Ann. occup. Hyg., Vol. 49, No. 5, pp. 375–384, 2005

Published by Oxford University Press
doi:10.1093/annhyg/meh102

Assessment of Pesticide Exposure in the Agricultural Population of Costa Rica

PATRICIA MONGE[1,2]*, TIMO PARTANEN[1], CATHARINA WESSELING[1,2], VIRIA BRAVO[1], CLEMENS RUEPERT[1] and IGOR BURSTYN[3]

[1]Central American Institute for Studies on Toxic Substances, Universidad Nacional, Heredia, Costa Rica; [2]Department of Public Health Sciences, Karolinska Institutet, Solna, Sweden; [3]Department of Public Health Sciences, University of Alberta, Canada

Received 2 September 2004; in final form 28 October 2004; published online 13 January 2005

We describe a model for the retrospective assessment of parental exposure to 26 pesticides, selected by toxicity-based prioritization, in a population-based case–control study of childhood leukaemia in Costa Rica (301 cases, 582 controls). The model was applied to a subset of 227 parents who had been employed or self-employed in agriculture or livestock breeding. It combines external data on pesticide use for 14 crops, 21 calendar years and 14 regions, and individual interview data on determinants (task and technology, personal protective equipment, field reentry, storing of pesticides, personal hygiene) of exposure. Recall was enhanced by use of checklists of pesticides in the interview. An external database provided information on the application rate (proxy for intensity of potential exposure) for each pesticide. The calendar time was individually converted to five time windows (year before conception, first, second and third trimester, and first year of the child). Time-windowed individual data on determinants of exposure and their expert-based general weights and their category-specific hazard values jointly provided an individual determinant score. This score was multiplied by the application rate to obtain an individual index of exposure intensity during application. Finally, average exposure intensity during entire time windows was estimated by incorporating in the model the individual time fraction of exposure during application. Estimates of exposure intensities were proxies assumed to be proportional to dermal exposure intensity, which represents the major pathway of occupational exposure to pesticides. A simulated sensitivity analysis resulted in a correlation coefficient of 0.91 between two sets of 10 000 values of individual exposure indices, based on two different but realistic sets expert-assigned weights. Lack of measurement data on concurrent exposures in comparable circumstances precluded direct validation of the model.

Keywords: cancer epidemiology; case–control; developing countries; exposure estimation; tropics

INTRODUCTION

Assessment of exposures in occupational and environmental epidemiology needs to cover the etiologically pertinent time periods. In retrospective studies, these periods lie by definition in the past of the study subjects. Ideally, the basic parameter to be estimated is the exposure intensity as a function of time. Exposure durations, average intensities, cumulated exposures, peak exposures and any other important parameters would be generated from it. In practice, the assessment of this function entails a number of assumptions, simplifications, approximations and surrogate measures, resulting in metrics of exposure that contain errors. Validation of historical exposure is hampered by the usual lack of 'true' exposure data in any population that might be considered for validation. This is in sharp contrast with the possibilities of validation of estimates of current exposures (Arbuckle *et al*., 2002). Apart from studies using biomarkers of exposure, the reconstruction of past exposures in population or hospital-based case–control studies is usually based on data from interviews of the study subjects or their proxies (Gérin *et al*., 1985; Siemiatycki, 1991; Stewart and Stewart, 1994a; Stewart *et al*., 1998; Teschke *et al*., 2002).

Chemical agents or even trade names of chemical products will often not be recalled to any significant detail or even known by the subjects themselves or

*Author to whom correspondence should be addressed. Fax: +506-277-3583; e-mail: pmonge@una.ac.cr

their next-of-kin. Farmers who select and purchase their pesticides may have the advantage of recall (Teschke *et al*., 2002). Changes in the pattern of pesticide use, however, tend to make recall of pesticides difficult for compounds used in the remote past. Checklists may enhance recall (Gérin *et al*., 1985; Blair *et al*., 1997; Teschke *et al*., 2002). Job histories, tasks and other determinants are easier to recall than exposure histories (Teschke *et al*., 2002). Strategies to circumvent these problems include expert assessment using historical data on jobs, tasks and other determinants of exposures (Stewart and Stewart, 1994b; Burstyn and Teschke, 1999), occasionally supported by data from external sources (data collected for purposes other than a particular epidemiological investigation).

We describe model-based pesticide assessment of exposure intensity in parents from a national case–control study of childhood leukemia in Costa Rica and present distributions of model-derived estimates of exposure intensity for the parents of the cases and the controls. A simple sensitivity analysis is described.

METHODS

Epidemiological study design

In a national population-based case–control study of childhood leukemia and parental exposure to pesticides, all cases of childhood leukemia (ages 0–14 at diagnosis; $n = 301$) diagnosed during 1995–2000 were identified at the Cancer Registry and the Children's Hospital of Costa Rica (ICD-0-1). Population controls ($n = 582$), frequency matched by age, were identified at the Population Birth Registry, with within-stratum replacement of refusers and subjects that were not found. We conducted face-to-face interviews during 2001–2003 with a total of 873 mothers and 763 fathers. The model was applied to the data of 227 parents (10 mothers and 78 fathers of cases, and 12 mothers and 127 fathers of controls) who were active in agriculture and livestock production, and completed an additional interview, which utilized icon-calendar forms (ICF) (Monge *et al*., 2004). The rate of ICF responses with sufficient data was 92%. The Costa Rican ICF was used in combination with a conventional interview form on demographic data and known and suspected risk factors of childhood leukemia.

Interview data on exposures and their determinants

No direct local industrial hygiene data were available for exposure intensities of the study subjects. In face-to-face interviews, data on parental use of pesticides, tasks, major determinants of pesticide exposure [task and technology, personal protective equipment, field reentry, storing of pesticides, personal hygiene further determinants such as meteorological conditions, physical workload and working tempo were judged too unreliable to assess in the interview], were retrospectively asked for the etiologically relevant time period on a month-to-month basis. The relevant time period was taken as the period from 12 months before conception until diagnosis of the cancer for cases, and until either the interview date or age 15 of the controls, whichever occurred first. Checklists of pesticides enhanced the interview. The pesticides selected for the checklists exposure assessment were based on a toxicity-based prioritization system that was designed for this study (Valcke *et al*., in press). The interview procedure is described in detail in the paper by Monge *et al*. (2004). In short, the icon based interview form included calendar sheets, icon stickers for life events, crops, jobs, geographical regions, icons that were shown as paper lists for pesticide application techniques and personal protective equipment, markers for durations of exposure patterns, and checklists of specific pesticides.

The performance of the interview format appeared satisfactory for congruity (90% of the interview responses were judged by experts and interviewers to be internally congruent) and recall of events, crops, tasks and timing and other determinants of exposure (satisfactory responses 84–90%). The ICF and a conventional interview agreed at 92% consistency on time periods working in agriculture and on exposures to herbicides, insecticides and fungicides. Jobs and tasks were described for all interviewed subjects, and the ICF was able to capture variations in job histories among interviewed subjects within particular crop-task combinations. Easily recalled events helped timing of recall. Although job data were satisfactory, data on pesticides, though clearly improved by pesticide checklists, remained more deficient and will be augmented with auxiliary external data in the final assessment of individual exposures (Monge *et al*., 2004). Eighty-nine percent of the parents who were in agriculture or livestock breeding reported trade names of pesticides they had handled. Our experts checked these reports for any obvious inconsistencies and made corrections when needed. The external database on pesticide use (see next section) was used for this purpose. For the 11% with missing information on frequency of pesticide use or trade names of pesticides, similar expert assessment was applied.

Missing interview data for determinants were very few (2% of the agricultural/livestock breeding subjects), and were left missing unless expert judgment indicated a high-probability 'obvious' value.

EXTERNAL DATA ON EXPOSURES AND THEIR DETERMINANTS

Two approaches were taken: one with a model for one year prior to conception to year 1, and one unmodeled for years 2–14. Since there were no measurement data, we used application rate as a surrogate for exposure intensity, since this information was available. The interview data were combined with external data on 26 pesticides used on 14 different crops, during 21 years in 14 geographical regions of Costa Rica. Thus, each pesticide-crop-year-region combination has an application rate in the data base. The external data on application rate were obtained from a *Central American Institute for Studies in Toxic Substances-Universidad Nacional* (IRET-UNA) database that draws its data from databases of ministries, specialized crop offices and agricultural bank loan records (Wesseling and Bravo, 2002). These data were scrutinized by two experts to convert the data in all measurement units into liters/hectare of active ingredient. This quantity was denoted by U_{pycr}, where p = pesticide (1, 2, . . . , 26; Table 1); y = calendar year (1982, . . . , 2003); c = crop (1, 2, . . . , 14; Table 2); and r = geographical region (1, 2, . . . , 14). We converted the calendar time y into individual time t that had birth of the child as the 'zero time' reference (Miettinen 1985). The time-converted application rates were denoted U_{ptcr}, where t took five values, namely, year before conception; first trimester; second trimester; third trimester and first year of life of the child. The modeling of exposures was not done for ages 1–14 because parental exposure was judged to play a minor role in the induction of leukemia in the offspring during this period.

Exposure model

Individual exposure intensities were assessed for the selected pesticides for each time window for interviewees who worked in agriculture or were involved in pesticide application on livestock at any time during the exposure assessment period. Exposure models modified the aggregated data on application rate by interview-based data on determinants of exposure. The modeled pesticides, selected to represent the most frequently used ones during the assessment period, and the time windows for assessment are shown in Table 1. For practical reasons of estimation, respiratory exposure intensities were taken to be directly proportional to dermal exposure intensities. For interviewees who did not work in agriculture or livestock breeding during the target time periods, exposures to all pesticides were assumed to be zero. There were no jobs in the data outside agriculture and livestock breeding that had potential occupational exposure to pesticides.

Individual data on determinants of exposure derived from ICF-enhanced interviews included retrospective monthly data on frequency of application, tasks, personal protective equipment, time of reentry to sprayed area, storing of pesticides and personal hygiene. These primary data were converted into scores C of determinants d during time window t for subject i:

$$C_{ti} = \sum_{d=1}^{5} w_d H_{dti}$$

where w = relative weight for determinant d; H_{dti} = hazard value of category of determinant d; $\Sigma w_d = 1$. Hazard values H and weights w are shown in detail in the Appendix. The weights were determined in a four-expert consensus, and were subjected to a sensitivity analysis (section sensitivity analysis). Owing to the complexities in actual exposure situations, various refinements were necessary for the model specification. Thus, determinant(s) may have changed during a time window t. C_{dti} was then calculated as a time-weighted mean of subperiod-specific C_{di} values. C_{ti} is the subject's determinant score that modifies the pesticide application rate U by multiplication, in order to obtain an estimate of the subject's intensity of exposure I_{pti}:

$$I_{pti} = U_{ptcr} C_{ti}$$

Since I_{pti} is an estimate of exposure intensity during active exposure (particularly during periods of pesticide application, mixing or being in the field while pesticides were used by other workers), it measures high exposure days rather than average exposure intensity over time. The latter was estimated for an entire time period t as

$$A_{pti} = \theta_{pti} I_{pti} + (0.001)(1 - \theta_{pti})\left(I'_{pti}\right)$$

where θ_{pti} denotes individual time fraction of exposure, defined as working hours during application-level exposure for each pesticide, divided by maximum potential working hours, and I'_{pti} was defined in the same way as I_{pti}, but using individual hazard values during non-application exposure. Actual working hours were obtained from interview data, and the number of maximal annual working hours was taken as 1560. The multiplier 0.001 assumes that exposure intensity during active exposure (pesticides not applied but may be present, e.g. in plants and soil) exceeds background exposure during non-application by a factor of 10^3. In addition to this overall reduction of exposure level during nonapplication, individual determinants and consequently individual hazard values may have changed, as documented in the interview data, resulting in values of I' that are different from I, e.g. when agricultural tasks change between active exposure and nonapplication.

Table 1. List of intensity-modeled and un-modeled (unexposed/exposed) pesticides and groups of pesticides and time windows of parental exposure assessment

Pesticide	Time window																		
	P	I	II	III	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
2,4-D	M					U													
Picloram																			
Glyphosate																			
Benomyl																			
Chlorothalonil																			
Paraquat																			
Carbofuran																			
Cyproconazole																			
Mancozeb																			
Terbufos																			
Methamidophos																			
Deltamethrin																			
Methomyl																			
Triadimefon																			
Fluazifop																			
Captafol																			
Lead arsenate																			
Fenamiphos																			
Phoxim																			
Malathion																			
Dichlorvos																			
Terbuthylazine																			
Diuron																			
Oxamyl																			
Quintozene																			
Aldrin																			
Groups																			
Phenoxyacetic acids	U																		
Organophosphates																			
Carbamates																			
Dithiocarbamates																			
Pirethroids																			
Triazines																			
Benzimidazoles																			
Chlorinated phthalides																			
Conazoles																			
Copper																			
Chlorinated urea derivatives																			
Others																			

Time windows: P: 12 months before conception; I, II and III: trimesters of pregnancy; 0, 2, ..., 14: age of child (years); M: modeled; U: unmodeled; 2,4-D: 2,4-dichlorophenoxyacetic acid.

The model does not address cumulative exposure over time windows. This will be done in the epidemiological phase.

A separate indicator of confidence overall level in the interview data was attached to each interview, with categories of low, medium and high confidence, based on criteria on internal consistency of the data. This indicator was not incorporated in the exposure model, but will be included in the epidemiological analysis.

Table 2. Crops associated with the target pesticides in the population (mothers and fathers) during 1982–2003

Pesticide	Crop
2-4-D	Coffee, banana, rice, beans, corn, sugarcane
Picloram	Rice, sugar cane, pastures, corn
Glyphosate	Coffee, banana, rice, beans, corn, sugarcane, ornamentals
Benomyl	Coffee, rice, melon, banana, orange, ornamentals, potato
Chlorothalonil	Coffee, banana, rice, potato, ornamentals
Paraquat	Coffee, banana, rice, beans, corn, sugarcane, orange, plantain, ornamentals, tomato, pineapple,
Carbofuran	Coffee, corn, banana, melon
Cyproconazole	Coffee, ferns
Mancozeb	Coffee, beans, corn, potato, ornamental plants, plantain
Terbufos	Coffee, beans, rice, ornamental plants, pineapple, potato, sugarcane
Methamidophos	Coffee, rice, beans, potato, tomato, melon
Deltamethrin	Beans, corn, ornamental plants, pineapple, pastures
Methomyl	Beans, corn, potato, pastures
Triadimefon	Coffee, rice, beans
Fluazifop	Coffee, rice, beans, banana, melon
Captafol	Coffee, onion, tomato
Lead arsenate	Coffee
Fenamiphos	Coffee, potato, banana
Phoxim	Rice, sugarcane, banana
Malathion	Coffee, corn, plantain, macadamia
Dichlorvos	Coffee, livestock breading
Terbuthylazine	Coffee, corn, rice, pastures
Diuron	Coffee, corn, sugar cane, pineapple
Oxamyl	Potato, ferns, ornamental plants
Quintozene	Coffee
Aldrin	Coffee, pastures, rice, corn

2,4-D: 2,4-dichlorophenoxyacetic acid.

Unmodeled exposures

Simple unmodeled binary (no/yes) indicators of occupational exposure in agricultural areas, were derived from the interview and, whenever necessary, augmented by external data, for

(i) all 26 modeled pesticides (Table 1) during the 2nd, 3rd, . . . , 14th year of life of the child; and
(ii) selected 14 chemical groups of pesticides (Table 1) for all t, where any exposure to one of the compounds of the chemical group was sufficient to trigger 'exposure'. The chemical groups included also the generic group 'any pesticides(s)'.

Sensitivity analysis

A sensitivity analysis of the exposure model was done by changing the weights w for each determinant within realistic limits. The weight for task and technology was changed from 0.4 to 0.7, that for personal protective equipment reduced from 0.2 to 0.15, and those for each of the remaining determinants to 0.05. The hazard values H were assumed to be reasonably valid and therefore were not subjected to sensitivity analysis.

A random number generator generated 10 000 sets of H_{di} from uniform distributions of each d. Original and changed weights were then applied to each of the 10 000 sets. Two C scores were thus calculated for each set and intercorrelated (Spearman coefficient of correlations).

The calculations were done with STATISTICA '99 edition, and the simulated data were generated with MINITAB software.

RESULTS

Table 2 shows the crops encountered for each pesticide during the entire relevant period of exposures (1982–2003). Table 3 shows application rates and numbers of subjects exposed to each modeled pesticide during 1982–2003. Table 4 shows the numbers of exposed fathers and mothers and the exposure intensities during active application (I) and all time (A) for each pesticide during second trimester of pregnancy. The second trimester was selected because of the highest frequency of reported agricultural activity. Spearman correlation coefficients between I and A values for each modeled pesticide are also shown for the entire period of exposure assessment, counting all time windows, and excluding zero (no exposure) values.

The number of exposed fathers were larger than those of exposed mothers, and median exposure intensities among exposed were for some pesticides higher for fathers and for others higher in mothers.

Differences between A and I values were determined primarily by time fraction of exposure (θ) and, to a lesser extent, by difference in determinant values between active and nonactive exposure. The highest correlations (Pearson coefficient) between A and I were obtained for deltamethrin (0.80), aldrin (0.79), fluazifop (0.73) and carbofuran (0.71). There were a number of pesticides with correlations <0.4 [2,4-dichlorophenoxyacetic acid (2,4-D), benomyl, paraquat, mancozeb, terbufos, triadimefon, lead arsenate, dichlorvos, terbuthylazine and quintozene]. As was already clear conceptually, I and A values thus appeared to measure different dimensions of exposure intensity also empirically.

Table 5 shows medians and ranges of annual numbers of work phases with application-level exposure ('active' exposure), and number of months and time

Table 3. Distributions of application rate *U* (liters of active ingredient/hectare) in the parents of children [mothers and fathers pooled; exposed subjects only (n_e)]

Pesticide	n_e	*U* l/ha (range)
2,4-D	89	0.28–1.44
Picloram	36	0.3–1.2
Glyphosate	122	0.1–2.0
Benomyl	47	0.1–1.0
Chlorothalonil	28	0.74–1.08
Paraquat	162	0.20–0.80
Carbofuran	31	0.05–2.5
Cyproconazole	23	0.08–0.08
Mancozeb	46	0.2–12.0
Terbufos	83	1.5–7.0
Methamidophos	42	0.6–0.9
Deltamethrin	21	0.005–0.25
Methomyl	14	0.67–0.68
Triadimefon	11	0.5–0.5
Fluazifop	12	0.18–0.25
Captafol	13	0.6–6.0
Lead arsenate	9	0.65–0.66
Fenamiphos	26	5.4–16.20
Phoxim	13	0.12–0.13
Malathion	17	0.43–0.60
Dichlorvos	30	0.10–0.10
Terbuthylazine	16	1.0–2.15
Diuron	23	0.56–3.20
Oxamyl	6	1.2–1.2
Quintozene	6	150–300
Aldrin	4	1.5–6.6

Values of *U* refer to all time periods (1982–2003). 2,4-D: 2,4-dichlorophenoxyacetic acid.

fraction (θ) of such work for all pesticides pooled and for the two most frequently used pesticides (glyphosate and paraquat).

In the sensitivity analyses, the correlation coefficient between (0.4, 0.2, 0.1, 0.15, 0.15)-weighted and (0.7, 0.15, 0.05, 0.05, 0.05)-weighted hazard values in the simulated data was 0.91.

DISCUSSION

We developed a model for retrospective assessment of parental exposure to 26 pesticides in a case–control study of childhood leukemia in Costa Rica. The model combined external data on pesticide application rate on 14 crops, 21 calendar years, and 14 geographical regions, with interview data on individual determinants of exposure.

The interview data combined a calendar based, time-windowed data on exposures of pesticide use, crops and determinants of exposure with chronicling of major life events to enhance recall (Hoppin *et al.*, 1998; Monge *et al.*, 2004). Validity of self-reported past exposures to specific agents and trade names of substances and mixtures is low, but checklists improve the assessment (Teschke, 2002). In general, validation of retrospective exposure data is extremely difficult, since the true exposure histories remain unknown (Blair *et al.*, 1997; Stewart *et al.*, 1998). Nevertheless, jobs and tasks were described in our ICF for all interviewed subjects, and individual variations in job histories of subjects and determinant data within particular crop-task combinations were obtained properly (Monge *et al.*, 2004). Another strength was the assessment by time windows, which was done in the context of the objectives of the study in relation with parental exposure to pesticides.

The model does not assess direct exposure of children or even trans-placental exposure of the fetus. The effects on the offspring may pertain to critical effects of xenobiotics in parents, such as genetic alterations in the sperm or ovum, which in turn influence the fetus and its development. The breakdown into trimesters have general etiologic significance, and mothers' exposure patterns also varied between trimesters in our data (not documented). Infant's and children's postnatal exposure will be assessed separately later in our study.

Being proportional measures, the intensities *I* and *A* do not measure absolute levels of exposure as do the conventional metrics of exposure intensity, and therefore are not comparable between different pesticides. Correlations between *I* and *A* tended to be low. This suggests that different dimensions of exposure are being measured, as intended, *I* values being influenced by shorter-term exposures, and *A* being akin to time-weighed average type of exposure indicator.

Few mothers were exposed compared with fathers. Exposure levels varied between fathers and mothers, depending on pesticide. Women usually helped in planting, harvesting, cutting and picking, nursery jobs, packing, or milking the cows, while men were involved in all types of jobs, including spraying and other application, mixing, and field preparation with pesticides.

The databank that provided application rates of pesticides by calendar year, crop and geographical region drew its data from official databases, crop offices, recommendations on pesticide use for bank loans for agricultural purposes and expert assessments. The data elements were usually single values, but occasionally in ranges (in the latter case, means were calculated). In addition, commercial names were used for the interviews, which sometimes involved different concentrations of active ingredient. The concentrations were checked from industrial sources and recommendations, and different units that appeared in the database were all converted to liters/hectare of active ingredient.

The validity of the present model cannot be directly evaluated in the lack of any meaningful empirical

Table 4. Distributions of exposure indicators in the parents of the children, between exposure intensity during active exposure (*I*) and during entire trimester (*A*)

Pesticide	During active exposure (*I*)						During entire trimester (*A*)				*R*
	Fathers			Mothers			Fathers		Mothers		
	n_e	Median	Range	n_e	Median	Range	Median	Range	Median	Range	
2,4-D	39	1.25	0.49–5.55	1	0.97	—	0.10	0.01–2.40	0.02	—	0.31
Picloram	13	2.06	0.64–3.13	4	2.21	0.71–2.94	0.20	0.02–2.9	0.10	0.006–1.06	0.57
Glyphosate	59	1.39	0.19–2.73	3	1.98	0.71–2.38	0.11	0.01–1.39	0.01	0.01–0.88	0.26
Benomyl	22	0.36	0.25–2.55	1	0.41	—	0.03	0.001–1.16	0.01	—	0.38
Chlorothalonil	11	2.60	1.89–14.80	1	8.70	—	0.54	0.01–4.64	1.30	—	0.62
Paraquat	74	1.28	0.38–2.17	4	0.95	0.70–1.02	0.10	0.001–0.16	0.12	0.04–0.26	0.16
Carbofuran	9	0.46	0.12–4.75	0	—	—	0.01	0.001–0.44	—	—	0.71
Cyproconazole	3	0.20	0.08–0.21	1	0.20	—	0.02	0.002–0.02	0.002	—	0.43
Mancozeb	28	2.31	0.42–4.50	1	2.60	—	0.08	0.01–2.90	0.40	—	0.38
Terbufos	34	7.82	3.47–16.66	2	5.29	2.60–7.98	0.35	0.01–9.90	0.14	0.11–0.17	0.35
Methamidophos	14	1.56	1.16–2.44	3	1.40	1.37–1.56	0.07	0.02–0.49	0.07	0.03–0.11	0.62
Deltamethrin	11	0.01	0.01–0.67		—	—	0.01	0.0001–0.04	—	—	0.80
Methomyl	3	1.48	1.48–1.74	2	0.87	0.87–0.87	0.07	0.02–0.22	0.09	0.04–0.13	0.15
Triadimefon	3	1.06	0.87–1.43	—	—	—	0.11	0.10–0.12	—	—	0.01
Fluazifop	2	0.50	0.36–0.64	—	—	—	0.26	0.05–0.48	—	—	0.73
Captafol	4	1.80	1.51–3.48	—	—	—	1.35	0.07–3.48	—	—	0.64
Lead arsenate	4	1.63	1.49–1.88	—	—	—	0.05	0.02–0.09	—	—	0.27
Fenamiphos	11	10.91	6.08–13.18	1	38.10	—	0.55	0.03–1.99	2.20	—	0.45
Phoxim	6	1.66	0.24–7.83	1	7.14	—	0.16	0.01–1.78	0.23	—	0.61
Malathion	7	1.30	0.75–1.93	—	—	—	0.12	0.002–1.11	—	—	0.50
Dichlorvos	13	0.26	0.19–0.29	—	—	—	0.00	0.001–0.11	—	—	0.07
Terbuthylazine	4	3.70	2.31–5.52	—	—	—	1.27	0.21–4.14	—	—	0.28
Diuron	10	4.15	1.06–7.78	1	3.81	—	0.60	0.06–4.61	0.18	—	0.54
Oxamyl	3	3.14	2.89–3.35	—	—	—	0.05	0.05–0.54	—	—	0.46
Quintozene	2	175.82	3.65–348.0	—	—	—	174.02	0.05–348.0	—	—	−0.17
Aldrin	—	—	—	—	—	—	—	—	—	—	0.79

Exposed subjects only [n_e]). n_es and medians and ranges of *I* and *A* refer to the second trimester of pregnancy. Spearman correlation coefficients (*R*) between *I* and *A* calculated for exposed subjects, pooling mothers and fathers and all time windows, thus counting all period-person combinations separately. 2,4-D: 2,4-dichlorophenoxyacetic acid.

Table 5. Annual number of work phases with application level exposure, time fraction (θ) and annual number of months of such phases for all pesticides, glyphosate and paraquat at all time during the assessment period

Pesticide	Fathers			Mothers		
	n	Median	Range	*n*	Median	Range
All pesticides						
No. of work phases per year	201	8.5	1–240	21	9.0	1–150
θ		0.04	0.001–1.00		0.05	0.001–0.38
No. of months/year		2.0	1–12		3.0	1–12
Glyphosate						
No. of work phases per year	112	12.0	1–240	10	5.0	2–50
θ		0.05	0.001–1.00		0.01	0.001–0.38
No. of months/year		3.0	1–12		3.0	1–12
Paraquat						
No. of work phases per year	149	12.0	1–240	13	12.0	2–72
θ		0.06	0.01–1.00		0.15	0.01–0.69
No. of months/year		3.0	1–12		3.0	1–12

All person-phases combinations during all subperiods of 1982–2003 counted. *n*, number of subjects.

criterion data. The validity issue may be approached by a critical scrutiny of the major components of the model and their interlinkages in terms of content and structure. First, the application rates were specific to combinations of crop, pesticide, calendar year and region. These data were further re-evaluated by our experts for the purposes of the study.

An important validity consideration pertains to the question of to what extent the application rate, expressed as volume of active ingredient per surface area, can be interpreted as a valid substitute for the intensity of potential individual exposure. It seems obvious that increasing rate of sprayed pesticide volume would increase the probability and intensity of potential individual exposure. However, application technology and other determinants modify the general exposure potential. The important modifying factors or individual determinants of exposure, assessed by the interviews, were therefore expressly built in the model, thus individualizing the general exposure potential.

The hazard values (H) were based on an inter-expert consensus after several group discussions on different candidate sets of values. The experts included persons with field experience in Costa Rica. Research reports were scrutinized for experiences gained elsewhere.

The validity of the weights (w) of the hazard values could not be directly assessed. In like manner with the hazard values, the final weights were results of expert consensus. In addition, a sensitivity check between two sets of weights resulted in a correlation of 0.91 between C values based on the sets, suggesting satisfactory robustness of the weighting.

Different models were originally tested for reasonableness. It was rather straightforward to agree that the application rates would need to be modified by individual determinant data by multiplication. Options for the structure of the modifier itself for the calculation of exposure intensities were (i) selection of the highest individual hazard value only; (ii) using an additive form to calculate the overall individual modifier C, which corresponds to the arithmetic mean of the products of weights and hazard values; and (iii) using the antilog of the products of weights and hazards, which corresponds to the geometric mean-type indicator. Alternative (i) was rejected because it is entirely determined by the highest individual hazard. Option (iii) was rejected because it reduces considerably the impact of a solitary high hazard value when such value exists. The additive structure (ii) was chosen since it considers all hazards and provides, as it was felt, an appropriate weight to high hazards.

Summing up the validity considerations, we feel that the application volume data are reasonably valid for the purpose of considering comparable databanks. The hazards (H) and the weights (w) of the hazards were selected to reproduce actual hazards and their weights, and the weights were subjected to a sensitivity test, which resulted in satisfactory repeatability with regard to final exposure estimates. The structure of the model was chosen that gives due weight to high hazards and includes the impact of lower hazards.

Acknowledgements—We thank Fabio Chaverri and Fernando Ramírez for their review of the external data on pesticide application used in the model in different times during the development of the model, and to Ingvar Lundberg for suggestions and comments.

REFERENCES

Arbuckle TE, Burnett R, Cole D *et al*. (2002) Predictors of herbicide exposure in farm applicators. Int Arch Occup Environ Health; 75: 406–14.

Blair A, Stewart P, Kross B *et al*. (1997) Comparison of two techniques to obtain information on pesticide use from Iowa farmers by interview. J Agricult Safety Health; 3: 229–36.

Burstyn I, Teschke K. (1999) Studying the determinants of exposure: A review of methods. Am Ind Hyg Assoc J; 60: 57–72.

Gérin M, Siemiatycki J, Kemper H *et al*. (1985) Obtaining occupational exposure histories in epidemiologic case-control studies. J Occup Med; 27: 420–6.

Hoppin JA, Tolbert PE, Flagg EW, *et al*. (1998) Use of a life events calendar approach to elicit occupational history from farmers. Am J Ind Med; 34: 470–6.

Miettinen OS. (1985) Theoretical Epidemiology: principles of Occurrence Research in Medicine. New York: Wiley.

Monge P, Wesseling C, Engel L *et al*. (2004) An icon-based Interview for the Assessment of Occupational Pesticide Exposure in a Case-Control Study of Childhood Leukemia. Int J Occup Environ Health; 10: 72–8.

Siemiatycki J. (1991) Risk factors for cancer in the workplace. Boca Raton: CRC Press.

Stewart WF, Stewart PA. (1994a) Occupational case-control studies I: collecting information on work histories and work-related exposure. Am J Ind Med; 26: 297–312.

Stewart PA, Stewart WF. (1994b) Occupational case-control studies II: recommendations for exposure assessment. Am J Ind Med; 26: 313–26.

Stewart PA, Stewart WF, Siemiatycki J, *et al*. (1998) Questionnaires for collecting detailed occupational information for community-based case-control studies. Am Ind Hyg Ass J; 58: 39–44.

Teschke K, Olshan AF, Daniels JL *et al*. (2002) Occupational exposure assessment in case-control studies: opportunities for improvement. Occup Environ Med; 59: 575–94.

Valcke M, Chaverri F, Monge P *et al*. (2005) Pesticide prioritization for a case-control study on childhood leukaemia in Costa Rica: a simple stepwise approach. Environmental research; 97.

Wesseling C, Bravo V. (2002) Pesticide use on the main crops of Costa Rica 1970–2000. Data for retrospective exposure assessment in epidemiologic studies. Report to the US National Cancer Institute. Heredia, Costa Rica: Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional.

APPENDIX

General relative weights (w_d) of determinants (d) and hazard values of tasks (H_d). $H_d = 0$: no exposure; $H_d \geqslant 4$: very high exposure

Determinant	H_d	Determinant	H_d
d_1: Task ($w_1 = 0.40$)		d_2: Personal protective equipment ($w_2 = 0.20$)	
1: Work with no exposure to pesticides		1: Work with no exposure to pesticides	0
Nonagricultural	0	Nonagricultural	0
Coffee picking	0	Coffee picking	0
Organic agriculture	0	Organic agriculture	1.2
2: Tasks with possible indirect contact with pesticides[a]		2: No hat	1.2
		3: No respirator	1.2
All agricultural work done without use of pesticides	1	4: No apron or back protection	1.5
		5: Short sleeves	1.5
Preparation/cleaning of field/weeding	1	6: Shorts	2.0
Planting	1	7: No gloves	2.0
Harvesting/cutting/picking	1	8: No boots	
Transportation	1	9: Combinations	
Tractor driving	1	All combinations have an attached hazard	
Foreman	1	value H_2, with a range	1.4
Agricultural teacher	1	from combinations 2, 3 or 2, 4 and 3, 4	
Garden maintenance	1	to combination 2, 3, 4, 5, 6, 7, 8	4.6
Work with cattle	1	d_3: Storage of pesticides ($w_3 = 0.15$)	
Watering of plants	1	1: Work with no exposure to pesticides	
Tree felling	1	Nonagricultural	0
Milking	1	Coffee picking	0
Country road or fence construction	1	Organic agriculture	0
3: Tasks with confirmed indirect and possible direct contact with pesticides[b]	2	2: Built storage outside house	1.0
		3: Outside house, no built storage	1.2
Packing plant	2	4: Inside house, e.g., kitchen	2.0
Planting	2	5: Bedroom	2.5
Preparation/cleaning of field/weeding	2		
Harvesting/cutting/picking	2	d_4: Field reentry ($w_4 = 0.10$)	
Foreman	2	1: Work with no exposure to pesticides	
Washing fruits or vegetables	2	Nonagricultural	0
Fertilizing	2	Coffee picking	0
Cutting sprouts	2	Organic agriculture	0
Defoliating	2	2: >1 week after application	1.0
Day laborer	2	3: 5 days–1 week	1.2
Nursery	2	4: 2–4 days	1.5
Maintenance of drainage canals	2	5: 1 day	2.0
Gardener	2	6: 1–12 h	3.0
Grafting	2	7: <1 h	4.0
Applicator on tractor	2		
4: Tasks with application or confirmed direct contact with pesticides[c]	3	d_5: Personal hygiene ($w_4 = 0.15$)	
		1: Work with no exposure to pesticides	
Backpack application	3	Nonagricultural	0
Mixing (occasional)	3	Coffee picking	0
Bathing, spraying or dipping of cattle	3	Organic agriculture	0
Bagging (of banana fruit)	3	2: Showering immediately, washing hands before	1.0
Spraying of product at packing plant	3	eating, and using clean clothes	
Pesticide storehouse keeper	3	3: Not showering immediately after work	1.5

Determinant	H_d	Determinant	H_d
Any other task involving application of pesticides or direct contact	3	4: Not washing hands before eating	2.0
		5: Reusing unwashed clothes	2.5
5: Professional mixer	3	6: 3, 4	2.5
6: Airport worker for aerial spraying	3	7: 3, 5	3.0
7: Application of pesticides with the hand	4	8: 4, 5	3.5
		9: 3, 4, 5	4.0

[a]Agricultural work without referral of use of pesticides, but where the possibility of being near sources of pesticide emissions cannot be excluded.
[b]Agricultural work close to known or referred sources of pesticide emissions.
[c]Agricultural work with pesticide use.