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Occupational exposure to endocrine-disrupting chemicals and the risk of uveal melanoma

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Objectives We investigated the association between occupational exposure to endocrine-disrupting chemicals (EDC) and the risk of uveal melanoma using international data of a case–control study from nine European countries.

Methods After exclusion of proxy interviews, 280 cases and 3084 control subjects were included in the final analysis. Information on possible exposure to EDC was derived from 27 job-specific questionnaires (JSQ), which solicited detailed questions on occupational tasks. Relative risk estimates were based on the JSQ and potential exposure to a group of endocrine-disrupting agents. We constructed several exposure scores, taking into account intensity of exposure, use of personal protective equipment, and exposure duration. We calculated unconditional logistic regression analyses, adjusting for country, age, sex, eye color and a history of ocular damage due to intense ultraviolet (UV) exposure.

Results The overall exposure prevalence to EDC was low reaching a maximum of 11% for heavy metals with endocrine-disrupting properties. Although working in some industries was associated with increased melanoma risk [such as dry cleaning: odds ratio (OR) 6.15, 95% confidence interval (95% CI) 2.0–18.96 and working in the glass manufacturing industry: OR 3.49, 95% CI 1.10–11.10], agent-specific risks were not elevated. The strongest possible risk increase was observed for organic solvents with endocrine-disrupting properties (OR 1.31, 95% CI 0.78–2.21). Calculation of exposure scores did not indicate consistently elevated results with higher score values. Sensitivity analyses did not alter these results.

Conclusion Occupational exposure to EDC was not associated with an increased risk for uveal melanoma.

Key terms cancer; EDC; endocrine-distrupting agent; exposure score; eye melanoma; multicenter study; ocular melanoma; rare cancer; solvent; xenoestrogen.

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Uveal melanoma, which comprises tumors of the choroidea, the iris, and the ciliary body, is the most common cancer of the eye among adults. However, its incidence compared to other cancers is low and varies between countries (1). Overall, its aetiology is not well understood. Light eye color is an established risk factor, while sunlight exposure has been implicated as a possible factor (2, 3).

Endocrine-disrupting chemicals (EDC) are defined as a heterogeneous group of exogenous agents that interfere with endocrine functions or pathways. Possible mechanisms of EDC include mimicking of hormonal effects, antagonization of hormone receptors, disturbance of hormonal synthesis pathways, or other interferences with hormonal function. Research groups, including our own, attempted to classify occupational exposure to several EDC in job-exposure matrices (JEM) for community- or industry-based settings (4–6).

Several reports have been published linking the risk of uveal melanoma to various occupations, including industries that increase the likelihood of workers being exposed to EDC. Such occupations include, among others, farm workers (exposed to pesticides) (7, 8), metal workers (exposed to endocrinally active heavy metals and metalworking fluids) (7–9), welders (possibly exposed to organic solvents and heavy metals) (10), medical and dental workers (potentially exposed to heavy metals and bisphenol A) (7, 10), workers in the leather industry (exposure to heavy metals and solvents) (9), and workers in the chemical industry (10). Although epidemiological evidence for exposure to EDC has so far been inconsistent (11–14), laboratory studies suggest that melanoma cells may be influenced by hormonal factors (15).

We therefore investigated the association between occupational exposure to potential EDC and the risk of uveal melanoma using international data of the case–control "Study of Occupational Risk Factors for Rare Cancers of Unknown Aetiology" from nine European countries (16).

Methods

The detailed study methods of the Study of Occupational Causes of Rare Cancers of Unknown Aetiology have been described elsewhere (16, 17). Briefly, the study population comprised the national populations of Denmark and Latvia; the population of certain administrative regions in France, Germany, Italy, and Sweden; hospital recruitment areas in Spain and Portugal; and a small non-representative sample from an eye clinic in the UK.

Incident primary cases of uveal melanoma (including ciliary body and iris melanoma) were identified through hospital records. Diagnosed between 1 January 1994 and 31 December 1997, 293 cases with a "definite" or "possible" diagnosis were interviewed. Cases were judged as definite or possible based on pathological specimens and the pathology report. Classification of possible cases of patients who were not enucleated was based on the ophthalmological report (16). However, all possible melanomas were clinically verified using documentation of state-of-the-art diagnostic procedures, such as ophthalmic ultrasound, computed tomography/magnetic resonance tomography (CT/MRT), and fluorescein angiography.

We frequency-matched 3198 population, hospital, and cancer controls (depending on the center) to cases by region, sex, and age. As previously described (16), control subjects were matched to cases at a minimum 4:1 ratio. In each country, all eligible controls were used from the pool of controls matched to the most frequent out of seven rare cancer sites in this study. We excluded proxy interviews, assuming that surrogate subjects are not able to report agent-related occupational exposures accurately (18), leaving 280 cases (159 men, 121 women) and 3084 control subjects (2038 men, 1046 women) for analysis.

Subjects were personally interviewed by trained interviewers using computer-based interviews. Subjects were asked about each job held for ≥6 months. Interviewers also applied 27 job-specific questionnaires (JSQ), soliciting detailed questions on occupational activities and occupational agent exposure.

After screening questionnaires, we eventually included 22 JSQ that addressed possible exposure to EDC. We selected the following JSQ: dentistry, cooking and food preparing, dry cleaning, metal production and iron and steel coating, foundries, electroplating, wood working, pulp and paper production, textile industry, tanneries, slaughtering and meat processing, shoe and leather industry, electrical work, welding, glass production, ceramic production, rubber production, plastic production, painting, paint manufacture, and the chemical industry. Although the JSQ related to working in the ceramics and chemical industry did not directly solicit exposure to any endocrine agent, we decided to include these industries in the list of those with potential EDC exposure (5, 10). Occupational exposure to pesticides in agriculture, animal husbandry, or forestry was not associated with an increased risk for uveal melanoma in a previous analysis of the Rare Cancer Study (19). We therefore did not include JSQ related to farming and forestry in the list of eligible industries.

Potential EDC were selected following the updated version of a job-exposure matrix on EDC from the UK (4) and grouped according to a previous analysis from this study (20): alkylphenols, bisphenol A (epoxy resins), brominated flame retardants, chlorophenols, oestrogens, metals (lead, cadmium, zinc, arsenic, copper), oils potentially including polychlorinated biphenyls (PCB), phenyl phenol and rubber, phthalates (softeners, plastics, polyvinyl chloride (PVC), polyurethane, polystyrene), polycyclic aromatic hydrocarbons (PAH) (application of coal tar-based products), organic solvents (styrene, trichloroethylene, perchloroethylene, glycol ethers), synthetic resins (furanic resins, phenolic resins, nitrocellulose), and waterproofing agents (in the shoe and leather industry) (see supplementary table A: http://www.sjweh.fi/data_repository.php). In contrast to our previous publication, which only relied on answers given in the study's core questionnaire (14), we based exposure to PCB solely on information from the JSQ for this analysis.

We conducted analyses by JSQ and for all agent groups. To quantify occupational EDC exposure, we adapted a method previously applied in an analysis from this study (20). For this purpose, we combined exposure duration, exposure intensity and probability into a weighted exposure score using the following formula:

$$Score_{EDC} = \sum_{k=1}^{K} P_k \times I_k \times D_k$$

where P_k indicates the exposure probability, I_k the intensity, and D_k the duration of exposure in years for job period k in K job periods.

If solicited in the JSQ, duration of EDC exposure was determined as the difference between year of beginning and end of application. Relative risk estimates based on duration were calculated for cumulative years up to the year of uveal melanoma diagnosis (cases) or one year prior to the interview (controls). Probability of exposure was assessed based on information of personal protective equipment (PPE) use. We coded the probability as 1 when subjects had used effective protection [filter mask, overall and gloves, or an application cabin or ventilation (if applicable)] and as 2 when ineffective protection was used (only dust mask, gloves, or overall). We assigned a weight of 3 to subjects without PPE use, and weighted unexposed subjects with 0. Exposure intensity was weighted with 2 when a subject had personally applied a particular agent and with 1 when no personal application was indicated, but the agent was applied in the work process in which the subject was involved. For unexposed subjects, exposure probability and intensity were coded with 0. Handling of hormonal drugs in health-related professions was not considered to yield any relevant exposure to hormones and was coded with 0. To calculate exposure scores, missing values for exposure duration were coded with 1 for all subjects exposed to a particular agent.

Exposure was classified as low, medium, and high based on the tertiles of the distribution of score values among controls and compared to unexposed subjects, who served as reference. Peak exposure was defined as having score values above the 90th percentile (with unexposed subjects as reference).

We constructed an overall exposure score to any EDC by summing up all agent-specific scores. Analogously, we created a sum score for exposures to organic EDC (all agent groups excluding heavy metals) and EDC with estrogenic properties (bisphenol A, alkyl phenols). To calculate sum exposure scores, all subjects with missing data in agent-specific scores were coded with 0. For the purpose of sensitivity analyses, we created an alternate score, which only took into account variables for which duration of exposure was solicited.

Since frequency matching in this study was performed on the most frequent out of seven cancer sites in each country, we calculated unconditional logistic regression analyses in accordance with previous publications from this study (9, 20, 21). Regression analyses adjusted for country, sex, age (continuous), eye color [(blue or grey, and green or hazel (light color) versus dark color (brown or black) as reference], and frequency of lifetime ocular damage due to intense UV exposure (>5 times, 1–≤5 times burned during lifetime versus no reported eye burns) were calculated. To test the stability of our results, we also calculated conditional logistic regression individually matched for country, sex, and 5-year age group, and adjusting for the confounders mentioned above.

Multiplicative effect measure modification by sex, age (<55 years versus ≥55 years), and eye color (light versus dark) was assessed by stratified analysis. We formally assessed statistical significance at the 95% level, using the method proposed by Altman & Bland (22).

We conducted sensitivity analyses excluding cases with a possible diagnosis, cancer controls, and the small sample of UK subjects (27 index case and 23 index control subjects). We also excluded tumors of the iris, as well as tumors with overlapping or unspecified localizations (N=37). All analyses were performed using SAS statistical package, version 9.2 (SAS Institute, Cary, NC, USA).

Local ethics committees approved the study. Study subjects or – in the case of deceased subjects – their relatives gave written informed consent to participate in the study.

Results

The prevalence of most industries or occupational activities with potential EDC exposure was low. Welding emerged as the most prevalent activity [11.1% among cases and 13.7% among controls (table 1)]. Pooling

Table 1. Odds ratio (OR) for application of industry job-specific questionnaires (JSQ). [95% CI=95% confidence interval; n/e= not estimable]

Industry	N exposed		OR_1 [a]	95% CI	OR_2 [b]	95% CI	OR_3 [c]	95% CI
	Cases	Controls						
Health services	25	198	1.14	0.73–1.79	1.11	0.70–1.76	1.27	0.76–2.12
Dentistry	2	11	1.62	0.35–7.40	1.59	0.34–7.37	1.38	0.29–6.62
Cooking	28	215	1.22	0.79–1.89	1.23	0.79–1.92	1.53	0.95–2.47
Dry cleaning	5	9	5.43	1.79–16.46	6.15	2.0–18.96	8.52	2.53–28.76
Metal industry	4	76	0.65	0.23–1.83	0.61	0.22–1.72	0.74	0.22–2.43
Foundries	7	38	2.31	1.0–5.29	2.17	0.94–4.99	1.97	0.74–5.24
Electro-plating	0	22	n/e		n/e		n/e	
Wood working	22	183	1.56	0.97–2.52	1.60	0.99–2.59	1.32	0.72–2.44
Paper and pulp production	7	25	2.79	1.18–6.61	2.40	0.95–6.03	1.74	0.50–6.08
Textile industry	7	84	0.94	0.42–2.07	0.95	0.43–2.11	1.10	0.46–2.66
Tanneries	2	7	3.32	0.66–16.62	3.15	0.61–16.25	6.30	1.06–7.51
Slaughtering and meat processing	2	49	0.45	0.11–1.88	0.44	0.11–1.84	0.32	0.04–2.35
Shoe and leather production	7	50	1.75	0.77–3.96	1.80	0.79–4.11	2.55	1.01–6.43
Electro-technics	12	170	0.88	0.47–1.62	0.84	0.45–1.56	0.93	0.45–1.90
Welding and soldering	31	423	0.87	0.57–1.30	0.71	0.46–1.11	0.99	0.60–1.62
Glass industry	4	18	3.37	1.08–10.51	3.49	1.10–11.10	3.53	0.95–13.04
Ceramic industry	3	37	0.96	0.29–3.18	0.92	0.28–3.07	0.47	0.06–3.59
Rubber and tyre industry	1	35	0.33	0.05–2.46	0.36	0.05–2.70	n/e	
Plastic industry	4	41	1.23	0.43–3.50	1.29	0.45–3.68	1.39	0.41–4.71
Painting and lacquering	11	150	0.89	0.47–1.67	0.86	0.45–1.63	0.95	0.45–2.0
Color production	0	15	n/e		n/e		n/e	

[a] OR_1 adjusted for country, sex, age (continuous).
[b] OR_2: OR_1+ adjusted for eye color and a history of ultraviolet (UV) radiation ocular damage.
[c] OR_3: OR_2 + but excluding cancer controls and UK subjects (253 cases, 2042 controls).

exposure to potential EDC across different industries also yielded low prevalences: for example, exposure to metals with endocrine properties showed a prevalence of 9.3% among cases and 11.5% among controls. Organic solvents with possible endocrine activities were used by 6.9% of cases and 5.4% of controls (table 2).

Among industries or activities with potential EDC exposure, some yielded positive associations with uveal melanoma. Notably, risk estimates for dry cleaning, and working in the glass, tannery, and shoe and leather production industries indicated elevated risks. Also, cooking and food preparation and working in foundries implied elevated associations with uveal melanoma (table 1). However, no clear risk increases were seen, when we assessed exposures to specific endocrine-disrupting agents with exposure to organic solvents showing the highest potential risk increase [adjusted odds ratio (OR_2) 1.31, 95% confidence interval (95% CI) 0.78–2.21] (table 2). In addition, a single question on the use of glues with solvents in the shoe and leather production yielded an increased risk (OR_2 2.50, 95% CI 0.92–6.78), which was based on 5 exposed cases and 26 exposed control subjects (not shown). However, as the respective solvent was not further specified, we did not include this variable in the agent-specific exposure estimates for organic solvents.

Calculation of exposure scores, taking into account duration of exposure, intensity of exposure, and use of PPE, did not yield consistently elevated risk estimates (table 3).

Applying the alternate exposure score, which only considered variables in which duration of exposure was solicited, yielded results which differed only slightly from the main exposure score. Results differed in total EDC exposure where the alternate score showed OR_1 1.27 (95% CI 0.71–2.28) for low, OR_1 1.46 (95% CI 0.68–3.15) for medium, and OR_1 1.45 (95% CI 0.77–2.74) for high score values (results not shown).

Although some risk estimates appeared to increase slightly, sensitivity analyses excluding UK subjects (27 cases, 23 controls) and cancer controls (N=1019) did not alter the overall results. However, in these sensitivity analyses, possible risk increases for uveal melanoma were seen with exposure to organic solvents, PAH, PCB, and impregnation agents, but the power remained low and point estimates showed wide confidence intervals (table 2). Exclusion of cases with a possible diagnosis (N=30) did not affect most results. Exceptions were exposure to synthetic resins (OR 1.47, 95% CI 0.61–3.55), working in tanneries (OR 1.72, 95% CI 0.20–14.96), and working in the shoe and leather industry (OR 1.47, 95% CI 0.57–3.83) (not shown). When we restricted the analyses to melanomas localized in the choroidea and the ciliary body (N=243 cases), the overall results for agent-specific exposures did not change either.

Conditional logistic regression analyses yielded similar results as compared to unconditional logistic regression. If results deviated, conditional logistic regression tended to yield higher point estimates and showed less precision (eg, for working in the glass

Table 2. Odds ratio (OR) for exposure to agents with potential endocrine-disrupting chemicals (EDC) properties. [95% CI=95% confidence interval; n/e= not estimable]

Agent group	N exposed		OR_1 [a]	95% CI	OR_2 [b]	95% CI	OR_3 [c]	95% CI
	Cases	Controls						
Organic EDC	48	572	0.93	0.67–1.30	0.91	0.65–1.27	1.16	0.80–1.70
Bisphenol A	6	99	0.70	0.30–1.62	0.67	0.29–1.56	0.96	0.40–2.27
Organic solvents	19	168	1.39	0.83–2.31	1.31	0.78–2.21	1.67	0.96–2.89
Synthetic resins	6	64	1.22	0.51–2.90	1.12	0.47–2.68	1.22	0.42–3.50
Chlorophenol	0	10	n/e		n/e		n/e	
Polyaromatic hydrocarbons (PAH)	11	114	1.24	0.65–2.38	1.18	0.61–2.27	1.71	0.84–3.47
Phthalates	6	99	0.79	0.34–1.83	0.79	0.34–1.85	0.78	0.28–2.20
Alkylphenols	11	138	0.68	0.36–1.30	0.70	0.37–1.34	0.84	0.42–1.69
Phenylphenol/rubber	5	127	0.45	0.18–1.12	0.43	0.17–1.08	0.66	0.26–1.69
Polychlorinated biphenyls (PCB)	7	67	1.23	0.55–2.74	1.20	0.54–2.70	1.91	0.83–4.41
Brominated flame retardants	0	2	n/e		n/e		n/e	
Impregnation agents	1	5	2.94	0.34–25.7	2.73	0.30–24.91	4.32	0.46–40.88
Heavy metals	26	356	0.87	0.56–1.35	0.76	0.48–1.20	0.98	0.58–1.64

[a] OR_1 adjusted for country, sex, age (continuous).
[b] OR_2: OR_1+ adjusted for eye color and a history of ultraviolet (UV) radiation ocular damage.
[c] OR_3: OR_2 + but excluding cancer controls and UK subjects (253 cases, 2042 controls).

Table 3. Odds ratios (OR) of uveal melanoma and exposure scores for endocrine-disrupting chemicals (EDC). [95% CI=95% confidence interval; n/e= not estimable]

Exposure score	N exposed		OR_1 [a]	95% CI	OR_2 [b]	95% CI	OR_3 [c]	95% CI
	Cases	Controls						
Solvents								
Low	11	68	2.05	1.05–3.99	1.80	0.91–3.56	2.22	1.07–4.62
Medium	4	40	1.27	0.45–3.62	1.30	0.45–3.74	1.78	0.61–5.19
High	4	51	0.93	0.33–2.61	0.88	0.31–2.51	1.18	0.41–3.42
Phthalates								
Low	3	48	0.83	0.25–2.71	0.82	0.25–2.68	1.21	0.36–4.08
Medium	1	17	0.77	0.10–5.92	0.93	0.12–7.24	1.82	0.23–14.32
High	2	31	0.82	0.19–3.48	0.78	0.18–3.34	n/e	
Total EDC								
Low	18	252	0.71	0.43–1.18	0.66	0.39–1.11	0.88	0.50–1.53
Medium	12	213	0.68	0.37–1.25	0.65	0.35–1.21	0.88	0.46–1.71
High	24	226	1.24	0.78–1.96	1.15	0.72–1.85	1.48	0.87–2.53
Peak	8	69	1.31	0.62–2.80	1.28	0.59–2.74	1.20	0.46–3.13
Organic EDC								
Low	18	232	0.79	0.48–1.31	0.79	0.47–1.31	1.09	0.63–1.88
Medium	15	150	1.19	0.68–2.08	1.11	0.63–1.96	1.46	0.80–2.69
High	15	179	1.0	0.57–1.74	0.98	0.56–1.73	1.11	0.58–2.15
Peak	8	56	1.62	0.75–3.47	1.58	0.73–3.43	0.69	0.09–5.34
EDC with estrogenic activity								
< median	13	183	0.65	0.36–1.17	0.66	0.37–1.19	0.86	0.46–1.62
≥ median	4	51	0.86	0.31–2.42	0.82	0.29–2.32	1.02	0.35–2.93
Peak	2	23	0.93	0.22–4.01	0.83	0.19–3.59	1.12	0.25–5.03

[a] OR_1 adjusted for country, sex, age (continuous).
[b] OR_2: OR_1+ adjusted for eye color and a history of ultraviolet (UV) radiation ocular damage.
[c] OR_3: OR_2 + but excluding cancer controls and UK subjects (253 cases, 2042 controls).

industry: OR_2 4.33, 95% CI 1.22–15.31 versus OR_2 3.49, 95% CI 1.10–11.10).

We did not observe joint effects with respect to sex or eye color. Although some risk estimates differed in the stratified analyses, the study did not have enough power to open up for an analysis of interaction terms. Possible joint effects were observed when stratifying by age group (<55 versus ≥55 years). For example, for dentistry we observed OR_1 4.32 (95% CI 0.80–23.27) among the older subjects, while no case was observed in the younger age group. In contrast, no case subjects were observed in the younger age group for working in tanneries, while subjects ≥55 years showed OR_1 6.09 (95% CI 0.95–39.03). Working in the dry cleaning industry was associated with an OR_2 of 3.1 (95% CI 0.63–15.52) among subjects ≥55 years of age as compared to OR_2 22.8 (95% CI 2.20–235.12) in the younger age group. However, the latter observation was based on only three cases and one control subject.

Discussion

These explorative analyses did not show an increased risk for uveal melanoma due to occupational EDC exposure. In contrast, occupation in some industries was associated with a risk increase for this rare tumor. Although the study base was fairly large, only a few of the 21 industries showed a prevalence >10%. Pooling of agent-specific exposures across different industries did not yield higher prevalences either, and thus most analyses were based on few exposed subjects, resulting in wide 95% CI.

When dealing with low numbers, non-differential exposure misclassification is a serious concern, possibly attenuating risk estimates towards unity (23). Therefore, we cannot rule out that misclassification of the exposure through the set of JSQ diluted a possible increased risk estimate. In contrast, misclassification of one or two case subjects when dealing with low prevalence may even bias estimates towards a spurious positive association. This is potentially illustrated by the contrasting findings we observed with respect to PCB: previous analyses from this study using questions from the core questionnaire found occupational PCB exposure to be a risk factor for uveal melanoma (14), while no risk was indicated when applying PCB-related questions from JSQ across two different industries (electro techniques and tire and rubber production) in the present analysis. However, one advantage of this study, with exposure estimates based on individually solicited JSQ, is the higher specificity in the assessment of job-related exposures as compared to, eg, JEM or job titles. Most JEM may have difficulties assessing exposures that may vary largely in-between individual workplaces and over time (23). Furthermore, the selection of possible EDC from reported exposures and work activities in this study was facilitated by our own experiences in designing a JEM with individual expert ratings on EDC exposure in the automobile industry (6) and by the availability of a community-based JEM from the UK focusing on exposure to EDC (4, 5). By excluding next-of-kin or other surrogate interviews, we further increased the specificity of exposure assessment in these analyses.

Although uveal melanoma and colon cancer do not share any known common risk factors, selection of colon cancer patients in some study centers may represent a limitation, which could potentially lead to selection bias. However, although exclusion of cancer controls tended to increase some of the agent-specific point estimates, the overall results did not change due to these sensitivity analyses. Exclusion of cases with a possible diagnosis according to the study protocol (including clinically verified cases using catamneses and documentation of state-of-the-art diagnostic procedures, such as ophthalmic ultrasound, CT/MRT, and fluorescein angiography), or the small non-representative sample of UK subjects did not change results either, which adds confidence that our results were not affected by bias.

Limitations of this study may also include that no clear distinction between iris and ciliary melanoma was made for some cases. Iris melanomas have different histopathological features and may be influenced by a different set of risk factors (24). However, restricting the analyses to choroidal tumors did not alter the overall results.

Potential occupational EDC may influence sexual hormones in various ways. Anti-estrogenic effects (brominated flame retardants and PAH), estrogenic effects (bisphenol A, some pesticides, alkyl phenols, and some organic solvents) (4, 25), as well as anti-androgenic effects (phthalates, glycol ethers, PCB, and other pesticides) (4, 26) have been described in the literature. In this study, exposure to organic solvents was the only EDC implying an elevated risk for uveal melanoma, although results were not statistically significant (OR_2 1.31, 95% CI 0.78–2.21).

In contrast, basing our analyses on JSQ employed for this study, we identified risk increases in various industries/occupations, including dry cleaning, shoe and leather production, foundries, and cooking. Exposures in these job categories may involve UV radiation, heat, melting fumes, metals, microwave or infrared radiation, which have been discussed as possible carcinogenic agents (9, 27–29). Nevertheless, the excess risks found in these industries could not be explained by EDC exposure.

For example, dry cleaning, which was the industry showing the highest risk in this study (OR_2 6.15, 95% CI 2.0–18.96), may involve exposure to organic solvents such as trichloroethylene and perchloroethylene. Likewise, a single question on the use of glues with solvents in the JSQ targeted at the shoe and leather industry yielded an elevated OR. Furthermore, use of alkylphenols while cleaning stoves was considered as a potential source of EDC exposure among cooks and kitchen workers. Although alkylphenols are considered endocrine disruptors with potential estrogenic activity (25), we did not find these agents to be a risk factor for uveal melanoma. In addition, the authors of a recent analysis from the Rare Cancer Study speculated that volatile organic compounds (VOC) with endocrine properties in wood could have been responsible for an increase in male breast cancer among wood workers (21). Although wood workers were also at increased risk for uveal melanoma, we could not analyze the influence of VOC, as exposure to this group of chemicals was not solicited in the JSQ. In addition, wood workers may be exposed to various other endocrinally active agents (such as heavy metals, organic solvents, or coal-tar-based agents). However, none of these agents suggested a strong association with eye melanoma in our analyses.

In summary, we observed elevated risks for several industries rather than specific endocrine agents. While in these industries, workers may be exposed to several possible carcinogenic agents, the observed excess risks were not explained by exposure to EDC. In conclusion, taking into account our previous inconsistent findings on a possible association between hormonal factors and uveal melanoma (14, 17, 19), the present study does not support the hypothesis that hormonal influences are an important factor in the aetiology of these tumors.

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