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Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN

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ABSTRACT

Background: Pesticides exposures could be implicated in the excess of Central Nervous System (CNS) tumors observed in farmers, but evidence concerning individual pesticides remains limited. Carbamate derivative pesticides, including herbicides and fungicides (*i.e.* (thio/dithio)-carbamates), have shown evidence of carcinogenicity in experimental studies in animals. In the French AGRICAN cohort, we assessed the associations between potential exposures to carbamate herbicides and fungicides and the incidence of CNS tumors, overall and by histological subtype.

Methods: AGRICAN enrolled 181,842 participants involved in agriculture. Incident CNS tumors were identified by linkage with cancer registries from enrollment (2005–2007) until 2013. Individual exposures were assessed by combining information on lifetime periods of pesticide use on crops and the French crop-exposure matrix PESTIMAT, for each of the 14 carbamate and thiocarbamate herbicides and the 16 carbamate and dithiocarbamate fungicides registered in France since 1950. Associations were estimated using proportional hazard models with age as the underlying timescale, adjusting for gender, educational level and smoking.

Results: During an average follow-up of 6.9 years, 381 incident cases of CNS tumors occurred, including 164 gliomas and 134 meningiomas. Analyses showed increased risks of CNS tumors with overall exposure to carbamate fungicides (Hazard Ratio, HR = 1.88; 95% CI: 1.27–2.79) and, to a lesser extent, to carbamate herbicides (HR = 1.44; 95% CI: 0.94–2.22). Positive associations were observed with specific carbamates, including some fungicides (mancozeb, maneb, metiram) and herbicides (chlorpropham, propham, diallate) already suspected of being carcinogens in humans.

Conclusions: Although some associations need to be corroborate in further studies and should be interpreted cautiously, these findings provide additional carcinogenicity evidence for several carbamate fungicides and herbicides.

1. Introduction

Adverse health effects of pesticides in humans, such as neurodegenerative diseases and cancers have been predominantly documented for insecticides, as evidenced by the large number of studies on organochlorines and organophosphates in recent decades (Ntzani et al., 2013; Institut national de la santé et de la recherche médicale [FRENCH], 2013). However, fungicides and herbicides are widely used in agriculture (on a wide range of crops) and outside agriculture (gardening, weeding roads and railways, wood industry, etc.) (Carles et al., 2017) and they are the most commonly sold among pesticides in Europe (173 and 131 kt in 2013, respectively), far ahead of insecticides (21 kt) (Eurostat, 2014).

Carbamates contain a wide variety of molecules used since the 1960s, both in humans as drugs acting on the central nervous system (e.g. meprobamate, felbamate) and in agriculture as insecticides, herbicides or fungicides. They share a set of common features, related to analogue pharmacophores (R-O-CO-NH-R′ for carbamates), sulfured in herbicide thiocarbamates (R-O-CS-NH-R′/R-S-CO-NH-R′) and di-sulfured in fungicide dithiocarbamates (R-S-CS-NH-R′). Among the 26.4 kt of carbamate pesticides (i.e. (thio/dithio)-carbamates) sold between 2011 and 2015 in France, 89% were fungicides, 8% were herbicides and 3% insecticides.(Agreste, 2017) In 2018, 5 of the 14 herbicides (7 carbamates and 7 thiocarbamates) and 10 of the 16 fungicides (5 carbamates and 11 dithiocarbamates) which have been marketed for various uses on crops in Europe, are still registered (Table 1).

Experimental studies on carbamate herbicides and fungicides show increased risks of tumors in various organs (liver, kidney, thyroid, adrenal gland, bladder, uterus, bones), so that some of them are considered as “probable human carcinogens” (benthiavalicarb-isopropyl, iprovalicarb, propineb, mancozeb, maneb, and metiram) or “possible human carcinogens” (asulam, triallate) by the Environmental Protection Agency (EPA) (EPA archives, 2018). In addition, they are “suspected of causing cancer” (chlorpropham, diallate) by the European Chemicals Agency (ECHA) (ECHA, 2018), but they are “not classifiable as to their carcinogenicity to humans” (chlorpropham, diallate, ferbam, maneb, propham, thiram, zineb and ziram) by the International Agency for Research on Cancer (IARC) because there are no adequate data in humans and inadequate evidence in animals (Table 1) (IARC, 2018).

In the epidemiologic literature, three meta-analyses showed higher risks of brain cancers in farmers (Blair et al., 1992; Acquavella et al., 1998; Khuder et al., 1998), and pesticide exposure — including herbicides and fungicides (Musicco et al., 1988; Samanic et al., 2005; De Roos et al., 2003; Cocco et al., 1999; Lee et al., 2005; Carreón et al., 2005; Ruder et al., 2004; Yiin et al., 2012) — is a leading hypothesis to explain these findings (Piel et al., 2017). Among the suspected carcinogenic mechanisms, those involving the generation of oxidative stress (Gupta, 2005; Mathieu et al., 2015; Ben Amara et al., 2015; Dennis and Valentine, 2015) could be particularly relevant for CNS tumors (Gupta, 2004). To date, two case-control studies conducted in US rural areas (mainly covered by open field crops) have explored the link between CNS tumors (only gliomas) and occupational exposures to carbamate insecticides, fungicides and/or herbicides: (Lee et al., 2005; Carreón et al., 2005; Ruder et al., 2004; Yiin et al., 2012) increasing risk trends were observed in exposed farmers (OR ranged from 1.2 to 3.0), but these studies were limited by statistical power (due to the number of exposed cases, between 4 and 55) and possible non-differential and differential classification errors (suggested by the authors due to the sensitivity of results to exclusion of proxy-respondents).

In the French agricultural cohort AGRICAN (AGRIculture & CANcer), analyses focusing on CNS tumors and adjusted for a variety of potential confounders (including age, gender, educational level, smoking history and alcohol consumption) provided more specific results on pesticides. The main increased risks were found among farmers using pesticides on beets (Hazard Ratio, HR = 2.7; 95% CI: 1.5–4.8) and potatoes (HR = 2.1; 95% CI: 1.2–3.8) (Piel et al., 2017), two crops requiring respectively, 15 herbicides treatments and 13 fungicide treatments on average each year in France (Agreste, 2014). Further analyses of carbamate insecticides showed consistent positive associations with CNS tumors (Piel et al., 2018): they reinforced carcinogenicity evidence for active ingredients that were already suspected (carbaryl, fenoxycarb and thiodicarb) and drew attention to additional active ingredients (formetanate, dioxacarb, promecarb, isolan, thiofanox and methomyl). Therefore, carbamate insecticide exposure appears to be a leading hypothesis to explain CNS tumor excess in farmers and the question may also be raised for the other carbamate pesticides.

The aim of this analysis was to investigate, within the French prospective cohort AGRICAN, the associations between the incidence of primary CNS tumors over the period 2005–2013 (overall and for gliomas and meningiomas) and lifetime agricultural exposures to carbamate herbicides and fungicides.

2. Material and methods

2.1. Population

The French longitudinal cohort AGRICAN has been previously described in detail (Levêque-Morlais et al., 2015). Briefly, a postal questionnaire was

Table 1
Summary of the carcinogenicity evaluations (IARC, EPA), hazard statements (ECHA) and registered uses in France of the carbamate herbicides and fungicides under study, AGRICAN

Pesticide carbamate		Carcinogenicity evaluation		ECHA Classification	Modes of action	Registered uses in France			
Name	CAS number	IARC [a]	EPA [b]	Hazard statements [c]	HRAC [d] / FRAC [e]	Period [f]		Crops (/11) [g]	PPP [h]
Carbamate herbicides									
Asulam	3337-71-1		C (2001)	ND	I	1971	2015	1	7
Barban	101-27-9			H302, H317, H400, H410	K2	1962	1988	1	1
Chlorbufam	1967-16-4			ND	K2	1961	1993	1	1*
Chlorpropham	101-21-3	3 (1987)	E (1997)	**H351**, H373, H411	K2	1962	> 2017	2	112*
Desmedipham	13684-56-5		E (1995)	H400, H410	C1	1989	> 2017	1	25*
Phenmedipham	13684-63-4		D (1993)	H400, H410	C1	1967	> 2017	1	111*
Propham	122-42-9	3 (1987)		ND	K2	1963	1999	1	21*
Thiocarbamate herbicides									
Butylate	2008-41-5		E (1992)	ND	N	1971	1992	1	1
Cycloate	1134-23-2		E (2003)	ND	N	1962	2005	1	7*
Diallate	2303-16-4	3 (1987)		H302, **H351**, H400, H410	N	1962	1999	3	6*
EPTC	759-94-4		E (1999)	H302	N	1975	2002	2	6*
Prosulfocarb	52888-80-9			H302, H317, H411	N	1989	> 2017	2	7*
Triallate	2303-17-5		C (1994)	H302, H317, H373, H400, H410	N	1967	> 2017	5	16*
Vernolate	1929-77-7			H302, H411	N	1975	2003	1	3
Carbamate fungicides									
Benthiavalicarb	177406-68-7		B (2008)	ND	H5	2008	> 2017	2	4*
Diethofencarb	87130-20-9			ND	B2	1987	2010	2	3*
Iprovalicarb	140923-17-7		B (2002)	ND	H5	2001	> 2017	1	10*
Propamocarb	24579-73-5			ND	F4	1996	> 2017	1	22*
Valifenalate	283159-90-0			ND	H5	2011	> 2017	1	5*
Dithiocarbamate fungicides									
Cupreb	16071-84-4			ND	M	1958	1968	2	1
Cuprobam	7076-63-3			ND	M	1962	1970	2	1
Ferbam	14484-64-1	3 (1987)		H315, H319, H335, H400, H410	M	1960	1997	3	4*
Mancopper	53988-93-5			ND	M	1968	2002	2	3*
Mancozeb	8018-01-7		B (1999)	H317, H361d, H400	M	1962	> 2017	5	412*
Maneb	12427-38-2	3 (1987)	B (1999)	H317, H319, H332, H361d, H400, H410	M	1960	> 2017	6	313*
Metiram	9006-42-2		B (1999)	ND	M	1959	> 2017	4	17*
Propineb	12071-83-9		B (2013)	ND	M	1963	> 2017	4	8*
Thiram	137-26-8	3 (1987)	E (2003)	H302, H315, H317, H319, H332, H373, H400, H410	M	1954	> 2017	6	140*
Zineb	12122-67-7	3 (1987)		H317, H335	M	1954	2002	3	231*
Ziram	137-30-4	3 (1987)	D (2003)	H302, H317, H318, H330, H335, H373, H400, H410	M	1956	> 2017	3	40*

CAS: Chemical Abstracts Service; ECHA: European Chemicals Agency; EPA: Environmental Protection Agency; FRAC: Fungicide Resistance Action Committee; HRAC: Herbicide Resistance Action Committee; IARC: International Agency for Research on Cancer; ND: Not Determined; PPP: Plant Protection Product
[a] IARC: 3 (not classifiable as to its carcinogenicity to humans); [b] EPA: B (probably carcinogenic to humans), C (possible carcinogenic to humans), D (not classifiable as to human carcinogenicity or suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential), E (evidence of non-carcinogenicity for humans or not likely to be carcinogenic to humans); [c] Hazard statements from Annex VI of the CLP Regulation (classification, labelling and packaging of substances and mixtures) according to GHS (globally harmonized system): H302 (harmful if swallowed), H315 (causes skin irritation), H317 (may cause an allergic skin reaction), H318 (causes serious eye damage), H319 (causes serious eye irritation), H330 (fatal if inhaled), H332 (harmful if inhaled), H335 (may cause respiratory irritation), **H351** (suspected of causing cancer), H361d (suspected of damaging the unborn child), H373 (may cause damage to organs through prolonged or repeated exposure), H400 (very toxic to aquatic life), H410 (very toxic to aquatic life with long-lasting effects), H411 (toxic to aquatic life with long-lasting effects); [d] HRAC: C1 (inhibition of photosynthesis at photosystem II), I (inhibition of dihydropteroate synthase), K2 (inhibition of mitosis / microtubule organization), N (inhibition of lipid synthesis); [e] FRAC: B2 (cytoskeleton and motor proteins, β-tubulin assembly in mitosis, N-phenylcarbamates), F4 (lipid synthesis and membrane integrity, cell membrane permeability, fatty acids), H5 (cell wall biosynthesis, cellulose synthase), M (multi-site contact activity); [f] Registered periods according to PESTIMAT; [g] Crops under study in AGRICAN: vineyards, wheat and/or barley, corn, fruits, rape, potatoes, sunflowers, peas and/or field beans, beets, tobacco and grassland; [h] Number of PPP registered in France (*: several active ingredients associated in at least one of the PPP)

sent to the source population: all adults living in one of the 11 selected administrative geographical areas (selected because covered by certified cancer registries: Bas-Rhin, Côte d'Or, Doubs, Gironde, Haut-Rhin, Isère, Loire-Atlantique, Manche, Somme, Tarn, Vendée) and affiliated during at least 3 years on January 1st 2004 to the French health insurance for people involved in agriculture-related activities [Mutualité Sociale Agricole (MSA)]. Between 2005 and 2007, 181,842 eligible individuals were enrolled by filling out and sending back the questionnaire and providing their informed consent: men and women, active and retired, farm owners, farmworkers and other individuals working in agricultural-related activities (gardeners, foresters, sawmill-workers, clerical workers in agricultural bodies, etc.). The study protocol was reviewed and approved by the Advisory Committee on Information Processing in Material Research in the Field of Health (Comité consultatif sur le traitement de l'information en matière de recherche; number: 01.148) and the French data protection authority (Commission Nationale de l'Informatique et des Libertés; number: 05.1292).

The enrollment questionnaire included a complete job calendar with a lifetime history of occupational activities, socio-demographic characteristics at enrolment (including occupational status, educational level, familial status), lifestyle habits (including history of tobacco smoking and alcohol consumption, by distinguishing occasional and regular consumers according to the median of consumption frequency: 23 and 8 glasses a month, respectively for men and women) and some health data (including history of allergic diseases, defined as hay fever and/or eczema). Participants were also asked if they had ever worked in farms, growing any of 13 crops (grassland, vineyards, corn, wheat/barley, pea/field bean, beet, sunflower, rape, tobacco, fruits, potatoes, field-grown vegetable and greenhouse) and 5 farm animals (cattle, sheep/goats, pigs, horses and/or poultry). Where applicable, farmers were asked if

they had ever performed specific tasks in relation to these crops (2 to 5 tasks: seeding treatment on the farm, sowing, pesticide treatment, harvesting, etc.) and if so, the start and end years and the surface of the crop for each task.

2.2. Cohort follow-up and case ascertainment

The observation time started from enrollment (date when the questionnaire was returned) and ended when participants were diagnosed with a CNS tumor, died, moved out of the study areas or when the follow-up ended (December 31st, 2013), whichever occurred first. Vital status and date of death (when appropriate) of all participants were checked annually by crossing the database with the MSA files and with the French National Death Index (Répertoire National pour l'Identification des Personnes Physiques). Place of residence and affiliation to the health insurance scheme were checked annually in the MSA database. Incident cases of primary CNS tumors were ascertained every 2 years through linkages to cancer registries in each study area. Dates of diagnosis were obtained as well as histological types, coded according to the International Classification of Diseases for Oncology (3rd edition): (Louis et al., 2016) neuro-epithelial tumors classified as gliomas (9380/3, 9382/3, 9383/1, 9391/3, 9400/3, 9401/3, 9411/3, 9413/0, 9440/3, 9442/3, 9450/3, 9451/3 and 9460/3), meningeal tumors classified as meningiomas (9530/0, 9530/1, 9530/3, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/1 and 9539/1) and other CNS tumors (9080/0, 9540/0, 9560/0, 9560/3, 9591/3, 9680/3, 8000/0, 8000/1 and 8000/3).

2.3. Exposure assessment

Seven carbamate herbicides (asulam, barban, chlorbufam, chlorpropham, desmedipham, phenmedipham, propham), seven thiocarbamate herbicides (butylate, cycloate, diallate, EPTC, prosulfocarb, triallate, vernolate), three carbamate fungicides (diethofencarb, iprovalicarb, propamocarb) and eleven dithiocarbamate fungicides (cupreb, cuprobam, ferbam, mancopper, mancozeb, maneb, metiram, propineb, thiram, zineb, ziram) were identified as potentially used in agriculture in mainland France between 1950 and enrolment (Table 1). Benthiavalicarb and valifenalate were not considered in the present study because they have been registered only after AGRICAN enrollment. The assessment of individual exposure to each of the 28 active ingredients under study was based on the combination of information on a complete job calendar with lifetime use of pesticides on crops (obtained from enrollment questionnaire) and the French PESTIMAT Crop-Exposure Matrix (CEM) (Baldi et al., 2017). This exposure assessment, allowed us to consider all carbamates registered in France, without relying on participant memory on use of specific pesticides.

The PESTIMAT CEM reviews pesticide use in France since 1950 on the main crops. For a given crop and a given active ingredient, annual exposure parameters were assessed through a combination of several sources of information about pesticide registration, sales and recommended use, the current version of PESTIMAT (December 1st, 2018) indicated whether a specific carbamate was registered for use on 11 of the 13 crops recorded in the AGRICAN questionnaire (information were not available for field-grown vegetables and greenhouses, as these agricultural sectors bring together a great diversity of crops with very different pesticides uses), every year since 1950. None of the 28 active ingredients under study had been used on farm animals according the specific source of veterinary drugs (Lepointvétérinaire, 2018).

For this analysis, participants were considered as potentially exposed to each carbamate on a given crop during a year if: (i) they reported cultivating the crop; (ii) they reported personally performing pesticide and/or seed treatments on this crop with information on start and/or end dates of pesticide use; and (iii) the active ingredient was registered and recommended for pesticide and/or seed treatments on the crop during that year according to the CEM. Then, for each carbamate, a dichotomous indicator of exposure (exposed versus never exposed) was estimated by combining information from each of 13 crops and each year since 1950. Participants who did not report any pesticide use on a crop were considered unexposed to the 28 active ingredients under study for that crop (e.g. a vineyard and fruit grower who applied pesticides on vineyard only in 1995 was considered exposed for one year to the (thio/dithio)carbamate herbicides and/or fungicides registered in 1995 for vineyard treatment, i.e. to diethofencarb). Exposure was undetermined when a participant provided incomplete answers on lifetime occupational history (i.e. crops and, specific tasks and/or start and end years). Lifelong duration of use of each active ingredient (in years) was calculated combining information on all crops (i.e. one year of use on several crops was counted as one year of use).

2.4. Statistical analysis

We included all the AGRICAN participants in our analysis, except prevalent cases of CNS (n = 109) and subjects living in Côte d'Or (n = 10,875) where the specialized cancer registries did not record CNS tumors. Hazard ratios and 95% CI were estimated using the Cox proportional hazard regression, with age as the underlying timescale. Therefore, left truncation (delayed entry data) was considered using age at enrollment. For each histological subtype, potential confounders (gender, occupational status, educational level, familial status, history of tobacco smoking and alcohol consumption and history of allergy diseases) were selected through univariate analyses ($p < 0.20$) and included in multivariate models after a backward stepwise selection (i.e. each time a covariate with a p-value above 5% was removed, we ensured that the impact on the main effect estimate was below 10%). In the main analyses, CNS tumor risks (overall and by histological subtype) were estimated in relation to each carbamate, when the number of exposed cases was 5 and over, considering participants unexposed to any of the 28 active ingredients under study as the reference group (no adjustment on co-exposures has been performed because of over-adjustment bias risks related to high frequencies of co-exposures). When exposures to specific carbamate herbicides or fungicides (ever vs. never) were highly correlated ($r > 0.80$), owing to significant similarities in registration periods, recommended uses and/or chemical structures, the active ingredients concerned were grouped in the analysis (since separate analyses for highly correlated pesticides gave similar results). We performed sensitivity analyses to help in interpretation of the results of the main analyses: (i) considering participants unexposed to the active ingredient analysis (but potentially exposed to other carbamates, whether herbicides or fungicides) as the reference group; (ii) including individuals reporting re-entry tasks in vineyards or fruit-growing (i.e. cutting) in the exposed group in order to consider potential indirect exposures (only for fungicides, herbicides being not used on these two crops); (iii) excluding participants who had never worked on a farm in this analysis to detect a potential effect of uncontrolled confounders related to farming; (iv) adjusting for the 10 administrative geographical areas of residence to assess a potential confounding effect (related to potential unmeasured risk factors, unequally distributed geographically). Findings from sensitivity analyses were compared to those obtained in the main analyses with relative variations ($RV = (HR_{sa}-HR_{ma})/HR_{ma}$). Additional analyses were performed considering lifelong duration of use for each carbamate, categorized in two, three or four 10-year classes (with only two 5-year classes for iprovalicarb and cuprobam) in order to detect duration effects. Tests for trend were computed using the median of each class in regression models. Finally, the proportional hazards assumption was tested for all analyses by modeling a linear interaction between the timescale and each independent variable ($p < 0.05$). We used 2-sided statistical tests and all statistical analyses were performed using SAS® (version 9.3).

3. Results

3.1. Study population

The baseline characteristics of the study population according to overall exposure to carbamate herbicides and fungicides are presented in Table 2. Among the 170,858 participants, 36,068 (21%) were considered as exposed to at least one of the 28 active ingredients under study and 59,030 (35%) as never exposed. A portion of the study population (44%) was not classified according to exposure (because of incomplete answers on the enrollment questionnaire) and this proportion ranged from 48% (maneb) to 64% (desmedipham). Participants with undetermined exposure were older (69 vs. 60 years old), more often women (52 vs. 41%), single (33 vs. 27%), self-

employed workers (46 vs. 44% employees), never smokers (67 vs. 59%), non-alcohol consumers (25 vs. 17%) and had a lower educational level (63 vs. 41%) than other participants (data not shown). The majority of carbamate users were exposed to both herbicides and fungicides (60%), and a minority were exposed to only one active ingredient (18%). Co-exposure to carbamate insecticides concerned the large majority of participants exposed to carbamate herbicides and fungicides (88 and 89%, respectively), but very few (2%) of the reference group (i.e. participants never exposed to carbamate herbicides and fungicides, but possibly exposed to carbamate insecticides through uses on animals). Compared to never exposed participants, subjects classified as exposed to carbamate herbicides and/or fungicides were of similar age (59 vs. 60 years old), more often men (91 vs. 40%), self-employed workers (77 and 72 vs. 42%), smokers or ex-smokers (46 and 48 vs. 37%) and regular alcohol consumers (48 and 51 vs. 39%). They also had a slightly higher educational level (high school or university: 62 vs. 58%), lived more often as a couple (78 vs. 71%) and had a similar history of allergic diseases (15 and 16 vs. 15%).

Participants were followed for 6.9 years (standard deviation (SD) = 1.7) on average, 26,180 died during follow-up (15%) and 2018 were lost for follow-up (1%). Between enrollment (2005–2007) and 2013, 381 incident primary CNS tumors were diagnosed, including 164 gliomas (43%), 134 meningiomas (35%), 40 neuromas (11%), 18 lymphomas (5%) and 25 unclassified CNS tumors. The glioma cases were 69.9 years old (SD = 12.3) on average at diagnosis and were more often men (63%), while meningioma cases were 74.9 years old (SD = 12.4) and were more often women (69%). Among CNS tumor cases, 202 (53%) were classified as malignant (essentially gliomas) and 162 (42%) as benign (mainly meningiomas).

3.2. Description of exposure to carbamate herbicides and fungicides

A summary of the carbamate herbicides and fungicides registered in France is presented in Table 1. Most herbicides are used only on one crop: barban on barley, butylate and vernolate on corn, propham on potatoes, chlorbufam on sunflowers, cycloate, desmedipham and phenmedipham on beets and asulam on grassland. Conversely, a minority of fungicides are used on only one crop: benthiavalicarb, iprovalicarb and valifenalate on vineyards and propamocarb on potatoes. The number of marketed commercial products varies considerably according to the active ingredient: from 1 (for barban, chlorbufam, butylate, cupreb and cuprobam) to > 100 (for chlorpropham, phenmedipham, mancozeb, maneb, thiram and zineb). Most active ingredients under study (10/14 herbicides and 14/16 fungicides) have been associated with other pesticides in one commercial product or more. A minority of carbamate herbicide users was exposed to only one active ingredient (19%) while a majority was exposed to 5 or more carbamate herbicides (52%). Similarly, one-third of fungicide carbamate users were exposed to 5 or less carbamate fungicides (35%) while 21% were exposed to > 10 carbamate fungicides. Correlations between carbamate herbicides and fungicides are shown in supplementary material (additional supporting documentation, Tables S1 to S4). Regarding the herbicides, barban, prosulfocarb and triallate (mean of r = 0.92, three herbicides registered for uses on wheat and/or barley), chlorpropham and propham (r = 0.92, two herbicides mainly used for sprout inhibition in potato storage), desmedipham, phenmedipham and cycloate (mean of r = 1.00, three herbicides mainly used on beets) and butylate, EPTC and vernolate (mean of r = 0.99, three herbicides mainly used on corn) were grouped in the analysis. Similarly, for the fungicides, diethofencarb and iprovalicarb (r = 0.82, two fungicides mainly used on vineyards), cupreb, ferbam, propineb, zineb and ziram (mean of r = 0.95, five dithiocarbamates mainly used on vineyards and fruits) and mancozeb, maneb and metiram (mean of r = 0.76, three dithiocarbamates broad-spectrum fungicides) were grouped.

The contributions of the different types of uses to individual exposure are presented in Fig. 1. Pesticide users were exposed to carbamate herbicides only through crop treatments. Exposures through seed treatments concerned only

Table 2
Baseline characteristics of the study population according to overall exposure to carbamate herbicides and fungicides, AGRICAN, N = 170,858, France, 2005-2007[a]

		Ever exposed to carbamate		Never exposed
		Herbicides [a]	Fungicides [a]	
		n (%)	n (%)	n (%)
Exposure to pesticide carbamates (N = 95,098)		25,990 (15.2)	31,857 (18.6)	59,030 (35.5)
	Single exposure	4,844 (18.7)	1,526 (4.8)	
	Insecticide exposure	22,944 (88.3)	28,237 (88.6)	1,311 (2.2)[b]
	Herbicide exposure		21,779 (68.4)	
	Fungicide exposure	21,779 (83.8)		
Age (mean ± SE, N = 95,098)		59.5 ± 14.9	59.3 ± 15.2	60.2 ± 16.3
Gender (N = 95,098)				
	Men	23,699 (91.2)	28,902 (90.7)	23,731 (40.2)
	Women	2,291 (8.8)	2,955 (9.3)	35,299 (59.8)
Educational level (N = 91,876)				
	Elementary	9,505 (37.7)	11,618 (37.5)	24,152 (42.4)
	High school	13,385 (53.1)	16,124 (52.0)	24,408 (42.9)
	University	2,330 (9.2)	3,246 (10.5)	8,374 (14.7)
Familial status (N = 93,187)				
	Single	5,663 (22.3)	7,021 (22.5)	16,802 (29.0)
	As a couple	19,785 (77.7)	24,193 (77.5)	41,084 (71.0)
Occupational status (N = 95,098)				
	Employee	5,978 (23.0)	8,805 (27.6)	33,997 (57.6)
	Self-employed worker	20,012 (77.0)	23,052 (72.4)	25,033 (42.4)
Smoking status (N = 92,739)				
	Never smoker	13,701 (54.1)	16,173 (52.0)	36,380 (63.2)
	Former smoker	8,789 (34.7)	11,041 (35.5)	14,295 (24.8)
	Current smoker	2,843 (11.2)	3,913 (12.6)	6,931 (12.0)
Alcohol consumption (N = 91,668)				
	Non-consumer	2,184 (8.6)	2,695 (8.7)	12,188 (21.6)
	Occasional consumer	10,792 (42.5)	12,734 (40.9)	22,548 (39.9)
	Regular consumer	12,416 (48.9)	15,713 (50.5)	21,786 (38.5)
History of allergic diseases (N = 85,667)				
	Non-allergic	19,705 (84.7)	24,186 (84.2)	45,494 (85.3)
	Allergic	3,570 (15.3)	4,546 (15.8)	7,857 (14.7)

[a] Because of incomplete answers on lifetime history of occupational activities in the enrollment questionnaire, 44.3% of participants could not be classified according overall exposure to carbamate herbicides and/or fungicides (non exclusive) and then total from exposed to non exposed was not 100%; [b] Through uses in livestock farming where carbamate herbicides and fungicides are not used

12% of pesticide users exposed to fungicides, but with significant changes according to active ingredient: from 0% for propamocarb and most of the fungicides to 44% and 77% for cuprobam and mancopper, respectively. The contribution of different types of uses related to each crop is presented in Fig. 2. Pesticide users were exposed to herbicides through treatments on field crops (35%; wheat and/or barley, corn, beet, rape, sunflower, pea and/or field bean or tobacco), grassland (16%), potatoes (6%) or several of these crops (43%). Participants were exposed to asulam only through grassland, to chlorpropham and propham mainly through potatoes and to the other herbicides mainly through field crops. Pesticide users were exposed to fungicides through field crops (50%), vineyards (17%), potatoes (5%), fruits (3%) or several of these crops (25%). Exposures to fungicides through treatments on vineyards only were predominant for diethofencarb and/or iprovalicarb (79%) and some dithiocarbamates (cupreb, ferbam, propineb, zineb and ziram: 49%; mancopper: 45%).

3.3. Role of exposure to herbicides and/or fungicides

Hazard ratios were adjusted for gender, educational level (but not for meningiomas) and smoking history (both status and number of pack years centered, only for all CNS tumors; additional supporting documentation, Fig. S1). Overall, an increased risk of CNS tumors was observed in pesticide users exposed to carbamate herbicides (HR = 1.44; 95% CI: 0.94–2.22; n_E = 52; Table 3). An increase in risk was seen for each herbicide and ranged from 1.13 to 2.37, reaching the statistical significance for chlorpropham and/or propham (HR = 2.37; 95% CI: 1.38–4.08; n_E = 21) and for cycloate, desmedipham and/or phenmedipham (HR = 2.32; 95% CI: 1.17–4.63; n_E = 12). For chlorpropham and/or propham, analyses by histological subtype showed also increased risks, for both gliomas (HR = 2.28; 95% CI: 1.06–4.91; n_E = 10) and meningiomas (HR = 2.64; 95% CI: 1.02–6.81; n_E = 6). Despite the limited number of exposed cases, an association was found with meningiomas among participants exposed to diallate (HR = 3.65; 95% CI: 1.24–10.71; n_E = 6).

Regarding fungicide carbamates, an increase in risk was observed among ever-exposed participants, both in analyses on all CNS tumors (HR = 1.88; 95% CI: 1.27–2.79; n_E = 75) and for both gliomas (HR = 1.91; 95% CI: 1.11–3.28; n_E = 42) and meningiomas (HR = 2.04; 95% CI: 1.07–3.86; n_E = 20). Considering all CNS tumors, the increase in risk was seen for each fungicide and ranged from 1.54 to 2.45, and significant associations were observed for cuprobam (HR = 2.45; 95% CI: 1.48–4.04; n_E = 31), thiram (HR = 1.80; 95% CI: 1.19–2.73; n_E = 67), some dithiocarbamates (cupreb, ferbam, propineb, zineb and/or ziram; HR = 1.89; 95% CI: 1.21–2.93; n_E = 46) and mancozeb, maneb and/or metiram (HR = 1.84; 95% CI: 1.23–2.74; n_E = 70). Associations were more pronounced when the analyses were restricted to gliomas (except for cuprobam) and meningiomas (except for mancopper and thiram). For gliomas, the strongest associations were observed in participants exposed to propamocarb (HR = 2.94; 95% CI: 1.09–7.90; n_E = 5), cuprobam (HR = 2.40; 95% CI: 1.19–4.84; n_E = 16) and some dithiocarbamates (cupreb, ferbam, propineb, zineb and ziram; HR = 2.16; 95% CI: 1.20–3.87; n_E = 27); and for meningiomas, in farmers exposed to cuprobam (HR = 3.22; 95% CI: 1.42–7.28; n_E = 10).

When the reference group included participants exposed to herbicides and/or fungicides other than the active ingredient under study, similar associations were seen (additional supporting documentation, Table S5, part A): most relative variations (RV) were negative, with medians of −8%, −17% and − 5% for analyses of all CNS tumors, gliomas and meningiomas, respectively. Inclusion of individuals reporting re-entry tasks in vineyards or fruit crops in the groups exposed to fungicides did not change considerably risks for all CNS and the subtypes (Table S5, part B; RV < 20%). Exclusion of participants who had never worked on a farm from the reference group did not modify associations when overall CNS tumors where considered (Table S5, part C; RV < 20%), even though relative variations were stronger and in opposite directions for gliomas and meningiomas (medians of RV: −13% and 32%, respectively). Similarly, the results remained unchanged when an additional adjustment for geographical area of residence was performed (Table S5, part D; RV < 20% except for cycloate, desmedipham and/or phenmedipham: RV = 26%), and stronger variations in risks were observed in analyses of gliomas and meningiomas (medians of RV: 12% and − 1%, respectively).

3.4. Role of lifelong duration of use

No association was found with duration of exposure to all carbamate herbicides (Table 4), but, consistent with the main analyses of all CNS tumors, significant relationships with duration of use were detected with chlorpropham ($HR_{\geq 30yrs}$ = 2.42; 95% CI: 0.94–6.21; p-trend = 0.02), phenmedipham ($HR_{\geq 30yrs}$ = 2.08; 95% CI: 0.49–8.80; p-trend = 0.04), propham ($HR_{\geq 30yrs}$ = 1.53; 95% CI: 0.58–4.04; p-trend = 0.02), cycloate ($HR_{\geq 30yrs}$ = 2.98; 95% CI: 1.04–8.55; p-trend = 0.03) and diallate ($HR_{\geq 30yrs}$ = 3.76; 95% CI: 1.43–9.88; p-trend = 0.01). Regarding carbamate fungicides, an association with the overall duration of use was found in analyses of all CNS tumors ($HR_{\geq 30yrs}$ = 2.21; 95% CI: 1.37–3.54; p-trend < 0.01). More specifically, linear relationships with duration of use were found with propamocarb ($HR_{\geq 10yrs}$ = 2.75; 95% CI: 1.07–7.04; p-trend = 0.05), cuprobam ($HR_{\geq 5yrs}$ = 2.43; 95% CI: 1.42–4.15; p-trend < 0.01), ferbam ($HR_{\geq 30yrs}$ = 2.58; 95% CI: 1.14–5.84; p-trend = 0.01), mancopper ($HR_{\geq 20yrs}$ = 1.78; 95% CI: 0.89–3.55; p-trend = 0.04), mancozeb ($HR_{\geq 30yrs}$ = 2.17; 95% CI: 1.30–3.62; p-trend < 0.01), maneb

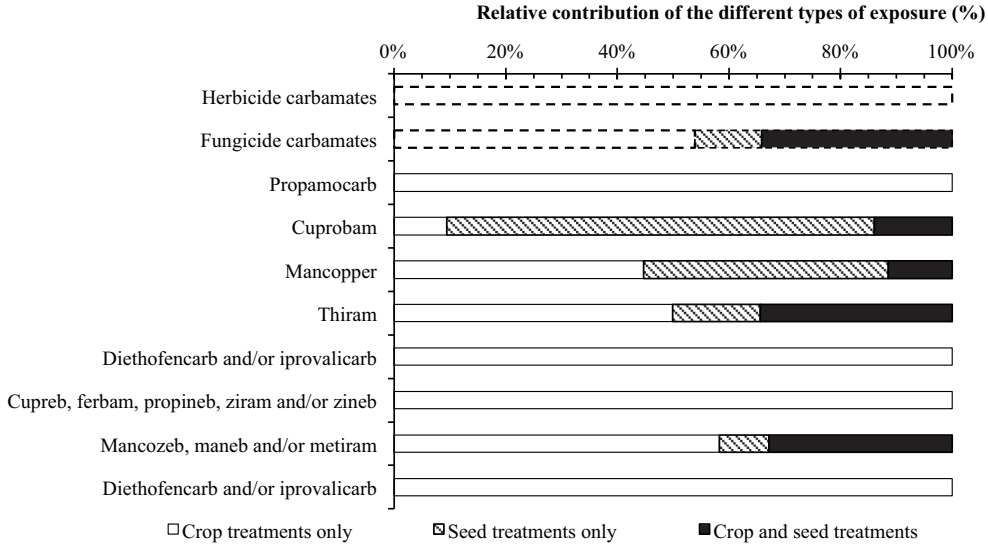

Fig. 1. Contribution of the different types of uses of carbamate herbicides and fungicides to individual exposure (%), AGRICAN, *N* = 36,068, France.

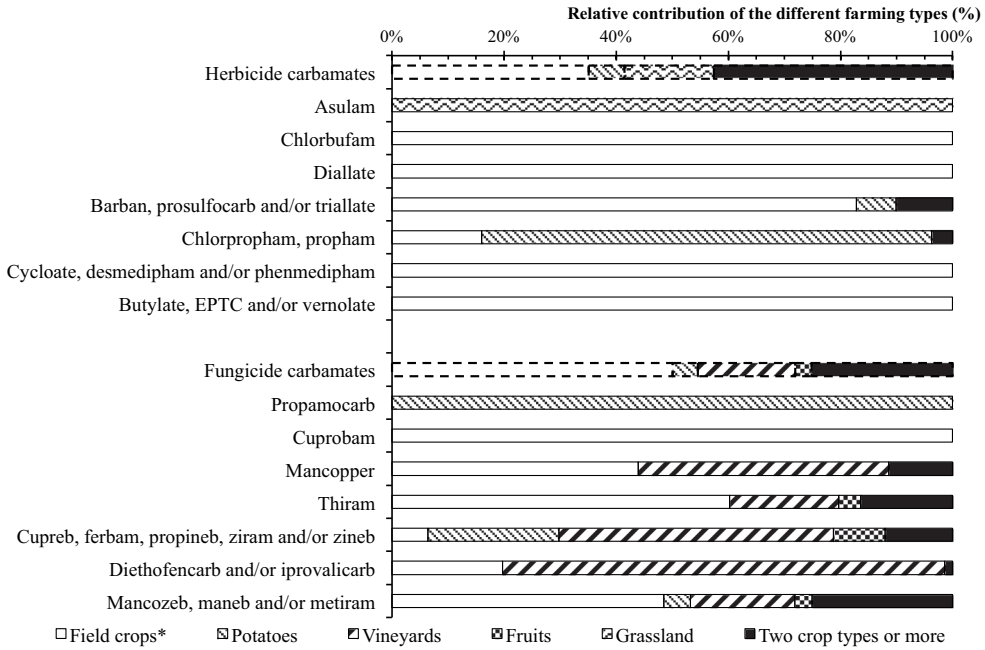

Fig. 2. Contribution of uses related to each crop and animal (%), AGRICAN, N = 36,068, France.
*Field crops: wheat and/or barley, corn, beet, rape, sunflower, pea and/or field bean and tobacco.

Table 3
Lifetime occupational exposures to carbamate herbicides and fungicides and primary CNS tumor risks, AGRICAN, France, 2005-2013a

	Study population	All CNS tumors		Gliomas		Meningiomas	
	N_E (%)	n_E (%)	HR [a] (95% CI)	n_E (%)	HR [a] (95% CI)	n_E (%)	HR [a] (95% CI)
Carbamate and thiocarbamate herbicides	25,220 (30.7)	52 (37.1)	1.44 (0.94-2.22)	29 (48.3)	1.52 (0.85-2.71)	15 (27.3)	1.72 (0.85-3.48)
Asulam	12,723 (18.3)	26 (22.8)	1.36 (0.80-2.31)	15 (32.6)	1.56 (0.79-3.10)	6 (13.0)	1.28 (0.50-3.31)
Chlorbufam	2,857 (4.8)	5 (5.4)	1.28 (0.49-3.34)	3 (8.8)		2 (4.8)	
Diallate	6,551 (10.3)	16 (15.5)	1.66 (0.89-3.11)	7 (18.4)	1.26 (0.52-3.04)	6 (13.0)	**3.65 (1.24-10.71)**
Barban, prosulfocarb and/or triallate	17,990 (24.0)	35 (28.5)	1.30 (0.79-2.13)	18 (36.7)	1.21 (0.63-2.32)	9 (18.4)	1.98 (0.79-4.95)
Butylate, EPTC and/or vernolate	14,450 (20.6)	25 (22.1)	1.13 (0.65-1.97)	15 (32.6)	1.25 (0.63-2.51)	5 (11.1)	1.35 (0.43-4.24)
Chlorpropham, propham	5,674 (9.1)	21 (19.3)	**2.37 (1.38-4.08)**	10 (24.4)	**2.28 (1.06-4.91)**	6 (13.0)	**2.64 (1.02-6.81)**
Cycloate, desmedipham and/or phenmedipham	3,381 (5.6)	12 (12.0)	**2.32 (1.17-4.63)**	5 (13.9)	1.79 (0.66-4.85)	4(9.1)	
Carbamate and dithiocarbamate fungicides	31,162 (35.2)	75 (46.0)	**1.88 (1.27-2.79)**	42 (57.5)	**1.91 (1.11-3.28)**	20 (33.3)	**2.04 (1.07-3.86)**
Propamocarb	2,249 (3.8)	6 (6.4)	1.92 (0.81-4.58)	5 (13.9)	**2.94 (1.09-7.90)**	0 (0.0)	
Cuprobam	7,989 (12.3)	31 (26.1)	**2.45 (1.48-4.04)**	16 (34.0)	**2.40 (1.19-4.84)**	10 (20.0)	**3.22 (1.42-7.28)**
Mancopper	15,667 (21.6)	36 (29.0)	1.59 (0.99-2.55)	22 (41.5)	1.80 (0.97-3.33)	8 (16.7)	1.55 (0.64-3.77)
Thiram	28,583 (33.4)	67 (43.2)	**1.80 (1.19-2.73)**	39 (55.7)	**1.89 (1.09-3.28)**	15 (27.3)	1.68 (0.82-3.45)
Cupreb, ferbam, propineb, ziram and/or zineb	16,502 (22.5)	46 (34.3)	**1.89 (1.21-2.93)**	27 (46.6)	**2.16 (1.20-3.87)**	11 (21.6)	1.94 (0.89-4.23)
Diethofencarb and/or iprovalicarb	8,898 (13.5)	20 (18.5)	1.54 (0.86-2.77)	13 (29.6)	1.85 (0.90-3.77)	3 (7.0)	
Mancozeb, maneb and/or metiram	29,402 (34.1)	70 (44.3)	**1.84 (1.23-2.74)**	40 (56.3)	**1.94 (1.12-3.35)**	17 (29.8)	1.91 (0.97-3.76)

Bold values indicates statistically significance at $p < 0.05$.
CI: Confidence Interval; HR: Hazard Ratios; N_E: number of exposed participants on complete data; n_E number of exposed cases
[a] Hazard ratios estimated by Cox models with age as the underlying timescale, when the number of exposed cases was sufficient ($n_E \geq 5$), adjusted for gender, educational level (not for meningiomas) and smoking history (only for all CNS tumors)

($HR_{\geq 30yrs}$ = 2.14; 95% CI: 1.30–3.52; p-trend < 0.01), metiram ($HR_{\geq 30yrs}$ = 2.01; 95% CI: 1.05–3.83; p-trend = 0.02), propineb ($HR_{\geq 30yrs}$ = 2.51; 95% CI: 1.35–4.64; p-trend < 0.01), thiram ($HR_{\geq 30yrs}$ = 2.30; 95% CI: 1.41–3.76; p-trend < 0.01), zineb ($HR_{\geq 30yrs}$ = 2.09; 95% CI: 1.16–3.77; p-trend < 0.01) and ziram ($HR_{\geq 30yrs}$ = 2.44; 95% CI: 1.30–4.61; p-trend = 0.01).

4. Discussion

In the large prospective French AGRICAN cohort, we found increased risks of primary CNS tumors in pesticide users potentially exposed to dithiocarbamate and carbamate fungicides (HR ranged from 1.54 to 2.45) and/or to thiocarbamate and carbamate herbicides (HR ranged 1.13 to 2.37). The strongest significant associations were observed with cuprobam (HR = 2.45; 95% CI: 1.48–4.04), with chlorpropham and propham (HR = 2.37; 95% CI: 1.38–4.08) and with cycloate, desmedipham and phenmedipham (HR = 2.32; 95% CI: 1.17–4.63). Similar trends were observed in subtype analyses, in sensitivity analyses assessing impact of changes in methodological choices (reference group definition, exposure assessment strategy, adjustment factor selection) and in additional analyses considering linear relationships with exposure duration.

One of the strengths of this analysis is the prospective study design of the cohort AGRICAN, which provides to get lifelong exposure data at enrollment, prior to and thus independently of the diagnosis of CNS tumors. The case identification involved all types of CNS tumors, regardless of topography (e.g. spinal cord tumors) or behavior (e.g. benign tumors), thanks to the linkage with population-based cancer registries certified and belonging to the French Network of Cancer Registries (FRANCIM), allowing separate study glioma and meningioma risks.(Bondy et al., 2008) The strategy for exposure assessment used both information on participant pesticide uses – reported in the

Table 4
Lifetime duration of occupational exposures to carbamate herbicides and fungicides and primary CNS tumor risks, AGRICAN, France, 2005-2013[a]

Exposure duration	All CNS tumors			Exposure duration	All CNS tumors		
	N_E	n_E	HR [a] (95% CI)		N_E	n_E	HR [a] (95% CI)
Carbamate and thiocarbamate herbicides p-trend = 0,25				Asulam			p-trend = 0,62
< 10 years	2,840	8	2.27 (1.06-4.84)	< 10 years	1,318	8	2.27 (1.06-4.84)
10-19 years	4,460	5	0.86 (0.34-2.19)	10-19 years	2,985	5	0.86 (0.34-2.19)
20-29 years	6,809	12	1.12 (0.58-2.17)	20-29 years	4,101	12	1.12 (0.58-2.17)
≥ 30 years	7,269	18	1.59 (0.88-2.87)	≥ 30 years	2,279	18	1.59 (0.88-2.87)
Barban			p-trend = 0,30	Chlorbufam			p-trend = 0,81
< 10 years	3,343	2	0.45 (0.11-1.89)	< 10 years	1,248	3	1.69 (0.51-5.62)
10-19 years	3,529	8	1.48 (0.67-3.31)	≥ 10 years	1,213	2	1.02 (0.24-4.32)
≥ 20 years	4,605	12	1.33 (0.67-2.63)				
Chlorpropham			**p-trend = 0,02**	Desmedipham			p-trend = 0,40
< 10 years	1,212	5	2.77 (1.09-7.04)	< 10 years	730	3	2.22 (0.67-7.32)
10-19 years	1,084	2	1.26 (0.30-5.22)	≥ 10 years	1,142	3	2.00 (0.60-6.65)
20-29 years	1,158	5	2.36 (0.92-6.06)				
≥ 30 years	1,190	5	2.42 (0.94-6.21)				
Phenmedipham			**p-trend = 0,04**	Propham			**p-trend = 0.02**
< 10 years	573	2	2.42 (0.58-10.12)	< 10 years	870	5	3.28 (1.29-8.35)
10-19 years	714	4	4.02 (1.42-11.38)	10-19 years	787	2	0.92 (0.33-2.59)
20-29 years	828	3	1.96 (0.59-6.45)	20-29 years	996	5	1.01 (0.44-2.30)
≥ 30 years	592	2	2.08 (0.49-8.80)	≥ 30 years	1,286	5	1.53 (0.58-4.04)
Butylate			p-trend = 0,53	Cycloate			**p-trend = 0.03**
< 10 years	2,386	2	0.60 (0.14-2.54)	< 10 years	593	1	1.17 (0.16-8.54)
10-19 years	4,479	8	1.08 (0.49-2.39)	10-19 years	697	5	5.08 (1.98-13.08)
≥ 20 years	4,059	10	1.27 (0.61-2.65)	20-29 years	769	1	0.75 (1.10-5.53)
				≥ 30 years	748	4	2.98 (1.04-8.55)
Diallate			**p-trend = 0,01**	EPTC			p-trend = 0,61
< 10 years	1,938	2	0.72 (0.17-3.03)	< 10 years	1,951	2	0.80 (0.19-3.36)
10-19 years	1,702	5	1.99 (0.76-5.17)	10-19 years	3,815	7	1.06 (0.46-2.42)
20-29 years	1,188	3	1.50 (0.46-4.93)	20-29 years	4,526	8	1.08 (0.49-2.40)
≥ 30 years	732	5	3.76 (1.43-9.88)	≥ 30 years	1,990	4	1.43 (0.48-4.25)
Prosulfocarb			p-trend = 0,25	Triallate			p-trend = 0,52
< 10 years	4,021	7	0.92 (0.40-2.12)	< 10 years	1,922	3	1.21 (0.37-3.95)
≥ 10 years	8,541	16	1.45 (0.77-2.72)	10-19 years	3,189	3	0.70 (0.21-2.32)
				20-29 years	4,992	11	1.25 (0.62-2.51)
				≥ 30 years	3,880	8	1.26 (0.56-2.82)
Vernolate			p-trend = 0,62				
< 10 years	1,940	1	3.28 (0.06-3.07)				
10-19 years	3,915	7	0.92 (0.44-2.28)				
≥ 20 years	6,131	12	1.01 (0.60-2.39)				
Carbamate and dithiocarbamate fungicides _ p-trend < 0.01				Diethofencarb			p-trend = 0,09
< 10 years	4,278	9	1.77 (0.86-3.65)	< 10 years	2,732	6	1.36 (0.57-3.27)
10-19 years	5,326	12	2.06 (1.06-3.99)	≥ 10 years	3,934	12	1.78 (0.90-3.50)
20-29 years	5,811	9	1.29 (0.62-2.68)				
≥ 30 years	10,586	35	2.21 (1.37-3.54)				
Iprovalicarb			p-trend = 0,15	Propamocarb			**p-trend = 0,05**
< 5 years	676	2	2.23 (0.53-9.34)	< 10 years	751	1	0.86 (0.12-6.29)
≥ 5 years	3,246	7	1.72 (0.74-3.98)	≥ 10 years	1,191	5	2.75 (1.07-7.04)
Cupreb			**p-trend = 0,03**	Cuprobam			**p-trend < 0.01**
< 10 years	3,614	10	1.56 (0.76-3.20)	< 5 years	1,421	4	1.91 (0.67-5.43)
≥ 10 years	1,781	8	2.31 (1.06-5.06)	≥ 5 years	5,560	24	2.43 (1.42-4.15)
Ferbam			**p-trend = 0.01**	Mancopper			**p-trend = 0,04**
< 10 years	2,840	11	2.91 (1.48-5.74)	< 10 years	3,635	5	1.13 (0.44-2.89)
10-19 years	3,294	5	0.99 (0.39-2.54)	10-19 years	5,953	17	1.76 (0.98-3.55)
20-29 years	3,235	12	2.17 (1.12-4.20)	≥ 20 years	3,739	11	1.78 (0.89-3.55)
≥ 30 years	1,427	7	2.58 (1.14-5.84)				
Mancozeb			**p-trend < 0,01**	Maneb			**p-trend < 0,01**
< 10 years	3,888	5	1.48 (0.66-3.33)	< 10 years	4,003	10	2.13 (1.06-4.28)
10-19 years	4,962	8	1.41 (0.65-3.04)	10-19 years	5,050	8	1.44 (0.67-3.10)
20-29 years	6,677	13	1.40 (0.74-2.67)	20-29 years	6,380	13	1.56 (0.83-2.95)
≥ 30 years	8,454	28	2.17 (1.30-3.62)	≥ 30 years	9,306	30	2.14 (1.30-3.52)
Metiram			**p-trend = 0,02**	Propineb			**p-trend < 0.01**
< 10 years	4,054	7	1.25 (0.56-2.80)	< 10 years	2,605	8	2.38 (1.11-5.12)
10-19 years	5,085	17	2.14 (1.21-3.78)	10-19 years	3,096	6	1.46 (0.62-3.45)
20-29 years	2,826	6	1.39 (0.58-3.31)	20-29 years	3,559	9	1.63 (0.78-3.39)
≥ 30 years	3,797	13	2.01 (1.05-3.83)	≥ 30 years	3,704	15	2.51 (1.35-4.64)
Thiram			**p-trend < 0.01**	Zineb			**p-trend = 0,01**
< 10 years	3,876	8	1.75 (0.81-3.77)	< 10 years	2,897	7	1.76 (0.78-3.98)
10-19 years	4,967	9	1.65 (0.79-3.45)	10-19 years	2,760	5	1.33 (0.55-3.40)
20-29 years	5,677	8	1.18 (0.55-2.56)	20-29 years	2,561	7	1.86 (0.83-4.21)
≥ 30 years	9,414	33	2.30 (1.41-3.76)	≥ 30 years	4,480	17	2.09 (1.16-3.77)
Ziram			**p-trend = 0.01**				
< 10 years	2,606	6	1.60 (0.67-3.79)				
10-19 years	3,856	11	1.82 (0.93-3.55)				

(*continued on next page*)

Table 4 (*continued*)

Exposure duration	All CNS tumors			Exposure duration	All CNS tumors		
	N_E	n_E	HR [a] (95% CI)		N_E	n_E	HR [a] (95% CI)
20-29 years	2,111	2	0.67 (0.16-2.81)				
≥ 30 years	3,274	14	2.44 (1.30-4.61)				

CI: Confidence Interval; HR: Hazard Ratios; N_E: number of exposed participants; n_E number of exposed cases

[a] Hazard ratios estimated by Cox models with age as the underlying timescale, when the number of exposed cases was sufficient ($n_E \geq 5$), adjusted for gender, educational level and smoking history

enrollment questionnaire – and information on pesticide use on several crops in France since 1950, from external data collected in PESTIMAT. This strategy enabled the investigation, for the first time in an epidemiological study, of the role of a wide range of carbamate herbicides and fungicides and CNS tumor occurrence. However, the enrollment questionnaire did not collect information on the type of pesticide used by participants (i.e. herbicides, fungicides and/or insecticides), and in addition, on the other hand, the current version of PESTIMAT provides information on registered uses but not on real uses. Consequently, we cannot rule out the possibility that some pesticide users may be wrongly considered as exposed to a carbamate herbicide or fungicide (e.g. if a participant has performed only insecticide treatments, or if an active ingredient has been registered but rarely used in practice). These potential misclassification errors, likely to lead to an overestimation of exposure frequencies, should be non-differential thanks to the prospective study design, and thus should lead to an underestimation of the strength of the associations we found. Conversely, since several hundred active ingredients have been marketed in France over the last few decades, we can assume that some of the positive associations we found being explained by co-exposures to other pesticides, including from carbamates, but also other chemical classes able to cross the blood brain barrier. These co-exposures, partially inherent to observational studies on long-term health effects of pesticide exposures, at least in the French agricultural context, imply the consideration of correlations during the interpretation of findings, especially with carbamate insecticides which have been linked with CNS tumors in AGRICAN (Piel et al., 2018) but for which it was not possible to adjust because of over-adjustment bias risks related to high frequencies of co-exposures (88 and 89% of users of carbamate herbicides and fungicides, respectively). Furthermore, false-associations resulting from multiple comparisons may be a relevant issue in our statistical analysis. However, even though conventional approaches to multiple-inference (e.g. Bonferroni correction) can be used to limit type I errors (i.e. false positive finding), they are too conservative and increase the risk of type II errors (i.e. false negative finding) and are then not relevant in a context of a large cohort study with data on multiple diseases (Rothman et al., 2008). Thus, findings should be considered carefully, taking into account, the number, the direction and the magnitude of all examined associations. Furthermore, the risks of CNS tumors were adjusted for gender, educational level and smoking habits after a conservative backward stepwise selection (RV < 10%), and non-parametrically for age. Indeed, age was chosen as the basic time scale in the analysis, allowing the most flexible control for age effects while avoiding the need to include an effect of age to satisfy the proportional hazard assumption underlying the Cox model (Commenges et al., 1998; Griffin et al., 2012). However, no information was collected on known (e.g. exposure to high doses of ionizing radiation) or suspected risk factors (e.g. family history of CNS tumors, residential proximity to farms) of CNS tumors. Nevertheless, even if we cannot exclude the possibility of a residual confounding related to these uncontrolled factors, a strong impact on the observed associations seems unlikely (little literature on these factors and/or no results showing strong associations with CNS tumors).

In the main analyses, all examined associations were in the direction of an increased risk of CNS tumors (all adjusted hazard ratios were above 1), which reinforce evidence of a relationship between occupational exposure to carbamate derivative pesticides (without distinction) and CNS tumors, although the consideration of the strength and the statistical significance of the associations could help to identify pesticides which might drive the observed increased risks of CNS tumors. Increased risks were more pronounced overall for fungicides (HR = 1.88; 95% CI: 1.27–2.79) than for herbicides (HR = 1.44; 95% CI: 0.94–2.22). Overall, sensitivity analyses of all CNS tumors did not show major changes in associations, thus strengthening the robustness of the main results (RV < 20%; except for cycloate, desmedipham and/or phenmedipham in sensitivity analyses adjusting for geographical areas of residence: RV = +26%). Interestingly, in the French study Pestexpo, from field observations with levels of exposure to dithiocarbamates in real working conditions, the authors showed that indirect exposures, occurring during the re-entry tasks in vine-growing and/or fruit-growing, may be similar or even higher than direct exposures.(Baldi et al., 2014) Thus, in sensitivity analyses, we included in the exposed groups the individuals reporting re-entry tasks in vineyards or fruit-growing, in order to limit these potential exposure misclassifications. However, while some associations were unchanged or strengthened, particularly for pesticides used in vineyards, most associations were attenuated, suggesting that pesticide users are generally the most affected by the excesses of CNS tumors. Relative variations in sensitivity analyses by tumor subtypes were stronger and often in opposite directions, suggesting that the stability of associations was affected by the limited number of exposed cases. Moreover, additional analyses investigating the role of lifelong duration of use showed linear exposure-responses relationships with several active ingredients, which were also associated with CNS tumors in the main analyses. Consequently, by corroborating the evidence brought by the main analyses and despite a limited number of exposed cases in most analyses, these additional associations support causal inference.

To date, only one case-control study has investigated the link between CNS tumors and fungicide carbamates. In the Upper Midwest Health Study, increases in risks were reported with exposure to dithiocarbamate fungicides among men (OR = 1.3; 95% CI: 0.4–5,0; $n_E = 4$) and women (OR = 1.6; 95% CI: 0.4–6.5; $n_E = 4$), but with a very limited number of exposed cases (probably because of the low frequencies of occupational use in this area, mainly covered by open field crops).(De Roos et al., 2003; Mathieu et al., 2015) In Europe, where fungicides are the most widely sold pesticide group, (Eurostat, 2014) an Italian case-control study found an excess of gliomas among farmers using fungicides (mostly for vineyards) and insecticides (OR = 2.0; 95% CI: 1.2–3.2; $n_E = 37$), but with no information on chemical groups.(Musicco et al., 1988) To our knowledge, the present study is the first to investigate associations between specific dithiocarbamate and carbamate fungicides and CNS tumors. Among the main findings, we reported a strong excess of CNS tumors following exposure to several dithiocarbamates: ferbam (registered in France between 1960 and 1997), mancozeb (registered in France since 1962), maneb (since 1960) metiram (since 1959), propineb (since 1963), thiram (1954–2002) and ziram (since 1956). In the Agricultural Health Study (AHS), a prospective cohort study of pesticide applicators from Iowa and North Carolina, information on the use of 50 pesticides (including six dithiocarbamates: ferbam, mancozeb/maneb, metiram, thiram, ziram) was collected with a self-administered questionnaire at enrollment (between 1993 and 1997). To date, none of these dithiocarbamates has been studied in relation with CNS tumors, but in an analysis focusing on cutaneous melanoma, a dose-response association was found with mancozeb/maneb ($OR_{\geq 63 exposure\text{-}days} = 2.4$; 95% CI: 1.2–4.9; p-trend = 0.006).(Dennis et al., 2010) Moreover, mancozeb, maneb, and metiram-zinc have been considered since 1999 (and since 2013 for propineb) as “probable human carcinogens” according the EPA in relation with one of their metabolites: ethylenethiourea (ETU) (EPA archives n.d.). Indeed, ETU is an environmental degradation product of ethylenebisdithiocarbamates and has been similarly classified on the basis of evidence from studies on animals (mainly excesses of thyroid and liver tumors in rats and mice). However, in 2001, based on mechanistic considerations, an

IARC Monographs Working Group concluded that the sufficient evidence from experimental animals would not be relevant to humans and therefore downgraded the overall evaluation of ETU to Group 3.(IARC, 2001) In the present study, we also report strong associations between CNS tumors and occupational exposure to the other dithiocarbamates investigated: cupreb (1962–1970), cuprobam (1962–1970), mancopper (1968–2002) and zineb (1954–2002). Although some dithiocarbamates were individually assessed by the IARC (ferbam, thiram, zineb, ziram), none has been classifiable as to its carcinogenicity to humans (assessment in 1987 on the basis of the absence of adequate data in humans and inadequate evidence in animals) (ECHA, 2018; IARC, 1987). Furthermore, excesses of gliomas were found following exposure to the carbamate fungicide propamocarb (registered since 1996). These findings should be interpreted cautiously since up to now, no epidemiologic study has investigated the associations between CNS tumors and exposure to individual fungicide carbamates, and so evidence is still limited. Indeed, to date, only two carbamate fungicides are "likely to be carcinogenic to humans" according to the EPA on the basis of evidence in animals (for several locations but not for CNS tumors): benthiavalicarb classified since 2008, registered too recently to be considered in the present analysis, and iprovalicarb classified since 2002, for which we report no association with CNS tumors. More broadly, most of the studied fungicides for which we report associations with CNS tumors were mainly used on vineyards, fruits and/or potatoes. Even though these crops are particularly dependent on fungicide treatments, high levels of correlation were observed with other carbamates such as fenoxycarb or dioxacarb, two insecticides previously associated with CNS tumor risk. Consequently, due to co-exposures to several (dithio/thio)-carbamates or to other pesticides associated to CNS tumors in epidemiologic literature, (Piel et al., 2018) the observed risk excesses cannot be definitively assigned to a specific active ingredient.

Regarding carbamate herbicides, we report consistent associations between CNS tumors and exposure to propham (1963–1999), chlorpropham (since 1962) and diallate (1962–1999; mainly for meningiomas). Interestingly, chlorpropham and diallate are classified as "suspected of causing cancer" by the ECHA but these three active ingredients are considered as non-classifiable as to their carcinogenicity to humans by the IARC (assessment in 1987 on the basis of the absence of adequate data in humans and inadequate evidence in animals).(ECHA, 2018; (IARC, 1987) Propham and chlorpropham have been mostly used on potato crops, as herbicides but also as plant growth regulators. Diallate has been used as herbicide on several field crops (e.g. beet, rape or sunflower). We also report a significant association between CNS tumor incidence and lifetime duration of exposure to cycloate ($HR_{\geq 30yrs}$ = 2.98; 95% CI: 1.04–8.55; p-trend = 0.03). This association, based on a limited number of exposed cases, need to be corroborated by other studies in the literature. Indeed, we cannot rule out the possibility that other herbicides registered for use on beet crops, including carbamates and thiocarbamates, impact upon the association we found with cycloate, as this carbamate herbicide has been used only on beet, a crop particularly dependent on herbicide treatments (on average in France, 15 of the 16 annual pesticide treatments on this crop are with herbicides)(Agreste, 2014) and already associated with a strong excess of CNS tumors in further analyses in AGRICAN (HR = 2.68; 95% CI: 1.49–4,80; n_E = 16).(Piel et al., 2017) To date, two thiocarbamates have been investigated in the AHS. Pesticide applicators exposed to butylate, mainly through treatments on corn crops, led to excess risks of prostate cancer and Non-Hodgkin's lymphoma,(Lynch et al., 2009) supported by several epidemiological studies.(McDuffie et al., 2001; Zheng et al., 2001; Alavanja et al., 2003) Similarly, with EPTC, widely used in the US both as a herbicide and a plant growth regulator on a wide variety of crops, associations were suggested between the highest category of exposure and colon cancer, leukemia and pancreatic cancer.(van Bemmel et al., 2008; Andreotti et al., 2009) The biological mechanism by which EPTC may be linked with cancer is not clearly known, but it was hypothesized that the potential carcinogenicity could be explained by the production of N-nitroso compounds (NOCs).(Andreotti et al., 2009; Lee et al., 2004) Indeed, according to the IARC, some NOCs are suspected of being potent carcinogens for various locations,(IARC,1987 IARC, 1978; IARC, 2012a; IARC, 2012b) including CNS (e.g. N-ethyl-N-nitrosourea, N).(Lee et al., 2005; International Agency for Research on Cancer, 1987; Preston-Martin and Mack, 1991) In agriculture, various pesticides have been identified as N-nitrosatable (i.e. able to form N-nitroso compounds in reaction with nitrite). This set of pesticides includes some thiocarbamates (e.g. EPTC, butylate, triallate), some other carbamates and dithiocarbamates (e.g. propham, phenmedipham, ferbam, ziram carbaryl, carbofuran), but also various other pesticides (IARC, 1983). In the present study, lifetime exposure to EPTC, butylate and/or triallate was not associated with CNS tumor risk. Consequently, even though we found increased risks with other N-nitrosatable carbamates, our findings provide limited support for the hypothesis of a causal relation between CNS tumor and exposure to N-nitroso compounds through carbamate uses. Other biological mechanisms have received more support in experimental studies, including oxidative stress potentially induced after exposures to thio-, (Mathieu et al., 2015) dithio-(Ben Amara et al., 2015; Dennis and Valentine, 2015; Iorio et al., 2015) or carbamates,(Gupta, 2005) and which could be more relevant to CNS tumors, as the brain is particularly sensitive due to high rates of dioxygen and relatively low levels of antioxidants. Thus, other pesticides able to produce oxidative stress and to cross the blood brain barrier should be explored in further research on CNS tumors.

5. Conclusions

From a large population of farmers enrolled in the prospective cohort AGRICAN, we found an excess of primary CNS tumors in pesticide users potentially exposed to carbamate fungicides and herbicides. The strongest associations — corresponding to risks two to three times higher — were observed with the (dithio/thio)-carbamates used by farmers growing vineyards, fruits, potatoes and beets. Some of the active ingredients studied were already suspected to be carcinogenic in humans by the international agencies, notably mancozeb, maneb, metiram, chlorpropham and diallate. Although co-exposures with (dithio/thio)-carbamates and other pesticides do not allow for firm conclusions on specific active ingredients, these findings reinforce evidence on the hypothesis of a link between exposure to carbamate pesticides and CNS tumors.

Declaration of Competing Interest

The authors declare they have no actual or potential conflict competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.070.

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