificate study. Am J Epidemiol 110:264-273, 1979.
32. Burmeister LF, Van Lier SF, Isacson P: Leukemia and farm practices in Iowa. Am J Epidemiol 115:720-728, 1982.
33. Gold E, Gordis L, Tonascia J, Szklo M: Risk factors for brain tumors in children. Am J Epidemiol 109:309-319, 1979.
34. General Accounting Office, Comptroller General of The U.S.: "Letter to EPA Administrator Re: Need for Formal Risk/Benefit Review of the Pesticide Chlordane." August 5, 1980.
35. Environmental Protection Agency, Region 2, New York: Quoted in "Environmental Facts: EPA Statement on Aldrin Termiticides," 1983. Washington, DC, USEDA.
36. Environmental Protection Agency (Administrator W.D. Ruckelshaus): Letter to Congressman R.J. McGrath, December 2, 1983, unpublished, Washington, DC.
37. Livingston JM, Jones CR, Lillie TH: "Airborne Chlordane Contamination in Homes Treated for Termites at a Midwestern Air Force Base." Report OEHL 81-11, USAF Occupational and Environmental Health Laboratory, Brooks Air Force Base, February 1981.
38. New York State Health Department, Bureau of Toxic Substances Assessment: Testimony on proposed amendments to termiticide regulations, May 24, 1984.
39. Consumer Alert, International Organization of Consumers Union, No. 4186 (69). September 19, 1986.
40. Environmental Protection Agency: "Guidance for the Reregistration of Pesticidal Products Containing as the Active Ingredient Chlordane." EPA, Washington, D.C.: EPA, December 31, 1986.
41. Atallah YH: "Residue Reduction Procedures." Workshop on Termiticides in Building Protection, Velsicol Chemical Company. September 22-23, 1982. Unpublished.
42. Raltech Scientific Services: "Applicator and Inhabitant Exposure to Chlordane During and After Termiticide Application in California." Report to Velsicol Chemical Company, October 8, 1979. Unpublished.
43. Wright CG, Leidy RB: Chlordane and heptachlor in the ambient air of houses treated for termites. Bull Environ Contam Toxicol 28:617-623, 1982.