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BRIEF REPORT

Cancer incidence among pesticide applicators exposed to captan in the Agricultural Health Study

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Abstract
Objective Captan is a widely used antifungal pesticide whose potential to cause cancer in humans is uncertain.
Methods We evaluated the incidence of cancer among pesticide applicators exposed to captan in the Agricultural Health Study. Detailed information on pesticide exposure and lifestyle factors was obtained from self-administered enrollment questionnaires completed between 1993 and 1997.
Results Of the 48,986 applicators enrolled 4,383 (9%) had applied captan. Median follow-up time was 9.14 years. Poisson regression analysis was used to estimate relative risks (RR) for cancer subtypes by tertiles of captan exposure. We investigated risk for all cancers combined and sites of cancer for which at least 15 cases occurred among captan-exposed applicators. These sites included cancers of the prostate, lung, and colon, blood-related cancers, and colorectal cancers. During follow-up 2,912 incident primary cases of cancer were identified. No association between the highest tertile of captan exposure (>67.375 intensity-weighted days) and development of all cancers (RR = 0.89; 95% CI, 0.71–1.13) or cancer of any specific site was observed.
Conclusion Although our study is limited by low numbers of observed cancer cases and follow-up time of 9.14 years, it does not provide evidence of an increased risk for the development of cancer at the investigated sites.

Keywords Captan · Cancer · Agricultural Health Study · Cohort · Prospective · Pesticide · Fungicide · CAS number 133-06-2

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health, or the Department of Defense.

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Introduction

Captan (1,2,3,6-Tetrahydro-*N*-(trichloromethylthio)phthalimide, CAS number 133-06-2) is a thiophthalimide broad-spectrum fungicide [1]. Since its introduction in 1951, the antifungal properties of captan have been applied in the cosmetic and agricultural industries. Captan is FDA approved for human use to treat dandruff, seborrhea, and psoriasis [2–5]. Agricultural uses of captan include application to terrestrial and greenhouse food and feed crops, post-harvest dipping of fruits, pretreatment of seeds, and on ornamental plants [6]. Applicators may be exposed to captan through oral, inhalational, and dermal routes. Captan use varies by region within the United States with the most detailed information concerning agricultural applications of pesticides collected by the state of California. In California in 2005, 447,418 pounds were applied to 236,679 acres [3].

Although a wide variety of crops are treated with captan, the most heavily treated crops in California during 2005 were peaches, prunes, cherries, and plums [3].

Animal studies support the concern that captan may be carcinogenic. Captan was shown to be acutely genotoxic to African clawed frogs and Spanish ribbed newts using the micronucleus test [7]. CD1 mice fed very high doses of captan developed duodenal adenomas and adenocarcinomas [8]. However, the mechanism of captan's potential carcinogenicity is not well understood. Captan is ultimately metabolized renally into noncarcinogenic tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA), but an intermediary of this process, thiophosgene, is highly reactive and a potential carcinogen [9]. However, an in vitro study suggests that any risk from captan exposure may be limited by the very brief half-life of captan and its metabolites in blood [10].

There have been few human studies on the carcinogenicity of captan. A small study evaluating the mutagenicity of post-exposure farmers' urine yielded inconclusive results [11]. An ecologic study suggested an increased risk of leukemia among Hispanic males and prostate cancer among black males in California counties where captan was used [12]. A Canadian population-based case-control study found a significant univariate relationship between any use of captan and development of non-Hodgkins lymphoma (NHL) [13]. When the authors controlled for potentially confounding variables the relationship between captan and NHL became nonsignificant. An earlier report from the Agricultural Health Study suggested a possible link between captan application by husbands and an increased incidence of breast cancer in applicators' wives [14].

Although animal and human data about captan's carcinogenicity are limited, the United States Environmental Protection Agency (EPA) classifies captan as not likely to be a potential carcinogen except at prolonged high-level exposures [15]. The International Agency for Research on Cancer (IARC) determined that the weight of existing evidence is insufficient for any conclusions to be drawn and classified captan as a group 3 carcinogen [16]. To further explore the possible relationship between captan exposure and development of malignancies, we investigated site-specific cancer incidence and risk among pesticide applicators exposed to captan in the Agricultural Health Study cohort.

Methods

Cohort enrollment and follow-up

The Agricultural Health Study is a prospective cohort study, composed of 57,311 private and commercial applicators licensed to apply restricted use pesticides who lived in Iowa or North Carolina (82.4% of eligible applicators in both states enrolled). A detailed description of the cohort has been previously described [17]. Follow-up time accrued for each individual from the time of enrollment (1993–1997) until either a first primary cancer was diagnosed, they died, they left Iowa or North Carolina, or through 31 December 2004 [18]. Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to state death registries and the National Death Index to ascertain vital status. Cases were coded according to the International Classification of Diseases for Oncology (ICD-O-2). Follow-up time averaged 9.14 years with 91% of the cohort accruing greater than 7 years of follow-up time. All participants provided verbal informed consent, and institutional review boards of the National Cancer Institute, Battelle (the field station in North Carolina), the University of Iowa (the field station in Iowa), Westat (coordinating center for the study) approved the protocol.

Exposure assessment

A self-administered enrollment questionnaire collected comprehensive exposure data on 22 pesticides, including captan, ever/never use information for 28 additional pesticides, information on use of personal protective equipment (PPE), pesticide application methods, mixing of pesticides, equipment repair, smoking, alcohol consumption, cancer history of first degree relatives, and basic demographic data [19]. The questionnaires may be accessed at http://www.aghealth.org/questionnaires.html.

We constructed two measures of cumulative captan exposure: lifetime days (LD) and intensity-weighted lifetime days (IWLD) of captan exposure. IWLD of captan exposure was calculated by multiplying LDs of captan exposure by the captan exposure intensity score. Methods for calculating the exposure intensity score are described in detail in Dosemeci et al. [20] and are based on an applicator's frequency of personally mixing pesticides, application methods used, involvement in repair of application equipment, and use of personal protective equipment while working with pesticides. Applicators who had any exposure to captan were divided into tertiles of captan exposure, based on levels among all cancer cases combined. We did this so that each of the exposed groups contained an approximately equal number of cancer cases (for specific cancers). We categorized captan exposure into tertiles as this resulted in meaningful exposure differences between groups and enabled us to evaluate for a dose-response relationship between exposure to captan and development of incident cancers. The IWLD tertiles were any exposure less than 0.064 IWLD, 0.065–67.375 IWLD, and greater than 67.375 IWLD.

Statistical analysis

Prevalent cancer case patients identified at or prior to enrollment ($n = 1{,}084$), applicators who did not provide information on captan use ($n = 6{,}933$) or their age ($n = 3$), and applicators for whom no follow-up information was available ($n = 305$) were excluded from analysis, leaving 48,986 applicators in our study.

Poisson regression analyses were carried out for all cancers and individual cancer sites to estimate relative risks (RR) and 95% confidence intervals (CI) associated with intensity-weighted lifetime days (RR_{IWLD}) of captan exposure. For IWLD, to evaluate which would be the most appropriate reference group, we carried out a comparison of baseline characteristics between different types of pesticide applicators: (1) applicator never exposed to captan, (2) applicators with captan exposure in the lowest tertile of IWLD, and (3) applicators with captan exposure in the highest two tertiles of IWLD exposure. We postulated that applicators with baseline characteristics similar to those of the applicators in the highest exposure group would be most appropriate as a reference group for the Poisson regression analyses.

We investigated cancer sites for which there were at least 15 cancer cases among captan exposed applicators. Cancers that met these criteria included: cancer at all sites, cancer of the prostate, lung, or colon. When we combined colon and rectal cancer cases as colorectal cancers and cases of leukemia, non-Hodgkins lymphoma, Hodgkins lymphoma, and multiple myeloma into blood-related cancers, both colorectal cancer and blood-related cancers met our inclusion criteria. Models were adjusted for family history of cancer in a first-degree relative, age (<40, 40–49, 50–59, 60 or older), gender, residence (Iowa vs. North Carolina), smoking history, use of alcohol within the past year (ever/never), education level (high school degree or less versus. beyond high school), applicator type (private vs. commercial), and year of enrollment. For cancer sites other than the lung, smoking was categorized as never, past, or current. To limit residual confounding between smoking and lung cancer, smoking was further categorized as never, past with ≤15 pack-years (py), past with >15 py, current with ≤15 py, and current with >15 py in our lung cancer models. Potential confounding from exposure to other pesticides was evaluated by identifying the pesticides most highly correlated with captan by use of the Spearman correlation coefficient for intensity weighted lifetime days. Although all correlation coefficients were <0.24 we evaluated potential confounding by the five most highly correlated pesticides. To employ the most parsimonious models we only retained variables that contributed to our models by altering our point estimates by more than 10% or were known risk factors for the cancer site of interest in our final models. *p*-trend values were calculated using captan exposure as a continuous variable, and all statistical tests were two-sided. All statistical analyses were performed using Stata version 9.2 (StataCorp, College Station, TX) and AHS data release P1REL0612.

Results

Selected characteristics of the 48,986 pesticide applicators are presented in Table 1. The cohort largely comprised whites (98%), males (97%), and private applicators (91%). The average age at enrollment was 46.1 years (SD = 13.0). Among the 48,986 subjects with complete exposure information on captan, 4,383 (9%) reported ever having used captan, and they contributed a total of 448,478 person-years with an average follow-up of 9.14 years. In this study 2,912 (5.9%) applicators developed a malignancy during the follow-up period. The most commonly observed cancers were prostate ($n = 1{,}171$), colorectal ($n = 299$), blood ($n = 278$), and lung ($n = 271$). Table 1 shows that there is no clear distinction of a better reference group as the highest exposed group is more similar to the non-exposed group for some characteristics but more similar to the lower exposed group for other characteristics. For this reason, we present results for IWLD using both reference groups.

Relative risks for IWLD of captan exposure and cancer sites that met our inclusion criteria are presented in Table 2. Because the model for each cancer site was adjusted for its own set of unique covariates, these are listed by site in the footnotes. We did not detect an increased risk for all cancers, whether we used the non-exposed group as the referent (highest tertile: RR = 0.89; 95% CI, 0.71–1.13; *p*-trend = 0.15) or the lowest tertile as the referent (highest tertile: RR = 0.84; 95% CI, 0.61–1.17; *p*-trend = 0.33). Relative risks were not elevated for any of the individual or collective cancer sites analyzed regardless of choice of reference category. Similarly, a relationship between captan exposure and development of any cancer or site-specific cancers was not detected when we used LD as the exposure metric regardless of choice of referent (data not shown). We did not find strong correlations between captan and other pesticides evaluated in the Agricultural Health Study, so we did not control our final models for other pesticide use.

Discussion

Although captan has not been shown to be acutely toxic in mammals, concern remains about its potential carcinogenicity [1, 6, 21–23]. Bacterial studies have shown that

Table 1 Selected characteristics of applicators by intensity-weighted lifetime days of captan exposure based on 1993–1997 enrollment data in the Agricultural Health Study

Characteristics	Non-exposed to captan		Lowest tertile of captan exposure		Upper 2 tertiles of captan exposure	
	$n = 44,603$	%	$n = 1,422$	%	$n = 2,961$	%
Age (year)						
<40	15,049	34	466	33	896	31
40–49	12,514	28	511	36	956	32
50–59	9,059	20	257	18	615	21
>60	7,981	18	188	13	494	17
Sex						
Male	43,462	97	1,403	99	2,853	96
Female	1,141	3	19	1	108	4
State of residence						
Iowa	30,231	68	1,290	91	1,744	59
North Carolina	14,372	32	132	9	1,217	41
Applicator type[a]						
Commercial	4,268	10	31	2	146	5
Private	40,335	90	1,380	98	2,826	95
Smoking history						
Never	23,681	53	890	63	1,572	53
Former smoker (≤15pack-years)	9,360	21	283	20	626	21
Former smoker (>15 pack-years)	3,590	8	89	6	294	10
Present smoker (≤15 pack-years)	3,713	8	78	5	178	6
Present smoker (>15 pack-years)	3,784	8	77	5	272	9
Missing	475	1	5	0.4	19	0.6
Alcohol[b]						
Never	13,892	31	311	22	885	30
Ever	30,116	68	1,097	78	2,067	70
Missing	595	1.3	3	0.2	20	0.7
Educational level						
High school/GED or lower	24,912	56	586	41	1,216	41
Beyond high school	18,761	42	819	58	1,703	57
Missing	930	2	17	1	42	1
Family history of cancer[c]						
No	25,389	57	784	46	1,526	51
Yes	16,600	37	599	42	1,317	44
Missing	2,614	6	28	2	129	4
Currently raising field corn						
No	13,266	29.7	531	16.9	708	57.2
Yes	31,337	70.3	2,615	83.1	529	42.8
Currently raising soybeans						
No	15,048	33.7	625	19.9	736	59.5
Yes	29,555	66.3	2,521	80.1	501	40.5

[a] The term "private" refers primarily to individual farmers, and "commercial" refers to professional pesticide applicators

[b] Based on the answer to the question "During the past 12 months, how often did you drink any kind of alcoholic beverage?"

[c] Family history of cancer in a first-degree relative

captan irreversibly binds DNA polymerase 1 of Escherichia coli and alters its catalytic functions [24]. In *Salmonella typhimurium* and *E. coli*, captan is mutagenic [25, 26]. In rat hepatocytes, metabolism of captan by microsomal p450 enzymes can induce lipid peroxidation which is thought to be a means of captan-induced cytotoxicity [27].

Table 2 Adjusted relative risks (RR) of cancer given intensity-weighted lifetime days of exposure to captan among pesticide applicators in the Agricultural Health Study

IWLD[a]	Cases	Referent = no exposure			Referent = lowest exposed tertile		
		RR	95% CI	p-trend[b]	RR	95% CI	p-trend[b]
All sites[c]							
No exposure	2,693	1.00		0.15			0.33
Lowest tertile	73	1.11	(0.88–1.40)		1.00		
Middle tertile	73	0.83	(0.66–1.04)		0.75	(0.54–1.04)	
Highest tertile	73	0.89	(0.71–1.13)		0.84	(0.61–1.17)	
Blood-related[d]							
No exposure	255	1.00		0.81			0.48
Lowest tertile	7	1.07	(0.50–2.27)		1.00		
Middle tertile	11	1.28	(0.70–2.34)		1.22	(0.47–3.14)	
Highest tertile	5	0.66	(0.27–1.60)		0.65	(0.20–2.04)	
Colon[e]							
No exposure	196	1.00		0.81			0.42
Lowest tertile	5	1.04	(0.43–2.52)		1.00		
Middle tertile	6	0.94	(0.42–2.12)		0.85	(0.26–2.79)	
Highest tertile	5	0.90	(0.37–2.20)		0.58	(0.16–2.17)	
Colorectal[e]							
No exposure	299	1.00		0.44			0.23
Lowest tertile	8	1.06	(0.52–2.13)		1.00		
Middle tertile	9	0.9	(0.47–1.75)		0.82	(0.32–2.14)	
Highest tertile	6	0.71	(0.32–1.60)		0.51	(0.17–1.54)	
Lung[f]							
No exposure	271	1.00		0.10			0.11
Lowest tertile	7	1.54	(0.72–3.28)		1.00		
Middle tertile	4	0.53	(0.20–1.42)		0.32	(0.08–1.20)	
Highest tertile	5	0.52	(0.21–1.26)		0.29	(0.07–1.25)	
Prostate[g]							
No exposure	1,078	1.00		0.76			0.94
Lowest tertile	30	1.13	(0.79–1.63)		1.00		
Middle tertile	29	0.82	(0.57–1.19)		0.73	(0.44–1.21)	
Highest tertile	34	1.02	(0.73–1.44)		0.97	(0.59–1.59)	

[a] IWLD = Intensity-weighted lifetime days

[b] *p*-trend values were calculated using captan exposure as a continuous variable

[c] Adjusted for age, smoking (never, former, current), family history of any cancer in first-degree relative, and enrollment year

[d] Adjusted for age and enrollment year. Blood-related cancers include non-Hodgkins lymphoma ($n = 123$), leukemia ($n = 90$), multiple myeloma ($n = 50$), and Hodgkins disease ($n = 15$)

[e] Adjusted for age, education level, family history of colon cancer in a first-degree relative, and enrollment year

[f] Adjusted for age, smoking (never, former (<15 py), former (≥15 py), current (<15 py), current (≥15 py), state, and enrollment year

[g] Adjusted for age, family history of prostate cancer, and enrollment year

Furthermore, captafol, a chemical closely related to captan, induces similar findings in rat and human kidney cells [28].

To further evaluate captan's potential carcinogenicity in humans, we assessed the risk of developing cancer among pesticide applicators exposed to captan in the Agricultural Health Study cohort. We found no relationship between exposure to captan and development of all cancers or any of the investigated site-specific cancers. These findings persisted regardless of our choice of exposure metric (LD or IWLD) or reference group (non-exposed or least exposed). We did not observe a dose-response relationship between captan exposure and development of any of the investigated cancer sites.

The Agricultural Health Study has several important strengths. It is the largest study to date of pesticide applicators exposed to captan. Recall bias was minimized as exposure information was collected prior to cancer diagnosis. Furthermore, it has been shown that farmers provide accurate and reliable information and considerable detail regarding their pesticide application history [29–33]. This study is unique because the detailed exposure assessment allowed us to more accurately classify captan exposure as well as evaluate for potential confounding with captan between commonly used pesticides and lifestyle characteristics.

Despite the strengths of this study it does contain limitations. While the Agricultural Health Study cohort is large only 4,383 (9%) applicators reported ever applying captan. The preponderance of white males limits generalizability of our results to other groups. The low number of cancer cases observed during the follow-up period restricted the cancer sites available for analysis to only the most commonly occurring sites. In addition, we combined leukemia, Hodgkins disease, non-Hodgkins lymphoma, and multiple myeloma into the blood-related cancers because there were too few cases to analyze these cancer types individually. Although we assessed for a dose-response to captan exposure by dividing captan exposure into tertiles, this analysis is limited since most applicators had low levels of lifetime captan use. Furthermore, many farmers may have had unmeasured exposure to captan through contact with seeds pretreated with captan. As farmers in our non-exposed group may have contacted captan our results may have been biased toward the null. Previous work suggests that the seeds most likely to expose farmers to captan are corn and soybeans [34]. We assessed for the potential impact of planting these crops by adjusting our models for raising corn and soybeans but found that they did not influence the relative risks when we controlled for these exposures in our models. We also evaluated cancer risk associated with raising these crops among only the applicators who reported never having used captan. No relationship between raising these crops and development of subsequent cancers was observed. We will be able to better address these limitations with additional follow-up time.

Conclusion

We found no evidence of increased risk for developing some of the more common cancers with exposure to captan. However, our study is subject to several limitations that may bias our results toward the null hypothesis of no association between captan exposure and development of malignancies. The relationship between captan and both the cancers analyzed here and less common cancers warrants repeat evaluation as follow-up time accrues in the Agricultural Health Study.

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References:

1. Gordon EB (2001) Captan and folpet. In: Krieger R (ed) Handbook of Pesticide Toxciology, vol 5th edn. Academic Press, Inc, San Diego, CA, pp 1711–1742
2. International Agency for Research on Cancer (IARC) – Summaries & evaluations. CAPTAN (1983) 30:295
3. PAN Pesticides Database – California Pesticide Use, vol 2006. http://www.pesticideinfo.org/Detail_ChemUse.jsp?chk=104&cok=00#TopSites, 2006
4. Vilaplana J (1993) C. R. Captan, a rare contact sensitizer in hairdressing. Contact Derm 29:107. doi:10.1111/j.1600-0536.1993.tb03502.x
5. U.S. Food and Drug Administration. Code of Federal Regulations, Title 21, vol 5, Chap 1, Subchapter D–drugs for human use, vol 2007
6. Reregistration Eligibility Decision (RED): Captan; EPA-738-R-99-015; U.S. Environmental Protection Agency, Office of Pesticide Programs, U.S. Government Printing Office: Washington, DC, Nov 1999; 2–49 1999.
7. Mouchet F, Gauthier L, Mailhes C, Ferrier V, Devaux A (2006) Comparative evaluation of genotoxicity of captan in amphibian larvae (*Xenopus laevis* and *Pleurodeles waltl*) using the comet assay and the micronucleus test. Environ Toxicol 21:264–277. doi:10.1002/tox.20180
8. Quest JA, Fenner-Crisp PA, Burnam W, Copley M, Dearfield KL, Hamernik KL, Saunders DS, Whiting RJ, Engler R (1993) Evaluation of the carcinogenic potential of pesticides. 4. Chloroalkylthiodicarboximide compounds with fungicidal activity. Regul Toxicol Pharmacol 17:19–34. doi:10.1006/rtph.1993.1003
9. Krieger R, Thonginthusak T (1993) Captan metabolism in humans yields two biomarkers, tetrahydrophthalmide (THPI) and thiazolidine–thione-4-carboxylic acid (TTCA) in urine. Drug Chem Toxicol 16(2):207–225. doi:10.3109/01480549309031997
10. Gordon EB, Ehrlich T, Mobley S, Williams M (2001) Measurement of the reactino between the fungicides captan or folpet and blood thiols. Toxicol Methods 11:209–223. doi:10.1080/105172301316871617
11. Lebailly P, Devaux A, Pottier D, De Meo M, Andre V, Baldi I, Severin F, Bernaud J, Durand B, Henry-Amar M, Gauduchon P (2003) Urine mutagenicity and lymphocyte DNA damage in fruit growers occupationally exposed to the fungicide captan. Occup Environ Med 60:910–917. doi:10.1136/oem.60.12.910
12. Mills PK (1998) Correlation Analysis of Pesticide Use Data and Cancer Incidence Rates in California Counties. Arch Environ Health 53(6):410–413
13. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW (2001) Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 10:1155–1163
14. Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, Samanic C, Sandler DP, Blair A, Alavanja MC (2005) Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Am J Epidemiol 161:121–135. doi:10.1093/aje/kwi022

15. Captan; Cancer Reclassification; Amendment of Reregistration Eligibility Decision (2004) Notice of Availability Federal Register Online, vol 69, pp 68357–36360
16. International Agency for Research on Cancer. Summaries and Evaluations. Captan. vol 30, Suppl 7; Lyon (France): World Health Organization, IARC; 1987. Available at http://monographs.iarc.fr/ENG/Classification/crthgr03lts.php. Last accessed November 9, 2006
17. Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MC (2004) Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst 96:1375–1382
18. Alavanja MC, Sandler DP, McDonnell C, Lynch C, Pennybacker P, Zahm S et al (1996) The Agricultural Health Study. Environ Health Perspect 104:362–369. doi:10.2307/3432672
19. Alavanja M, Sandler D, McDonnell C, Lynch C, Pennybacker M, Zahm S (1999) Characteristics of pesticide use in a pesticide applicator cohort: the Agricultural Health Study. Environ Res 80:172–179. doi:10.1006/enrs.1998.3888
20. Dosemeci M, Alavanja MCR, Rowland AS, Mage D, Zahm SH, Rothman N, Lubin JH, Hoppin JA, Sandler DP, Blair A (2001) A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg 46:245–260. doi:10.1093/annhyg/mef011
21. The Pesticide Manual: A world Compendiumed. Farnham, UK: British Crop Protection Council, (2000)
22. Edwards I, Ferry D, Temple W (1991) Fungicides and related compounds. In: Hayes W, Laws E (eds) Handbook of pesticide toxicologyed. Academic Press, Inc, New York City, NY, pp 1410–1415
23. Reigart J, Roberts J (1999) Organophosphate insecticide. In: U.S. environmental protection agency: office of prevention, pesticides, and toxic substances, 5th edn. U.S. Government Printing Office, Washington, DC
24. Freeman-Wittig MJ, Welch W, Lewis RA (1989) Binding of captan to DNA polymerase I from Escherichia coli and the concomitant effect on 5′–3′ exonuclease activity. Biochemistry 28:2843–2849. doi:10.1021/bi00433a015
25. Ficsor G, Bordas S, Wade S, Muthiani E, Wertz G, Zimmer D (1977) Mammalian host- and fluid-mediated mutagenicity assays of captan and streptozocin in *Salmonella typhimurium*. Mutat Res 48:1–15. doi:10.1016/0027-5107(77)90185-3
26. Moriya M, Ohta T, Watanabe K, Miyazawa T, Kato K, Shirasu Y (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185–216. doi:10.1016/0165-1218(83)90059-9
27. Suzuki T, Nojiri H, Isono H, Ochi T (2004) Oxidative damages in isolated rat hepatocytes treated with the organochlorine fungicides captan, dichlofluanid and chlorothalonil. Toxicology 204:97–107. doi:10.1016/j.tox.2004.06.025
28. Robbiano L, Baroni D, Carrozzino R, Mereto E, Brambilla G (2004) DNA damage and micronuclei induced in rat and human kidney cells by six chemicals carcinogenic to the rat kidney. Toxicology 204:187–195. doi:10.1016/j.tox.2004.06.057
29. Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP (2002) Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am J Respir Crit Care Med 165:683–689
30. Hoppin JA, Yucel F, Dosemeci M, Sandler DP (2002) Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 12:313–318. doi:10.1038/sj.jea.7500232
31. Engel LS, Seixas NS, Keifer MC, Longstreth WT Jr, Checkoway H (2001) Validity study of self-reported pesticide exposure among orchardists. J Expo Anal Environ Epidemiol 11:359–368. doi:10.1038/sj.jea.7500176
32. Blair A, Tarone R, Sandler D, Lynch C, Rowland A, Wintersteen W, Steen W, Dosemeci M, Alavanja M (2000) Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from iowa. Ann Epidemiol 10:478. doi:10.1016/S1047-2797(00)00113-7
33. Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, Steen WC, Samanic C, Dosemeci M, Alavanja MC (2002) Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13:94–99. doi:10.1097/00001648-200201000-00015
34. White K, Hoppin JA (2004) Seed treatment and its implication for fungicide exposure assessment. J Expo Anal Environ Epidemiol 14:195–203. doi:10.1038/sj.jea.7500312