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# Pesticide Prioritization for a Brain Cancer Case-Control Study[1]

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**The incidence of brain cancer is rising in the United States while the causes remain largely unknown. Epidemiologic studies indicate that individuals working in agriculture have an increased risk of brain cancer. The National Institute for Occupational Safety and Health is conducting a case-control study of incident brain cancer cases in Iowa, Michigan, Minnesota, and Wisconsin to evaluate the risk associated with several environmental exposures, in particular agricultural pesticides. Hundreds of different pesticides are used in agriculture and it is not feasible to evaluate the association between brain cancer and exposure to each of these chemicals; therefore, a strategy was developed to identify which pesticides would be targeted in the study. First, lists of pesticides were created, documenting usage in each of the four states and the United States as a whole, by using data from reports prepared by the U.S. Department of Agriculture and Departments of Agriculture and land grant colleges within the four states. Then the following factors were considered in prioritizing pesticides for evaluation in the study: total volume of use prior to 1985, ranking of use in the four states and the United States as a whole by pesticide category, and toxicological evidence of carcinogenic, teratogenic, or mutagenic effects. Pesticide usage prior to 1985 was determined to allow for a minimum 10-year latency for the incident brain cancer cases diagnosed in 1995 or later. The selected pesticides include 56 herbicides, 49 insecticides, 12 fungicides, and 17 fumigants, accounting for over 99% of the total pounds of herbicides and insecticides and over 98% of the total pounds of fungicides and fumigants applied pre-1985. Prompt lists of the pesticides are sent to study participants a few days before the study questionnaire is administered to allow them time to recall past use of pesticides; the lists include the common chemical names, trade names, the crops that the pesticides are most commonly used on, and the years that the pesticides have been marketed. The methods used to select this subset of 134 pesticides document historical pesticide usage and may be useful in prioritizing pesticides for other research studies.** 

## INTRODUCTION

The incidence and mortality for brain cancer are rising in the United States, but the causes responsible remain largely unknown (Salcman and Kaplan, 1991; Ahlbom *et al.*, 1986; Ries *et al.*, 1991; Grieg *et al.*, 1990). Improvements in the ability to diagnose brain cancer may account for part of the apparent rise in incidence, but are unlikely to explain the increase entirely (Ahlbom *et al.*, 1986; Davis *et al.*, 1990). It has been hypothesized that this increasing risk is largely due to greater exposure to environmental carcinogens (Polednak, 1991).

Epidemiologic studies of groups with higher rates of brain cancer than the general population may provide clues to environmental factors that contribute to the rising national rate. Even though farmers experience a lower overall mortality than the general population, there are indications that farmers or agricultural workers may have an excess brain cancer risk (Blair *et al.*, 1992; Wingren and Axelson, 1992; Brownson *et al.*, 1990; Reif *et al.*, 1989; Musicco *et al.*, 1982). To evaluate exposures possibly responsible for this excess risk, the National Institute for Occupational Safety and Health (NIOSH) is con-

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ducting a brain cancer case-control study of rural residents in four upper midwestern states: Iowa, Michigan, Minnesota, and Wisconsin. This study focuses on gliomas, the most common form of brain cancer occurring in adults (Page and Asire, 1985).

As an occupational group, farmers encounter a number of environmental exposures including pesticides, fertilizers, fuels, engine exhausts, organic and inorganic dusts, solvents, ultraviolet light, and zoonotic bacteria and viruses. Associations between these agents and brain cancer have not been fully evaluated, but because a number of pesticides have demonstrated carcinogenic potential in animal bioassays much attention has been focused on these agrichemicals (Blair and Zahm, 1993; IARC, 1987; Hoover and Blair, 1991). Therefore, a major hypothesis to be tested in the NIOSH study is that long-term exposure to pesticides increases glioma risk.

Pesticides have been used since ancient times; however, until this century only a few compounds were available and use was not widespread (Hayes and Laws, 1991). Beginning in the middle of this century, the introduction of important new pesticides began to increase dramatically, as did the number of pounds of various pesticides used on cropland (Fig. 1). The annual agricultural use of pesticides in the United States generally increased throughout the 1960s and 1970s but has been relatively stable at about 850 million pounds during recent years (Fig. 2). The growth in the use of pesticides has slowed because of lower application rates due to the introduction of more potent pesticides, more efficient use of pesticides, and lower farm commodity prices (Aspelin, 1994).

Farming is a diverse business and farmers vary dramatically in the types and amount of pesticides they use. For example, grain farmers are more likely to use large volumes of herbicides to control weed pressure on their crops, whereas livestock farmers are more likely to use insecticides to control parasites in their flocks and herds, and fruit and vegetable growers are more likely to use insecticides and fungicides to reduce crop damage.

Approximately 24,000 registered pesticide products are currently on the market, and although many of these have no routine use in agriculture, farmers may still choose from hundreds of different pesticides to control weeds, insects, rodents, fungi, and algae (vs GAO, 1990). In addition, farmers may have used pesticides such as aldrin and toxaphene which were once heavily used in agriculture but are now banned in the United States because of environmental and health concerns (USEPA, 1990).

Because of the large number and variety of uses for pesticides, it would be difficult to evaluate the association between cancer and exposure to each of

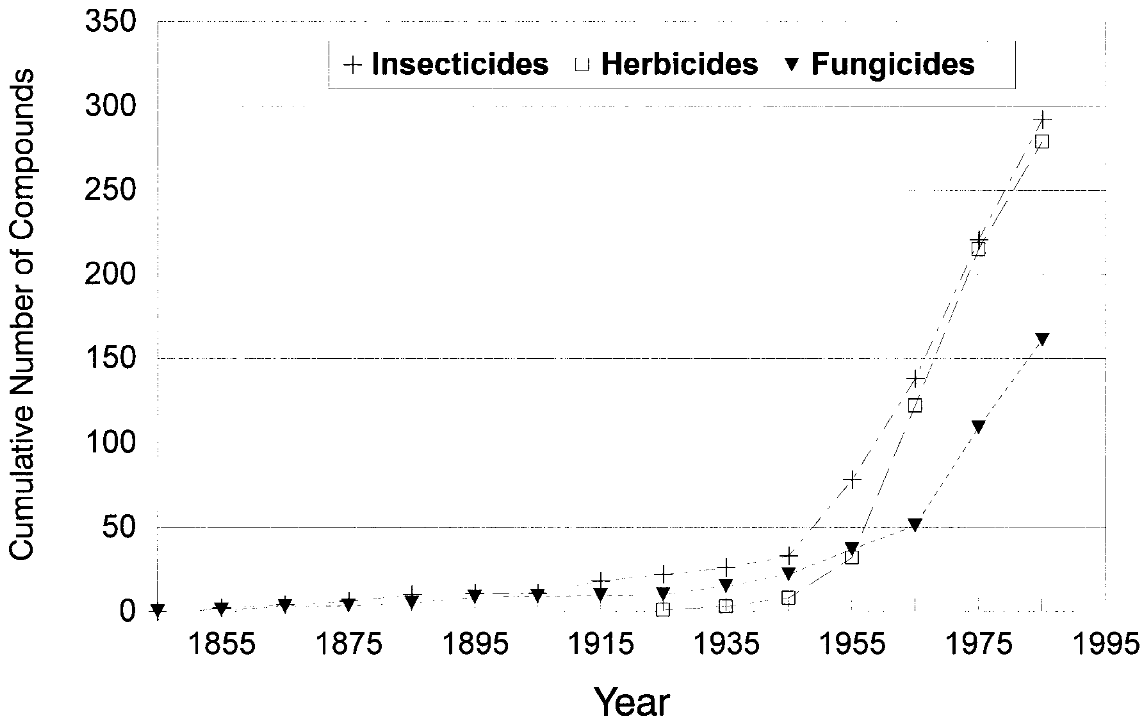


**FIG. 1.** Cumulative number of important herbicides, insecticides, and fungicides introduced over time. (Reproduced, by permission from W. Hayes and E. Laws, "Handbook of Pesticide Toxicology," Vols. 1–3, Academic Press, San Diego.)

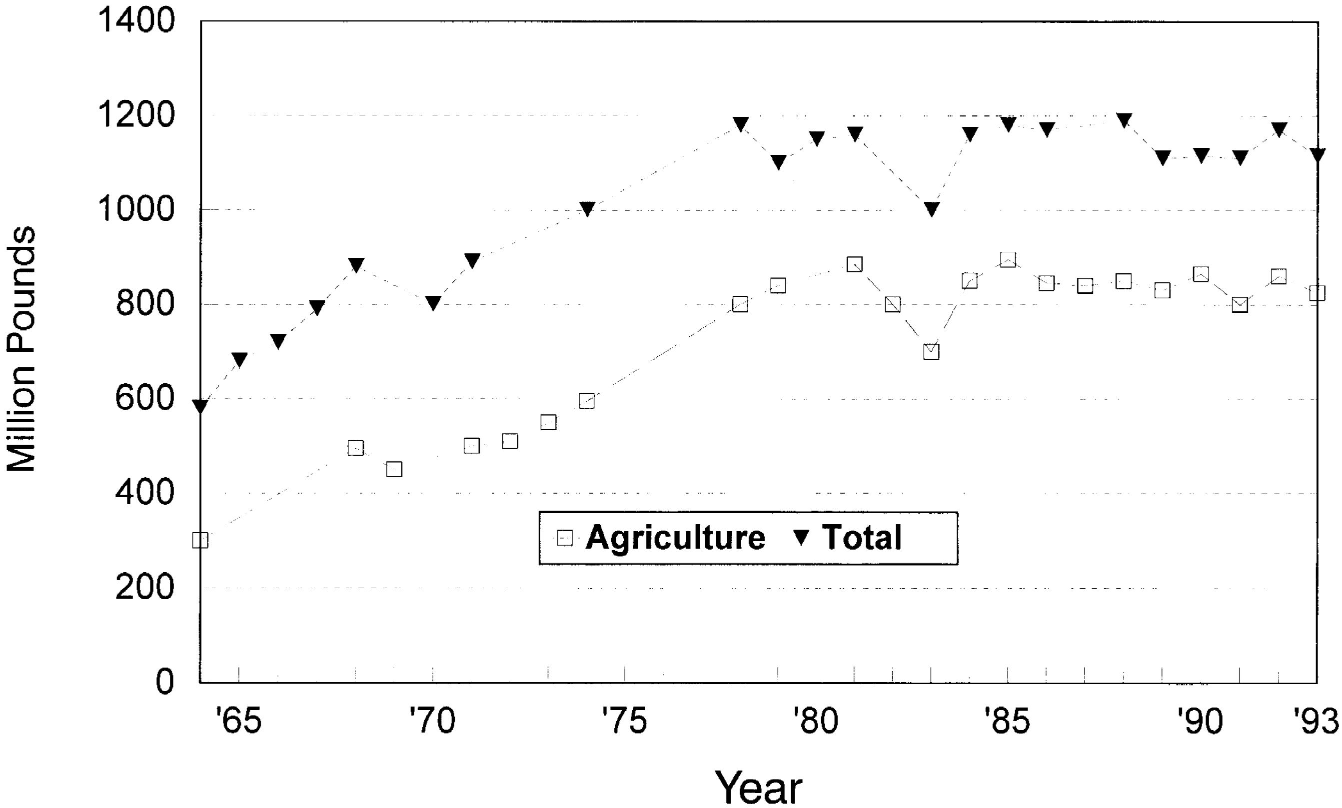


**FIG. 2.** Million pounds of pesticides used in the United States by year. (Reproduced from U.S. Environmental Protection Agency Pesticide Industry Sales and Usage: 1992 and 1993 Market Estimates (June 1994).)

the different pesticides to which farmers as a group may have been exposed. Since statistical power is limited for extremely rare exposures, it is desirable to evaluate exposure to the more commonly used pesticides. It is also desirable to evaluate pesticides which have some toxicologic evidence of being cancer initiators or promoters.

The primary source of epidemiologic data for the case-control study is an in-person interviewer-administered questionnaire. During the interview, information is obtained pertaining to demographics, medical history, potential confounders, and exposures of interest. To evaluate pesticide exposures, we had initially planned to include specific questions about past use of a few dozen selected pesticides. However, we were concerned the questionnaire would be too tedious to administer with this many pesticide questions incorporated directly into the questionnaire, and yet, decreasing the number of pesticide questions increased the probability that pesticides potentially associated with brain cancer would not be evaluated.

Additional concerns were that farmers may identify pesticides by their trade name rather than chemical composition, and a particular chemical may be an active ingredient in several different trade name products. Therefore, a procedure was needed to allow study subjects to recall pesticide usage by either trade or chemical names.

Subsequently, we decided not to include questions about a few specific pesticides in the questionnaire, but to leave questions about pesticide usage "open ended." The study participants are asked to provide information on each pesticide they have previously used, including when they first used the pesticide, how many years they used the pesticide, how many acres and days per year on average the pesticide was used, and if they wore a protective mask or rubber gloves when they handled the pesticide.

To help the study participants remember their past pesticide usage, two lists of pesticides are sent to study participants a few days before the questionnaire is administered. One list provides the common chemical names and the most frequent trade names under which the pesticides are marketed. The other list provides the chemical names, the crops that the pesticides are most commonly used on, and if available, the years that the pesticides have been marketed.

This manuscript describes the methods used to select pesticides for inclusion on the prompt lists and to develop information to aid study subjects in their recall of pesticides used in the past (Blair and Zahm, 1990).

## METHODS

### *Collection of Data*

The first step in selecting pesticides to include on the prompt lists was to create comprehensive lists of the major pesticides that have been used in Iowa, Michigan, Minnesota, and Wisconsin and the United States as a whole. These lists were generated from reports on pesticide usage from several sources, in particular the Departments of Agriculture and land grant colleges in the four states and from the U.S. Department of Agriculture (USDA). Table 1 lists the years for which pesticide usage information was available for each of the four states and for the United States at large. These reports included pesticide chemical names, the major crops on which the pesticides were used, and the number of pounds of each pesticide used. The state lists were developed from usage surveys specifically conducted by the state Departments of Agriculture. The United States list was developed from usage surveys conducted nationwide by USDA. Since 1990 the USDA has published annual reports of nationwide pesticide usage on field crops.

The information in the reports was typically collected through interviews with farmers who raised selected commodities. The sampling universe of farms was stratified by principal type of commodity grown and substratified by size of farm to improve precision (USDA, 1993; Wisconsin Agricultural Statistics Service, 1991). The fields were randomly sampled such that the probability of including a particular field in the survey was directly proportional to the total acres of the field crop planted. The surveys were conducted late in the growing season after chemical applications had been completed. These surveys primarily collected information on grain, vegetable, and orchard crops, which are the commodities upon which the vast majority of agricultural pesticides are used. Therefore, pesticides frequently used in other farm activities—livestock production, crops such as hay and pasture, and around farm buildings, lanes, and fence rows—may be underrepresented.

From these reports, five separate pesticide data sets were prepared—one for each of the four states plus the United States as a whole. Pesticides that were not marketed until 1985 or later were excluded from the lists. The chemical names of the pesticides and the number of pounds of each pesticide applied per year were entered into a computer spread-sheet program organized by types of pesticides—herbicides, insecticides, fungicides, and fumigants. The pesticides were sorted alphabetically by chemical name to form a list of all the pesticides with the number of pounds used in each year for which data were available.

**TABLE 1**
**Years for Which Pesticide Usage Information Was Available**

| Site | Number of reports | Years |
|---|---|---|
| Iowa | 5 | 1977–1979, 1985, 1990 |
| Michigan | 4 | 1969–1971, 1978 |
| Minnesota | 15 | 1969–1975, 1977–1979, 1981–1982, 1984, 1990–1991 |
| Wisconsin | 6 | 1969–1971, 1978, 1985, 1991 |
| United States | 10 | 1964, 1966, 1971, 1976, 1982, 1990–1994 |

### *Selection of Pesticides*

The pesticide usage data was used to select the more heavily used pesticides, thereby including pesticides on the prompt lists to which study subjects were more likely to have been exposed and excluding pesticides to which they were less likely to have had contact. To estimate the overall historical usage of each pesticide, the number of pounds of each pesticide used were summed across all the years prior to 1985 for which data were available. The pesticides were then ranked in decreasing order by number of pounds used. The ranked state lists were compared to each other to evaluate the relative usage of the various pesticides across the four states. This comparison determined whether there were significant differences in pesticides usage from state to state and whether separate pesticide lists would have to be prepared for study participants from each of the four states.

To compare the relative usage of specific pesticides in the United States as a whole to usage in the four study states, the ranked list from the United States as a whole was compared to the ranked lists from the four states. Because the nationwide surveys included a larger number of contacts and were possibly more comprehensive than the individual state surveys, pesticides with potentially wide usage in the states may have been recorded in the national surveys but not in the state surveys. Also, some heavily used pesticides in the overall U.S. market might not have been used heavily in these four upper midwestern states because they were predominantly applied to crops which are not commonly grown in these states. Based on comparisons of the state survey data with the U.S. data, a master list of pesticides was created—ranked by usage—which residents of Iowa, Michigan, Minnesota, and Wisconsin would most likely have used.

To select pesticides from the ranked master list to which study participants were most likely to have been exposed, the cumulative percentage of the herbicides, insecticides, fungicides, and fumigants were plotted by number of pounds applied pre-1985. To determine the usage level at which pesticides would be excluded these plots were then used to detect points where the slopes of the plots dramatically changed, indicating comparatively greater increments of pounds applied separating the successive pesticides.

To include pesticides which have been documented to have carcinogenic, teratogenic, or mutagenic effects, a search of the toxicological literature was carried out on the list of pesticides. The Registry of Toxic Effects of Chemical Substances (RTECS) was searched for all compounds associated with farming which had been tested for carcinogenicity. The following criteria were used to rank the compounds. First, priority was given to those compounds found to have caused brain or nervous system tumors in humans or animal species. Then, compounds which were regarded as probable or possible carcinogens were included. Compounds which were equivocal in carcinogenicity studies but positive in other genotoxicity studies were also included, while equivocal carcinogens which were not positive in other tests were generally not included. Compounds which were not tested in carcinogen studies, but were active in mutagenicity studies, were then evaluated and included on the list particularly if they shared structural or chemical homology with carcinogens. Compounds which were negative in carcinogenicity studies but positive in one or more other genotoxicity assays were evaluated based on the preponderance of the mutagenicity data. Pesticides which had been deleted based on low usage were put back on the list if there was toxicological evidence that they were potentially carcinogenic.

*Preparation of Prompt Lists*

Once the pesticides were selected, prompt lists were created to be sent to study participants a few days before the questionnaire is administered. One prompt list contains the trade names under which the selected pesticides have been marketed associated with the common chemical names of the pesticides. The second prompt list contains the common chemical names of the pesticides associated with the crops on which the pesticides have been used and if available the years that the pesticides were first marketed in the United States. If a pesticide is no longer sold in the United States, the list also includes the year the pesticide was removed from the market. This information was obtained through a search of a variety of reference materials on pesticides (Hayes and Laws, 1991; Meister, 1994; Chemical and Pharmaceutical Press, 1990; Weed Science Society of America, 1974). The questionnaire was pretested on 10 volunteers who lived in rural areas, and these volunteers were sent the pesticide lists a few days before the interviewer gave them the questionnaire.

## RESULTS

The usage for 240 pesticides was reported in the four state and USDA survey reports—102 herbicide; 81 insecticides; 35 fungicides; and 22 fumigants (Table 2).

When the lists of pesticides—ranked by usage pre-1985—were compared across the four states it was clear that basically the same pesticides were used in all four states in very similar amounts. As an illustration, Table 3 presents the 10 most heavily used herbicides and 10 most heavily used insecticides in each of the four states. Six herbicides—atrazine, alachlor, cyanazine, propachlor, 2,4-D, and chloramben—appear in the top 10 list of all four states, and two additional herbicides—butylate and trifluralin—appear among the top 10 herbicides in three of the states. Three insecticides—terbufos, carbofuran, and fonofos—appear in the top 10 list of all four states, and five additional insecticides—diazinon, phorate, carbaryl, aldrin, and bufencarb—appear among the top 10 insecticides in three of the states. Since these four states share similar geography, soils, climate, and therefore farm products, it is logical that the same pesticides would be used. Based on these observations, separate pesticide lists for each state were judged to be unnecessary. Fungicide and fumigant usage were usually not reported in the state data; therefore, comparisons for usage of these pesticides across states could not be made.

The 10 most frequently used herbicides, insecticides, fungicides, and fumigants—as determined from the USDA data—are given in Table 4. When herbicide and insecticide usage within the four

**TABLE 2**

**Selection of Pesticides for Inclusion in the Study**

| Selection criteria | Herbicides | Insecticides | Fungicides | Fumigants | Total |
|---|---|---|---|---|---|
| Total no. of pesticides with reported usage pre-1985 | 102 | 81 | 35 | 22 | 240 |
| Pesticides included on study prompt lists based on selection criteria | | | | | |
| No. of pesticides selected because >1 million lb used pre-1985 | 40 | 35 | 7 | 10 | 90 |
| No. of pesticides selected because high level of usage in four states and included in studies by other researchers | 13 | 10 | — | — | 15 |
| No. of pesticides selected because evidence of carcinogenicity, teratogenicity, or mutagenicity | 3 | 4 | 5 | 7 | 19 |
| Total number of each type of pesticide selected for prompt lists | 56 | 49 | 12 | 17 | 134 |

states is compared to the USDA usage data, the relative rankings of the pesticides differ, but the most frequently used herbicides and insecticides in the United States as a whole are, in general, commonly used pesticides in the states. Five herbicide—atrazine, alachlor, cyanazine, propachlor, and 2,4-D—ranked among the top 10 used in the United States also appear in the top 10 lists of all four states, and two more—trifluralin and butylate—appear among the top 10 in three of the states (Table 3). Only one insecticide in the United States top 10 list—carbofuran—appears in the top 10 lists of all four states, and three—carbaryl, aldrin, and phorate—appear among the top 10 in three of the states. Since some pesticides on the USDA list are predominantly used on crops such as cotton, tobacco, and citrus products, which are not commonly grown in these four upper midwestern states, it is reasonable that the relative rankings of the pesticides by usage would vary between the United States and individual states. However, the state lists did not include any pesticides that were not also included on the USDA list.

**TABLE 3**

**Ten Most Frequently Used Herbicides and Insecticides in Iowa, Michigan, Minnesota, and Wisconsin (Pre-1985)**

| Iowa | Michigan | Minnesota | Wisconsin |
|---|---|---|---|
| Ten most frequently used herbicides in four states | | | |
| Alachlor[a] | Atrazine[a] | Alachlor[a] | Atrazine[a] |
| Butylate[b] | Alachlor[a] | Chloramben[a] | Diphenamid |
| Cyanazine[a] | Chloramben[a] | Propachlor[a] | Benefin |
| Atrazine[a] | Butylate[b] | Atrazine[a] | Alachlor[a] |
| Trifluralin[b] | Linuron | 2,4-D[a] | Pebulate |
| Metribuzin | Cyanazine[a] | Triallate | Butylate[b] |
| Propachlor[a] | Trifluralin[b] | Trifluralin[b] | 2,4-D[a] |
| 2,4-D[a] | 2,4-D[a] | Metribuzin | Cyanazine[a] |
| Chloramben[a] | EPTC | Cyanazine[a] | Propachlor[a] |
| Metolachlor | Propachlor[a] | Linuron | Chloramben[a] |
| Ten most frequently used insecticides in four states | | | |
| Terbufos[a] | Aldrin[b] | Carbofuran[a] | Phorate[b] |
| Fonofos[a] | Carbaryl[b] | Bufencarb[b] | Diazinon[b] |
| Carbofuran[a] | Fonofos[a] | Phorate[b] | Carbofuran[a] |
| Phorate[b] | Diazinon[b] | Aldrin[b] | Bufencarb[b] |
| Chlorpyrifos | Carbofuran[a] | Fonofos[a] | Dimethoate |
| Ethoprop | Malathion | Diazinon[b] | Fensulfothion |
| Toxaphene | Methoxychlor | Terbufos[a] | Terbufos[a] |
| Carbaryl[b] | Azinphosmethyl | Fensulfothion | Chlordane |
| Malathion | Bufencarb[b] | Ethoprop | Fonofos[a] |
| Heptachlor | Terbufos[a] | Carbaryl[b] | Aldrin[b] |

[a] Pesticide appears in the top 10 list of all four states.
[b] Pesticide appears in the top 10 list of three of the four states.

Since the list of most commonly used pesticides across the four states was very similar to the national list and only the national list included fungicides and fumigants, the mast pesticide list—from which pesticides were ultimately selected for the prompt lists—was basically the USDA list with the usage of some pesticides estimated to be somewhat lower or higher based on usage in the four study states. For example, the herbicide cacodylic acid, which is primarily used as a cotton defoliant, ranked ninth in amount of usage on the national list; but since it had very low usage in the four study states it was estimated to have rather low usage. On the other hand, the herbicide chloramben had relatively low usage pre-1985 nationwide, but since it ranked among the top 10 herbicides in three of the four states it was estimated to have much higher usage.

As an example of how the usage data were used to select pesticides, a plot of the cumulative percentage

**TABLE 4**

**Major Pesticides Used in the Unites States: Ten Most Frequently Used Herbicides, Insecticides, Fungicides, and Fumigants—Pre-1985**

| Herbicides | | Insecticides | | Fungicides | | Fumigants | |
|---|---|---|---|---|---|---|---|
| Chemical name | No. lb. used in 1000s | Chemical name | No. lb. used in 1000s | Chemical name | No. lb. used in 1000s | Chemical name | No. lb. used in 1000s |
| Atrazine[a] | 257,888 | Toxaphene | 134,229 | Captan | 12,600 | Ethylene dibromide | 39,786 |
| Alachlor[a] | 187,225 | Methyl parathion | 78,590 | Copper compounds | 9,412 | D–D mixture | 8,342 |
| 2,4-D[a] | 154,603 | DDT | 72,161 | Maneb | 8,891 | Tetradifon | 6,434 |
| Butylate[b] | 85,225 | Carbaryl[b] | 53,050 | Zineb | 8,763 | Telone | 5,019 |
| Trifluralin[b] | 81,582 | Aldrin | 34,627 | Chlorothalonil | 4,100 | Ethylene dichloride | 3,599 |
| Propachlor[a] | 44,814 | Parathion | 34,140 | Ferbam | 2,573 | Methyl bromide | 2,709 |
| Cyanazine[a] | 31,865 | Carbofuran[a] | 20,743 | Dinocap | 2,324 | Chloropicrin | 2,509 |
| Propanil | 28,347 | Phorate[b] | 15,665 | Metalaxyl | 400 | Chlorobenzilate | 1,277 |
| Cacodylic acid | 23,980 | Malathion | 12,387 | Mancozeb | 300 | Dicofol | 1,000 |
| EPTC | 21,558 | Disulfoton | 12,227 | Benomyl | 100 | Dibromochloro propane | 940 |
| All herbicides | 1,091,891 | All insecticides | 585,842 | All fungicides | 49,563 | All fumigants | 72,305 |

[a] Pesticide appears in the top 10 list of all four states.
[b] Pesticide appears in the top 10 list of three of the four states.

of the 102 herbicides—increasing by number of pounds applied pre-1985—is presented in Fig. 3. For almost 50% of the herbicides fewer than a few thousand pounds were applied pre-1985. The plot also shows that the cumulative percentage of the total number of herbicides increases more rapidly per incremental change in number of pounds applied for the low-usage herbicides than it does for the high-usage herbicides. In other words, the high-usage herbicides are separated by comparatively greater increments of pounds applied than are the low-usage herbicides. The increase in cumulative percent by pounds applied begins to level off in the plots after approximately one million pounds. Based on these data, herbicides of which one million pounds had been used before 1985 were selected for inclusion on the pesticide lists; those with less than one million pounds were considered for elimination be-

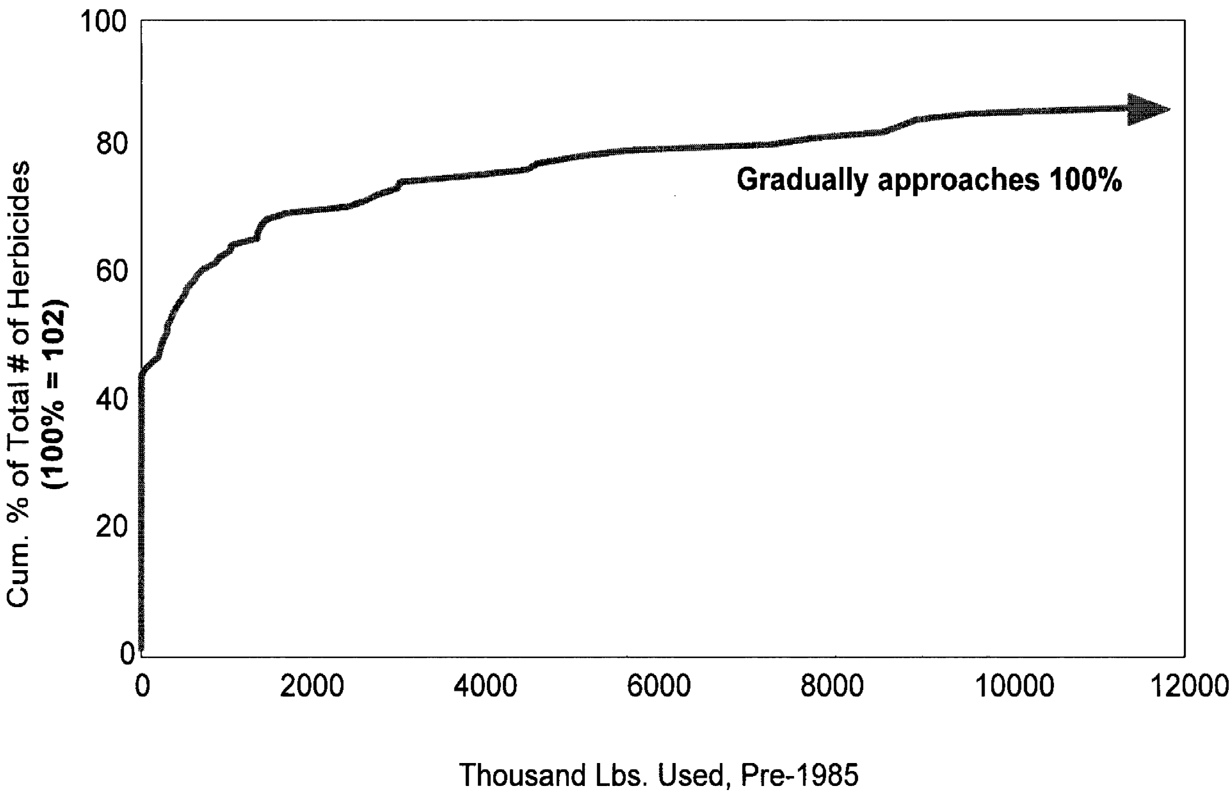


**FIG. 3.** Cumulative percentage of 102 herbicides by number of pounds applied pre-1985.

cause study subjects were less likely to be exposed to these pesticides.

The same approach was used to select insecticides, fungicides, and fumigants. Accordingly, 40 (39%) herbicides, 35 (43%) insecticides, 7 (20%) fungicides, and 10 (41%) fumigants were selected based on usage (Table 2). These selected pesticides account for over 99% of the total pounds of herbicides, 99% of the total pounds of insecticides, and approximately 98% of the total pounds of fungicides and fumigants applied nationwide before 1985. As illustrated in Fig. 4, the top 20% of the 102 herbicides accounted for 95% of the total pounds of herbicide use recorded pre-1985, and the 40 selected herbicides (39%) accounted for over 99% of the total pounds of herbicide use recorded pre-1985.

Out of the original list of 102 herbicides, an additional 13 herbicides and 10 insecticides were selected for inclusion because they had relatively high usage in these four states and had been selected for evaluation by other researchers studying brain cancer (Heineman, 1992). Therefore, they were included to improve comparison with other studies.

A review of the toxicological literature indicated that 41 pesticides are potentially mutagenic or carcinogenic. Twenty-two of these pesticides had already been selected for inclusion based on usage. The 19 remaining pesticides were added to the list based on toxicological evidence: 3 herbicides, 4 insecticides, 5 fungicides, and 7 fumigants (Table 2). This resulted in a final list of 134 pesticides—56 herbicides, 49 insecticides, 12 fungicides, and 17 fumigants.

From the pretests with 10 volunteers who lived in rural areas, we determined that it was reasonable to ask participants about usage of 134 different pesticides. By receiving the lists a few days before the interview, the participants expressed that they had time to recall past pesticide usage and check any usage records they had available. This component of the questionnaire required about 10 to 15 min to administer and subjects did not report problems in recall.

Subsequently, for the overall study, two prompt lists were created to send to the participants a few days before they were to be interviewed. One list gives all of the major trade names for the 134 pesticides with the common chemical names of the pesticides in parentheses. An excerpt of this list is presented in Table 5. The second list gives the chemical names of the pesticides, the years they were marketed, and the major crops to which the pesticides are applied. An excerpt of this list is presented in Table 6.

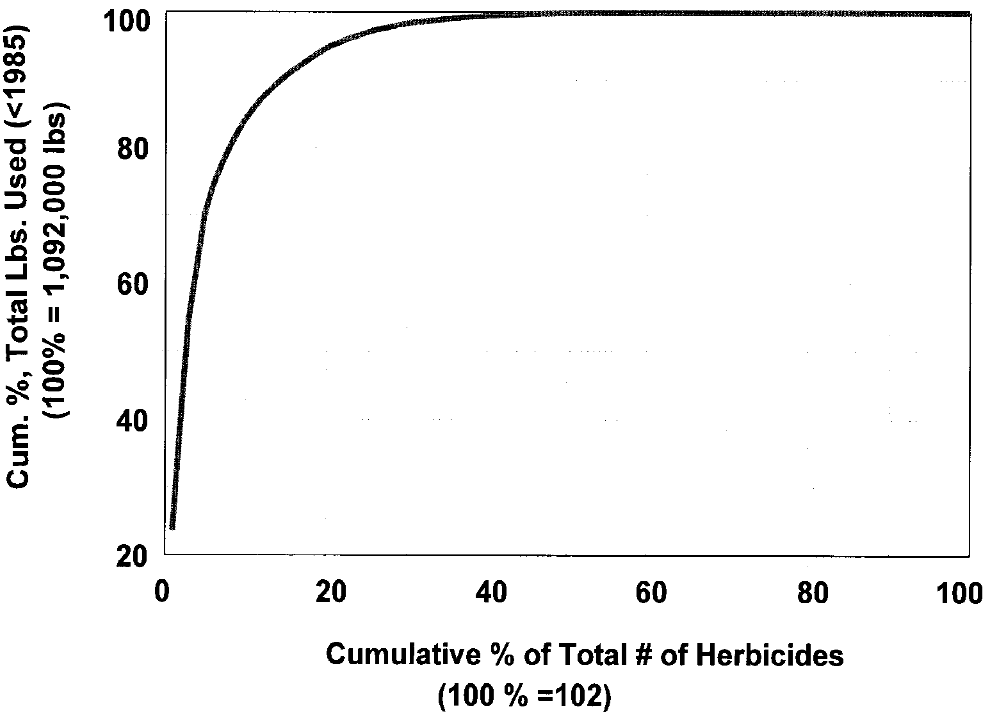


**FIG. 4.** Cumulative percentage of 102 herbicides by cumulative percentage of the estimated total pounds of herbicides used pre-1985.

**TABLE 5**

**Excerpt from List of Pesticide Trade Names**

| Herbicides | Insecticides | Fungicides | Fumigants |
|---|---|---|---|
| Aatrex (atrazine) | Aldrex (aldrin) | Apron (metalaxyl) | Acaraben (chlorobenzilate) |
| Basagran (bentazon) | Belt (chlordane) | Arathane (dinocap) | Aracide (aramite) |
| Bicep (atrazine & metolachlor) | Counter (terbufos) | Benlate (benomyl) | Brocide (ethylene dichloride) |
| Bladex (cyanazine) | Cythion (malthion) | Bluestone (copper sulfate) | Bromogas (methyl bromide) |
| Crossbow (2,4-D) | Dinocide (DDT) | Botec (captan) | Chlor-O-Pic (chloropicrin) |
| Eradicane (EPTC) | Dyfonate (fonofos) | Bravo (chlorothalonil) | D-D Mix (dichloropropane & dichloropropene) |
| Lasso (alachlor) | Fosferno (parathion) | Dithane (maneb, mancozeb, or zineb) | EDB (ethylene dibromide) |
| Lorox (linuron) | Furadan (carbofuran) | Fermate (ferbam) | Kelthane (dicofol) |
| Rad-E-Cate (cacodylic acid) | Guthion (azinphosmethyl) | Karathane (dinocap) | Mitotane (TDE) |
| Ramrod (propachlor) | Lorsban (chlorpyrifos) | Manzate (mancozeb) | Nemagon (dibromochloropropane) |
| Round-Up (glyphosate) | Mocap (disulfoton and ethoprop) | Manzeb (mancozeb) | Nematicide (telone) |
| Sencor (metribuzin) | Penncap-M (methyl parathion) | Orthocide (captan) | Nia (tetradifon) |
| Stampede (propanil) | Sevin (carbaryl) | Ridomil (chlorothalonil) | Picfume (chloropicrin) |
| Sutan (butylate) | Strobane (toxaphene) | Tersan (benomyl) | TCDS (tetradifon) |
| Treflan (trifluralin) | Thimet (phorate) | Zidan (zineb) | Vortex (telone) |

When the interviewer administers the questionnaire, the questions about pesticide usage are "open-ended." The study participants are asked to provide information about all the pesticides they have previously used, including pesticides that are not on the pesticide lists. The participants are asked when they first used each of the pesticides, how many years they used the pesticides, on average on how many acres and days per year the pesticides were used, and if they wore a protective mask or rubber gloves when they handled the pesticides. The responses of cases and controls will be compared to evaluate significant differences in the types, amounts, and duration of pesticides used.

## DISCUSSION AND CONCLUSIONS

Historical pesticide usage data were used to develop lists of agricultural pesticides—ranked by number of pounds applied—and to prioritize the pesticides for inclusion on "prompt" lists which will be sent to participants in the glioma case-control study a few days before they answer a questionnaire. Hopefully this strategy will improve the participants' recall of use of the major pesticides which rural residents in the upper midwest were most likely to have been exposed. The selected pesticides account for over 99% of total pounds of herbicides and insecticides and over 98% of the total pounds of fungicides and fumigants applied pre-1985. The participants may provide information on any pesticides they have used in the past, but epidemiologic analyses will be focused on the most prevalently used pesticides.

Providing study participants with lists containing the pesticide chemical names, trade names, years marketed, and crops on which they were used—and time to reflect on their past pesticide use before they are interviewed—should improve their recall and make administration of the questionnaire more efficient and accurate. However, no comparison analyses are being conducted in this study to determine whether this technique truly improves recall.

In a case-control study of lymphoma and soft tissue sarcoma in Kansas, Hoar *et al.* compared information on pesticide use reported by farmers to information obtained from their pesticide suppliers (Hoar, 1986). In this study participants were asked about the past use of specific pesticides during a telephone interview. The authors reported that agreement between the farmers and suppliers was approximately 60%, suggesting some error in subject recall about past pesticide use. In-person interviews of subjects who have had time to reflect on past pesticide use, aided by prompt lists, may result in less recall error.

The addition to the prompt lists of pesticides suspected of being carcinogens, teratogens, or mutagens, even if they were not heavily used pesticides, provides for the inclusion of pesticides of greatest toxicological concern. An association could possibly be seen in this study between glioma and rarely used, but highly carcinogenic pesticides. However, the omission of pesticides not identified as poten-

**TABLE 6**

**Excerpt from List of Pesticide Chemical Names, Years Marketed, and Crops**

| | Marketed | Products used on |
|---|---|---|
| Insecticides | | |
| Aldrin | 1952–1987 | Termites and ants around buildings, soil insects |
| Azinphosmethyl | 1953 | Soybeans, wheat, cotton, potatoes, oats, apples, peaches, pears, cranberries, blueberries |
| Carbaryl | 1956 | Corn, soybeans, wheat, cotton, rice, potatoes, sorghum, apples, peaches, cherries |
| Carbofuran | 1967 | Cotton, corn, potatoes, wheat, oats, soybeans, tobacco, rice, cranberries, sorghum |
| Chlordane | 1950–1988 | Cotton, potatoes, sugarcane, small grains, sugar beets |
| Chlorpyrifos | 1965 | Cranberries, corn, peaches, onions, sorghum, tobacco, apples, pears, peaches, soybeans |
| DDT | 1946–1973 | Apples, mosquito and fly control around livestock and buildings |
| Disulfoton | NK | Corn, potatoes, soybeans, tobacco, vegetables |
| Fonofos | 1967 | Corn, potatoes, sorghum, tobacco, tomatoes, onions |
| Malathion | 1950 | Corn, soybeans, wheat, cotton, rice, potatoes, sorghum, oats, apples, peaches |
| Methyl parathion | 1952 | Corn, soybeans, wheat, cotton, rice, potatoes, apples, peaches, cherries, pears |
| Parathion | 1950 | Ornamentals, fruit trees, grapes, general insecticide use |
| Phorate | 1954 | Corn, soybeans, wheat, cotton, potatoes, sorghum, root crops |
| Terbufos | 1973 | Corn, sorghum |
| Toxaphene | 1948–1982 | Soybeans, cotton |
| Herbicides | | |
| 2,4-D | 1942 | Wheat, barley, pasture, fence rows, woodland |
| Alachlor | 1967 | Corn, soybeans, cotton, potatoes |
| Atrazine | 1958 | Corn, sorghum |
| Bentazon | 1972 | Alfalfa, potatoes, soybeans, vegetables |
| Butylate | 1959 | Corn |
| Cacodylic acid | 1922 | Cotton, nuts, fruit and citrus orchards, fence rows |
| Cyanazine | 1968 | Corn, cotton, sorghum |
| EPTC | 1972 | Corn, cotton, potatoes, tomatoes |
| Glyphosate | 1969 | Corn, soybeans, wheat, cotton, hay, sorghum, apples, cherries, pears |
| Linuron | 1960 | Corn, soybeans, wheat, cotton, potatoes, sorghum |
| Metolachlor | 1974 | Corn, soybeans, cotton, potatoes, sorghum |
| Metribuzin | 1945 | Soybeans, wheat, corn, cotton, rice, sorghum, apples, pears, tobacco, potatoes |
| Propachlor | 1965 | Corn, sorghum |
| Propanil | 1960 | Rice, potatoes, tomatoes |
| Trifluralin | 1959 | Corn, soybeans, wheat, cotton, potatoes, sorghum, peaches, tomatoes, peanuts, sugar beets |
| Fungicides | | |
| Benomyl | 1967 | Soybeans, apples, blueberries, rice, pears, cherries, peaches, tomatoes, sugar cane, sugar beets |
| Captan | 1949 | Peanuts, apples, fruits, nuts, grapes, vegetables, berries, ornamental |
| Chlorothalonil | 1965 | Corn, soybeans, potatoes, cranberries, peaches, tomatoes, onions, peanuts, carrots, cabbage |
| Copper sulfate | 1807 | Fruits, vegetables, seed treatment |
| Dinocap | 1934 | Apples, cherries, peaches, pears, grapes, apricots, cantaloupes, cucumbers, melons, squash |
| Ferbam | 1950 | Fruits, cranberries, tobacco, vegetables |
| Mancozeb | 1968 | Fruits, nuts, vegetables, corn, potatoes, grains |
| Maneb | 1950 | Wheat, potatoes, tobacco, tomatoes, onions |

**TABLE 6—***Continued*

| | Marketed | Products used on |
|---|---|---|
| Metalaxyl | 1980 | Seed treatment, corn, sorghum, pasture grasses, beets, vegetables, soybeans |
| Zineb | 1953 | Fruits, vegetables |
| Miticides fumigants | | |
| Chlorobenzilate | 1952 | Citrus fruit, beehives, mites |
| Chloropicrin | 1908 | Grain |
| Dibromochloro-propane | 1955 | Cotton, soybeans, berries, grapes, melons, citrus, peanuts, vegetables |
| Dicofol | 1955–1986 | Citrus fruits, nuts, cotton, bean |
| Ethylene dibromide | 1946 | Grains, nuts, vegetables, flour |
| Ethylene dichloride | 1927 | Grain |
| Methyl bromide | 1932 | Flour, fruits, grains, food warehouses, greenhouses, vegetables |
| TDE | 1944 | Cereal grains |
| Telone | 1945 | Potatoes, tobacco, vegetables, ornamentals, soil fumigant |
| Tetradifon | 1962 | Fruits, vegetables, ornamentals, spider mites |

*Note.* Pesticides are listed by category (herbicides, insecticides, fungicides, and miticides and fumigants). The chemical name of the pesticide is listed first. The next column lists the year the pesticide went on the market. If two separate years are shown, the second year indicates when the pesticide was removed from the market. The last column provides the crops that the pesticide was commonly used on. NK, date not known.

tially carcinogenic and used in low quantities may be a limitation in this study.

This strategy for selecting pesticides adds objectivity to the process of evaluating associations between glioma and pesticide usage. The selection strategy could be used as a model for other researchers needing to compile a list of pesticides for their studies. For example, the pesticide lists—ranked by usage—could be used to prioritize pesticides for further toxicological or health effects studies or to select pesticides for environmental screening studies of ground and surface water contamination.

The historical usage data has limitations for prioritizing pesticides, however. The number of years in which pesticide usage data were collected varies by state, as is evident in Table 1. The survey methods may have varied from state to state and across time, diminishing the comparability of the state and national data. The usage data reported in these surveys have not been validated. Also, the pesticide usage surveys have collected more complete data on herbicides and insecticides used on field crops, fruits, and vegetables, while pesticides used in other farm operations are underrepresented. Therefore, the infrequency of the surveys and the sampling methods used in the past somewhat limit comparisons of the relative rankings of the pesticides, particularly from state to state. In 1990 the USDA began collecting comprehensive state-specific usage data annually. This more complete surveying of pesticide usage should help overcome limitations of the historical surveys.

Although usage data may rank pesticides to reflect the widespread use and likelihood that individuals have encountered various pesticides, these data are probably not directly correlated with individual exposure. For example, pesticides are applied using a variety of methods and application rates; more individuals may have much greater exposures to pesticides applied at low application rates using backpack sprayers than pesticides applied at high application rates using large tractors with enclosed cabs. The questionnaire in the brain cancer case-control study includes questions on the types and sizes of farms on which pesticides are applied, types of crops, methods of application, and work practices used when applying the various pesticides.

The usage surveys and the brain cancer study focus on the active chemical ingredients in pesticides, but pesticide formulations often also contain carrier solvents—commonly called inert ingredients. Since solvent exposures have also been associated with increased brain cancer risk, carrier solvents may confound associations between the active ingredients and brain cancer. Unfortunately, pesticide users are unlikely to recall and generally do not know the solvents used in pesticide formulations. Therefore, if associations are observed in the brain cancer study between particular active ingredients and increased brain cancer risk, then the solvents historically used in formulations with these active ingredients will be evaluated for potential confounding effect.

The data collected for this effort demonstrate that there have been changes in the types and amounts of pesticides used over time. Several pesticides are no longer marketed in the United States and the usage of once popular pesticides has declined because of substitution by other pesticides. It is important that we continue to document pesticide usage, on a national as well as a state-specific basis, in order to evaluate associations between health effects and exposure more accurately in the future.

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